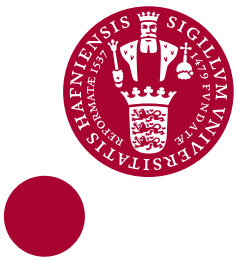

The efficacy of vortioxetine in adult patients with a recurrent major depressive episode (MDE)

A randomized, double-blind, placebo-controlled study

McIntyre, R.; Lophaven, S. N.; Olsen, C. K.

Published in:
International Journal of Neuropsychopharmacology

DOI:
10.1017/S1461145714000741

Publication date:
2014

Document version
Publisher's PDF, also known as Version of record

Plenary Lectures

Monday 23 June 2014

PL-01. The Arvid Carlsson Lecture: The ups and downs of amphetamines: A diversity of actions on cellular signaling pathways

PL-01-001 **The ups and downs of amphetamines: A diversity of actions on cellular signaling pathways**

S. G. Amara. *National Institute of Mental Health, Bethesda, MD, USA*

Neurotransmitter transporters present at the plasma membrane contribute to the clearance and recycling of neurotransmitters and have a profound impact on the extent of receptor activation during neuronal signaling. These carriers also are the primary targets for psychostimulant drugs of abuse, antidepressant medications, and drugs such as methylphenidate and amphetamines, which are used to treat attention deficit disorders. This lecture will highlight several of the major signaling pathways that regulate dopamine transporter function and will also consider recent work showing that amphetamine-like drugs can directly activate intracellular signaling pathways in dopamine neurons to trigger changes in membrane protein trafficking and other cellular activities. Although several steps in the process remain undefined, the intracellular actions of amphetamine modulate both dopaminergic and glutamatergic signaling and contribute to the acute behavioral effects of the drug. These actions of amphetamine within dopamine neurons have implications for mechanisms of neuroplasticity and neurotoxicity associated with psychostimulant use and suggest novel drug targets for modulating the actions of amphetamines.

Policy of full disclosure: None.

PL-02. Nobel Lecture – Structural insights into G protein coupled receptor signaling

PL-02-001 **Nobel Lecture – Structural insights into G protein coupled receptor signaling**

B. Kobilka. *Department of Molecular and Cellular Physiology, Stanford University, USA*

G protein coupled receptors (GPCRs) conduct the majority of transmembrane responses to hormones and neurotransmitters, and mediate the senses of sight, smell and taste. The β2 adrenergic receptor (β2AR) and the M2 muscarinic receptors are prototypical Family A GPCRs that mediates physiologic responses to autonomic nervous system activity. We have obtained three-dimensional structures of the β2AR and the M2 muscarinic receptor in inactive and active conformations, as well as a structure of the β2AR in complex with the G protein Gs. We have also used fluorescence, EPR and NMR spectroscopy to study the dynamic properties of the β2AR, and to map ligand-specific conformational changes. I will discuss what we these studies have taught us about allosteric regulation of GPCR structure by G proteins and ligands.

Policy of full disclosure: There is no financial conflict of interest.

Tuesday 24 June 2014

PL-03. The endocannabinoid system – a fifty years trip

PL-03-001 **The endocannabinoid system – a fifty years trip**

R. Mechoulam. *Institute for Drug Research, Hebrew University, Jerusalem, Israel*

The endocannabinoid system was discovered and we learned about its involvement in biological processes only over the last two decades – many years after the better known adrenergic, serotonergic or cholinergic systems. However it has already been suggested that " modulating endocannabinoid system activity may have therapeutic potential in almost all diseases affecting humans, including . . .neurodegenerative, inflammatory,. . . . pain, . . . psychiatric disorders, amongst many others " – as stated in a recent review. I shall discuss the development of the endocannabinoid system – from the isolation and structure elucidation of delta-9-tetrahydrocannabinol in 1964, through the identification of the CB1 and CB2 receptors and the specific agonists anandamide and 2-AG, to the involvement of endocannabinoids and structurally related endogenous molecules in a long list of biological processes. Recent progress in several areas will be discussed: A. Endocannabinoids as endogenous neuroprotective agents, particularly in traumatic injury; B. The CB2 cannabinoid receptors as part of a general protective system; C. Acyl fatty acids as novel endocannabinoid-like compounds; D. Cannabidiol as a novel therapeutic entity.

Policy of full disclosure: 1. I have no significant financial interest or other affiliation with a funding organization or with a commercial supporter of the session and/or provider of commercial services. 2. I had a grant from NIH (ended 30 Nov 2013).

PL-04. Brain science using iPS cell technology non-human primates

PL-04-001 **Brain science using iPS cell technology non-human primates**

H. Okano. *Keio University, Tokyo, Japan*

What makes the investigation of human psychiatric/psychiatric disorders so difficult? This could be attributed to the following reasons 1) Diseases model mice do not always recapitulate the pathophysiology of human diseases, 2) It is extremely difficult to investigate what is taking place in vivo at the onset of the disease due to the low accessibility to the pathological foci in the brain, and 3) The responsible neuronal circuits for the phenotype are not identified. In order to overcome these difficulties, we took advantage of iPS cell technologies and transgenic non-human primates for modeling human psychiatric/psychiatric disorders. So far, we have established iPS cells from the patients of more than 25 human psychiatric/psychiatric disorders and characterized their pathophysiology. For example, in collaboration with the group of RIKEN BSI and University of Tokyo, we established iPS cells from the schizophrenia patients containing 22q11 deletions (Bundo et al., Neuron, 2014). Interestingly, we found that the copy number of a retrotransposon, long interspersed nuclear element-1 (L1), was increased in neurons induced from iPS cells from schizophrenia patients containing 22q11 deletions, indicating that hyperactive retrotransposition of L1 in neurons triggered by genetic risk factors may contribute to the susceptibility and pathophysiology of schizophrenia. Furthermore, for faithfully modeling the human human psychiatric/psychiatric disorders in vivo, we developed transgenic non-human primates (common marmosets) with germline transmission (Sasaki et al., Nature, 2009). In the present talk, we also wish to mention our recent data of generation of common marmoset transgenic models of neurodegenrerative diseases, including Parkinson disease, Alzheimer disease and ALS. I will also mention about our recent trials on the development of knock-in and knock-out technologies of common marmoset using genome editing technologies for the generation of transgenic marmoset model of autism and psychiatric disorders.

Policy of full disclosure: H. Okano is the scientific consultant of San Bio, Inc; Eisai Co Ltd; and Daiichi Sankyo Co Ltd.

Wednesday 25 June 2014

PL-05. Preventive strategies in emerging mental disorders in young people: Clinical staging and translational research

PL-05-001 Preventive strategies in emerging mental disorders in young people: Clinical staging and translational research

P. McGorry. *Orygen Youth Health Research Centre, University of Melbourne, Melbourne, Australia*

A key goal in psychiatry is to build new diagnostic, therapeutic and translational tools and capacity to reduce the impact of emerging mental disorders in young people on survival, distress, quality of life and productivity. Young people bear the major burden of onset for mental disorders with 75% of such illnesses appearing before age 25 years. This can only be done within a novel non-stigmatising interface between young people and clinical care in mental health such as that recently created by headspace in Australia and increasingly in some other developed nations. We must also develop new terminology enabling early clinical phenotypes of mental disorders to be defined in a normalizing and health-promoting way that will promote trust and confidence. A transdiagnostic strategy is critical, transcending existing subthreshold risk syndromes, with new "pluripotential" criteria capturing clinical high risk for multiple syndromes. This strategy seeks to solve problems with specificity, power and reduce false positives. Secondly, we must focus on novel therapeutics. This starts with the development and evaluation of novel forms of psychosocial intervention for early stage illness. A complementary strategy needs to focus upon candidate biomarkers as therapeutic probes within a reverse translation strategy moving towards biosignatures or profiles of emerging disorder. Relationships between response and baseline levels of and changes in biomarkers may create a pathway to personalised / stratified medicine. Finally translation of existing expertise and systematic reform of clinical practice and cultures of care is something that is achievable with the present state of knowledge yet is poorly implemented. McGorry PD, van Os J. 2013. Redeeming diagnosis in psychiatry: timing versus specificity. Lancet 381:343–345. McGorry PD. 2013. Early clinical phenotypes, clinical staging and strategic biomarker research: Building blocks for personalized psychiatry. Biological Psychiatry 74:394–395 McGorry PD, Bates T, Birchwood M. 2012. Designing youth mental health services for the 21st century: Examples from Australia, Ireland and the UK. British Journal of Psychiatry Suppl. 54:s30–s35.

Policy of full disclosure: None.

PL-06. Optical deconstruction of fully-assembled biological systems

PL-06-001 Optical deconstruction of fully-assembled biological systems

K. Deisseroth. *Stanford University, Stanford, USA*

This talk will report on recent results in development of both optogenetics (a technology for precisely controlling millisecond-scale activity patterns in specific cell types using microbial opsin genes and fiberoptic-based neural interfaces (1, 2) and CLARITY (a technology to optically resolve high-resolution structural and molecular detail within intact tissues without disassembly). In the optogenetics domain, strategies will be discussed for targeting microbial opsins and light to meet the challenging constraints of the freely-behaving mammal, newly engineered microbe al opsin genes spanning a range of optical, kinetic, and ion permeability properties, high-speed behavioral and neural activity-readout tools compatible with real-time optogenetic control, and application of these tools to develop circuit-based insight into anxiety, depression, and motivated behaviors (3, 4). Distinct from optogenetics, new advances in the CLARITY technology (5) will be covered that accelerate (by orders of magnitude) the extraction of information from intact biological tissue that has been transformed into a hybrid form in which components are removed and replaced with exogenous elements, resulting in a transparent tissue-hydrogel that both preserves, and makes accessible, struc-tural and molecular information for visualization and analysis (both for whole mouse brains and banked human brain tissue). Together these complementary approaches help to unlock rich sources of information for probing disease mechanisms as well as the native structure and complexity of the nervous system (6).

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Policy of full disclosure: no disclosures.

Thursday 26 June 2014

PL-07. CINP/CCNP Lecture: Interactions between neurotransmitters – The key to remission for depression

PL-07-001 CINP/CCNP Lecture: Interactions between neurotransmitters – The key to remission for depression

P. Blier. *University of Ottawa, Ottawa, Canada*

Current antidepressants target neuronal elements controlling the release of serotonin (5-HT) and/or norepinephrine (NE). The interference with such targets triggers negative feedback mechanisms preventing an immediate and sustained increase in the synaptic availability of these neurotransmitters. After prolonged administration, these mechanisms exerted by cell body and/or terminal autoreceptors become less effective thereby producing a sustained elevation of transmission in the targeted systems. One way to understand the low remission rates with antidepressants is that an increase in one transmission system can dampen the activity of other neurotransmitters. For instance, selective 5-HT reuptake inhibitors, while enhancing 5-HT transmission, dampen NE and dopamine neuronal activity. Another way to understand low remission rates in major depression is to realize that its pathophysiology may differ widely: it is possible to have two patients meeting diagnostic criteria and yet not have a single sign or symptom in common. The treatment of depression therefore often requires more than one mechanism. Consequently, the therapeutic principles for depression do not differ from those of other medical diseases, such as hypertension whereby more than one mechanism is used even from treatment initiation. In fact, some of the first antidepressants, such as clomipramine and MAO inhibitors, target more than one mechanism. Now that we have wide choices of antidepressants that have fewer side effects, it is possible to go back to the multiple target approach. A better understanding of the reciprocal interactions between monoaminergic transmitter systems allows clinicians to follow a neurobiological algorithm. This consists in combining various strategies acting on different neuronal elements and avoiding pharmacologically redundant strategies. Double-blind controlled studies have indeed shown that combinations of antidepressants with a variety of other medications, for example low doses of atypical antipsychotics, can lead to remission in treatment-resistant patients, and in some cases to a more rapid onset of action.

Policy of full disclosure: Dr Blier received grants and/or honoraria for giving lectures and/or participating in advisory boards for Astra Zeneca, Bristol Myers Squibb, Eli Lilly, Forest, Janssen, Lundbeck, Merck, Pfizer, Pierre Fabre Medicaments, Servier, Sunovion, Takeda, and Valeant.

Monday 23 June 2014

S-01. Remodeling the neurocircuitry of depression: Ketamine and glutamate

S-01-001 Current treatments of depression: Impact of monoamine and glutamate

P. Blier[1], K. El Iskandarani[1], C.A. Oosterhof[1], M. El Mansari[1]. [1]*University of Ottawa, Ottawa, Canada*

Objective: Ketamine is a non-competitive NMDA antagonist that acts primarily by blocking the NMDA receptor at the PCP site. The antidepressant qualities of ketamine were demonstrated in the clinic and in several behavioral models of depression in rodents. We hypothesized that the rapid antidepressant effects of ketamine are due to, at least in part, its effects on the monoaminergic systems.

Methods: Experiments were carried out on male Sprague Dawley rats. Rats were anesthetized with chloral hydrate (400 mg/kg; ip) and mounted on a stereotaxic frame. Recordings were carried out in the locus coeruleus (LC) and the ventral tegmental area (VTA), 30 minutes following intraperitoneal ketamine administration (10 mg/kg) for acute experiments. The responsiveness of CA3 pyramidal neurons to iontophoretically applied AMPA and NMDA was assessed prior to, and up to 30 minutes following administration of ketamine.

Results: Following acute ketamine administration, an immediate and significant increase in the firing rate of NE neurons was observed (29%). Additionally, there was an enhancement in the number neurons exhibiting bursting activity (control: 17%±1.7, ketamine: 30%±3.8, $p<0.01$). A doubling in the number of spontaneously firing DA neurons was also observed (control: 1.2±0.08 neurons/track, ketamine: 2.6±0.4 neurons/track, $p<0.01$). The effect of ketamine on these electrophysiological parameters was prevented by pre-administration of the AMPA receptor antagonist NBQX 10 minutes prior to ketamine administration. A significant increase (60%) in the responsiveness to iontophoretically applied AMPA was observed 30 minutes following ketamine administration at a dose of 10 mg/kg.

Conclusion: The present results show that acute ketamine administration produces an increase in NE and DA activity. These enhancements were blocked by NBQX, indicating that these effects are mediated, at least in part, via AMPA receptors. Furthermore, ketamine administration caused an increase in the responsiveness of pyramidal neurons to iontophoretically applied AMPA, suggesting an increased responsiveness of these receptors.

Policy of full disclosure: Dr Blier received grants and/or honoraria for giving lectures and/or participating in advisory boards for Astra Zeneca, Bristol Myers Squibb, Eli Lilly, Forest, Janssen, Lundbeck, Merck, Pfizer, Pierre Fabre Medicaments, Servier, Sunovion, Takeda, and Valeant.

S-01-002 Results of brain imaging of Ketamine using fMRI and PET

R. Lanzenberger. *Medical University of Vienna, Psychiatry, Vienna, Austria*

Policy of full disclosure: R. Lanzenberger received travel grants and conference speaker honoraria from AstraZeneca, Roche and Lundbeck A/S.

S-01-003 Prefrontal-amygdala attenuation of dopamine neuron activity in animal models of depression: Reversal by Ketamine

A. Grace[1], P. Belujon[1], C.-H. Chang[1]. [1]*University of Pittsburgh, Pittsburgh, USA*

Objective: Imaging studies reveal that depression correlates with hyperactivity in Area 32 (infralimbic) PFC and hyper-responsivity in the amygdala. We used the chronic mild stress (CMS) and learned helplessness (LH) models of depression to examine this circuitry, how it impacts dopamine neuron responsivity, and the therapeutic actions of ketamine.

Methods: Rats were exposed to either the CMS model or LH models of depression/anhedonia. Dopamine neuron activity was sampled in the ventral tegmentum, and rats were tested for escape behavior and forced swim. Ketamine was administered in a subgroup of rats prior to recording/assessing escape behavior.

Results: Rats exposed to CMS showed decreased dopamine neuron activity and increased immobility in forced swim. Dopamine activity was restored by inactivating the infralimbic PFC, the basolateral amygdala, or blocking amygdala drive of the ventral pallidum. Only LH rats that exhibited helpless behavior showed a deficit in the number of dopamine neurons firing spontaneously, and a switch from hippocampal-accumbens plasticity from LTP to LTD. Escape behavior, dopamine neuron firing, and hippocampal-accumbens plasticity was restored to baseline following ketamine.

Conclusion: The number of dopamine neurons firing is a measure of the level of responsivity of the dopamine system, with fewer neurons active greatly diminishing the ability of rewarding stimuli to activate the dopamine system. This would be expected to lead to anhedonia; a major feature of depression. Dopamine neuron activity is regulated by two systems: a facilitatory system originating in the ventral hippocampus that, via the accumbens, activates dopamine neurons. This contrasts with an inhibitory circuit driven by the ilPFC-amygdala-ventral pallidal pathway. These data suggest that in models of depression, there is an imbalance between the hippocampal dopamine excitatory circuit and the ilPFC-amygdala dopamine inhibitory circuit, in which the excitatory system is taken off-line. This balance is restored by acute administration of ketamine.

Policy of full disclosure: Johnson & Johnson, Lundbeck, Pfizer, GSK, Puretech Ventures, Merck, Takeda, Dainippon Sumitomo, Otsuka, Lilly, Roche, Asubio, Abbott.

S-01-004 Too little or too much? The place of glutamate in depression

M. Popoli. *University of Milan, Milan, Italy*

The glutamate system is recognized as a primary mediator of psychiatric pathology and a target for rapid-acting antidepressants. Brain imaging studies of depressed patients provided evidence of decreased volume of cortical/limbic regions, suggestive of neuronal atrophy related to length of illness and time of treatment. At the same time, rodent studies provided evidence of dendritic remodeling and loss of synapses in depression/stress models, suggesting neurocircuitry remodeling as a main factor in volumetric changes. Destabilization (enhancement) of glutamate release and transmission, in turn induced by acute stress and glucocorticoids, is a major factor for structural/functional changes in cortical and limbic areas (1,2). Conversely, antidepressants dampen the stress-induced enhancement of glutamate release in prefrontal and frontal cortex (PFC/FC), an action that may contribute to stabilize neurotransmission during therapy (3). Further support for the glutamate hypothesis comes from studies showing rapid and sustained antidepressant action of NMDA receptor antagonists, particularly ketamine, whose rapid action has been linked to a burst of glutamate release and transmission (4). However, the nature and direction of changes in the glutamate system, in pathophysiology and during treatment, is not clear. While acute stress in adulthood induces enhancement of glutamate release/transmission, through distinct structural and functional changes at different synapses of PFC, the behavioral consequences of prenatal stress in adulthood have been shown to be associated with reduced glutamate release in hippocampus (5). This talk will propose a speculative model on changes associated with stress and stress-related neuropsychiatric disorders, based on current available evidence.

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Policy of full disclosure: None.

S-02. Neuron-glia interaction in schizophrenia: Focus on D-serine

S-02-001 Neuron-glia regulation of D-serine signaling: Implication in schizophrenia

T. Nishikawa. *Tokyo Medical and Dental University, Tokyo, Japan*

Objective: D-Serine, a putative endogenous coagonist for the NMDA type glutamate receptor (NMDAR), and its metabolism and extracellular signaling systems in the brain could dysfunction in schizophrenia and could be the targets for the development of a novel pharmacotherapy for this intractable disorder, because (1) NMDAR antagonists cause schizophrenia-like symptoms and (2) D-serine has been reported to improve these symptoms in schizophrenic patients as well as their animal models. We therefore have investigated the molecular and cellular mechanisms underlying these D-serine regulation systems by in vivo and in vitro experiments and human sample analyses.

Methods: A molecular cloning, gene expression analysis, quantitation of various amino acids by high-performance liquid chromatography, in vivo microdialysis, and single nucleotide polymorphism genotyping technique were applied to the present animal and human studies that have been approved by the ethics committees of the Tokyo Medical and Dental University and National Center of Neurology and Psychiatry.

Results: In the rodent brains, the selective manipulations of the neurons and glia resulted in the changes in the tissue and extracellular contents of D-serine, suggesting the involvement of neuron-glia interaction in the regulation of D-serine signaling. In vivo microdialysis experiments have demonstrated that AMPA type glutamate receptors, GABAA receptors, neutral amino acid transporters, Asc-1 and ASCT2, and neuronal serine racemase participate in the control of extracellular D-serine contents in the medial frontal cortex or hippocampus. Moreover, we have isolated a gene, D-serine-modulator-1, that encodes the protein influencing the intra- and extracellular D-serine contents when expressed in the Xenopus oocytes.

Conclusion: The present findings suggest that neuron-glia communication could integrate the D-serine signaling by linking to glutamate-GABA interaction and D-serine metabolism-related molecules. These systems and molecules are under investigations of their genetic association with schizophrenia and of their expressions in the postmortem brains.

Policy of full disclosure: None.

S-02-002 D-Serine localization: Fact or artifact

J. Coyle[1], D. Balu[2], M. Puhl[2], M. Benneyworth[2], S. Takagi[2]. *[1]Harvard University, Boston, USA; [2]McLean Hospital, Belmont, USA*

Recent results from genome wide association studies and from copy number variants associated with schizophrenia (SCZ) have implicated genes encoding proteins involved in glutamatergic neurotransmission. This includes serine racemase (SR), the enzyme responsible for the synthesis of D-serine, the co-agonist at NMDA receptors (R), which is concentrated in the cortico-limbic regions. Mice with null mutations of SR exhibit many of the pathologic stigmata of SCZ including impaired working memory, increased ventricular volume, decreased cortical volume, reduced BDNF, phospho-TrkB, phospho-mTOR, dendritic complexity and dendritic spines on pyramidal neurons. To understand better the localization of SR and D-serine, we used a combination of quantitative genetic and immunologic methods. SR expression was blocked in a cell specific fashion using mice expressing Cre in astrocytes with a GFAP promoter and in forebrain glutamatergic neurons with CAMKIIα promoter. Cortical D-serine levels were unaffected in the astrocyte SR knock-out (KO) and were reduced by only 30% in the glutamatergic SRKO. Less than 15% of SR was expressed in astrocytes and ~65% in glutamatergic neurons. Using the SR-/- mouse as a control for immuno-specificity, we found that neither SR nor D-serine was expressed in the astrocytes in the adult brain, but virtually all SR and D-serine was localized to neurons in neocortex. Notably, only a subset of D-serine positive neurons contained SR in the neocortex and hippocampus. Over half of the D-serine positive neurons were GABAergic interneurons with the majority of these expressing somatostatin and/or parvalbumin. These findings are consistent with D-serine serving as the co-transmitter with glutamate in cortico-limbic glutamatergic neurons and raise questions about the role of D-serine localized to GABAergic interneurons.

Policy of full disclosure: JT Coyle, MD has consulted with AbbVie and EnVivo within the last 2 years and holds a patent on the clinical use of D-serine that is owned by Massachusetts General Hospital. D. Balu, M. Puhl, M. Benneyworth and S. Tagaki report no conflicts of interest. This research was supported by grants from the N.I.H.

S-02-003 Role of glia-neuron crosstalk and the neuronal Asc-1 transporter in D-serine dynamics: Implications for schizophrenia

H. Wolosker. *The Rappaport Family Institute, Haifa, Israel*

Objective: D-Serine is a physiologic regulator of NMDA receptors (NMDARs) that mediates several NMDAR-mediated processes, ranging from normal neurotransmission to neurodegeneration. Until recently, D-serine was thought to be exclusively released by exocytosis from astrocytes, a type of glia cells that ensheath synapses. However, recent data demonstrate that neurons are the main site of D-serine production and storage in the brain. D-Serine is synthesized from L-serine by the enzyme serine racemase (SR), which is predominantly expressed in neurons. Yet, little is known about the regulation of D-serine synthesis and release from nerve cells. We now sought to investigate the role of glia-neuron crosstalk and plasma membrane transporters in regulating D-serine dynamics.

Results: We demonstrate that neurons are indeed the major D-serine producing cells in the CNS, but D-serine synthesis depends on glial metabolism as well. Glia-selective knockout of 3-phosphoglycerate dehydrogenase, a key enzyme in L-serine synthesis, markedly decreases the levels of D-serine in neurons. By exporting L-serine to neurons, astrocytes are essential for the neuronal synthesis of D-serine in a process we call "serine shuttle". Using pharmacological approaches and mice lacking the neuronal Asc-1 transporter, we demonstrate that this transporter mediates neuronal D-serine release and regulates synaptic NMDAR potentials and plasticity. Long term potentiation at hippocampal CA1 and isolated NMDAR synaptic potentials were mostly dependent on endogenous D-serine release, thought glycine also contributed to optimal NMDAR activity.

Conclusion: Our results highlight the role of glia-neuron metabolic crosstalk for optimal synthesis of D-serine. The data also suggest a novel role of Asc-1 transporter in regulating NMDARs by mediating non-vesicular release of D-serine. Drugs that enhance D-serine release via Asc-1 might be useful to counteract the NMDAR hypofunction thought to play a role in schizophrenia.

Policy of full disclosure: None.

S-02-004 DISC1-serine racemase interaction in astrocytes: At the intersection of two major pathways of schizophrenia

M. Pletnikov. *Johns Hopkins University, Baltimore, USA*

Objective: Genetic polymorphisms of Disrupted-In-Schizophrenia-1 (DISC1) and D-serine/NMDA receptor hypofunction have both been associated with schizophrenia. Recent reports have identified expression of DISC1 in astrocytes that are the main source of D-serine in the brain. Thus, we studied a pathogenic role of DISC1 in D-serine metabolism in astrocytes.

Methods: We evaluated interplay between DISC1 and serine racemase (SR), the enzyme that coverts L-serine to D-serine. The effects of mutant DISC1 on D-serine production were also assessed in primary astrocytes and brain tissue derived from transgenic mice that selectively express mutant DISC1 in astrocytes. Glutamate uptake and expression of the major astrocytic markers were measured in the same samples as well. In a series of behavioral tests, we analyzed schizophrenia-related behavioral alterations and ameliorative effects of D-serine treatments in GFAP-mutant DISC1 mice.

Results: We found that DISC1 binds to and stabilizes SR. Pathogenic disruption of this interaction by mutant DISC1 leads to accelerated ubiquitination of SR and decreased D-serine production. We also observed decreased expression of GlyT1 and increased expression of ASCT2 in mutant astrocytes and transgenic mice with astrocytic expression of mutant DISC1. On the contrary, mutant DISC1 does not change levels of ALDH1L1, connexins, GLT-1 or binding partners of DISC1 and SR, LIS1 or PICK1. Consistently with our biochemical findings, transgenic mice display greater responses to an NMDA antagonist, MK-801, in open field and pre-pulse inhibition of the acoustic startle tests and are more sensitive to the ameliorative effects of D-serine.

Conclusion: Our results indicate that DISC1 plays an important role in regulation of D-serine production in astrocytes and for the first time links DISC1 and NMDA pathophysiological mechanisms of schizophrenia.

Policy of full disclosure: None.

S-03. Developing novel drug classes for bipolar disorder

S-03-001 Development of mood stabilizers based on mitochondrial dysfunction hypothesis of bipolar disorder

T. Kato. *RIKEN Brain Science Institute, Wako, Japan*

Objective: Except for lithium, currently available drugs for bipolar disorder are antiepileptics or antipsychotics. There have been no novel drugs developed specifically for bipolar disorder. This is partly because lack of animal models to test prophylactic efficacy of mood stabilizers. Animal models based on genetics should be developed to promote drug discovery. There are two strategies for development of novel mood stabilizers; one is to mimic lithium's effect, and the other is to identify new drug targets based on genetic animal models.

Methods: Mitochondrial diseases, especially chronic progressive external ophthalmoplegia (CPEO), frequent accompany bipolar disorder and recurrent depression. Mitochondrial dysfunction is suggested in bipolar disorder. Thus, we developed a transgenic mouse carrying a dominant negative mutant of Polg (mitochondrial DNA polymerase), a causative gene for CPEO, in a forebrain specific manner. The mice showed periodic alteration of wheel running activity, which was suppressed by lithium treatment. To search for a new drug target, we searched for the common gene expression changes in the transgenic mice and postmortem brains of patients with bipolar disorder.

Results: We identified that Ppif encoding cyclophilin D was commonly altered both in the transgenic mice and postmortem brains. Cyclophilin D is a component of mitochondrial permeability transition pore, which acts as a mitochondrial calcium efflux channel. NIM811, an inhibitor of cyclophilin D, enhanced the calcium uptake in mitochondria isolated from mouse brains. NIM811 was effective for the behavioral phenotype of the transgenic mice.

Conclusion: Based on a genetic animal model of bipolar disorder, we identified a candidate target molecule of mood stabilizers. This proof of concept study would facilitate further screening of compounds acting on mitochondria as candidates of new mood stabilizers.

Policy of full disclosure: Dr. Kato received a research grant from Takeda Pharmaceutical Company Limited and honorarium for lectures, manuscripts, or consultancy from Kyowa Hakko Kirin Co., Ltd., Eli Lilly Japan K.K., Otsuka Pharmaceutical Co., Ltd., GlaxoSmithKline K.K., Taisho Toyama Pharmaceutical Co., Ltd., Dainippon Sumitomo Pharma Co., Ltd., Meiji Seika Pharma Co., Ltd., Pfizer Japan Inc., Mochida Pharmaceutical Co., Ltd., Shionogi & Co., Ltd., Janssen Pharmaceutical K.K. and Astellas Pharma Inc.

S-03-002 Roles of genetics-based animal models in drug development in bipolar disorder

T. Petryshen. *Massachusetts General Hospital, Harvard Medical School, Boston, USA*

Objective: The development of new treatments for bipolar disorder has been hindered by sparse knowledge of the neural mechanisms underlying this disorder and the use of animal models with questionable validity. Human genome-wide association studies (GWAS) have consistently identified the ankyrin 3 gene (ANK3) among the strongest genetic risk factors for bipolar disorder. We are conducting a series studies using mouse genetic models to investigate the disease mechanism of ankyrin 3 and evaluate new pharmacological agents as potential therapeutics.

Methods: Using transgenic, RNA interference, and genome editing methods, we are examining the behavioral, neurobiological, and molecular effects of modulating ankyrin 3 expression in mouse brain. Treatment of ankyrin 3 mouse models with mood stabilizers highlights effects that are relevant to the clinical disorder and implicates potential new drug targets. Therapeutic potential of novel agents, such as inhibitors of glycogen synthase kinase 3 beta (GSK3B), is evaluated in behavioral studies of ankryin 3 mouse models.

Results: Ankryin 3 reduction in mouse brain robustly increases impulsivity, exploration, and motivation for reward, heightens stress response, and alters synaptic function. Transcriptional and proteomic changes in Ank3+/- mouse brain implicate specific pathways containing potential new treatment targets. The behavioral and synaptic changes are reversed by chronic lithium treatment, supporting the clinical relevance of ankryin 3 mouse models for evaluating the therapeutic potential of novel agents.

Conclusion: Behavioral, neurobiological, and molecular alterations in mice with reduced ankyrin 3 expression that are reversed by mood stabilizers suggest potential new drug targets for bipolar disorder and support the use of mouse genetic models for examining novel agents. These studies support the investigation of genetic risk factors using mouse models to elucidate the neural mechanisms underlying bipolar disorder as a critical step in the development of new treatments.

Policy of full disclosure: Research supported by the NIMH, Stanley Medical Research Institute, and Avis and Clifford Barrus Medical Foundation.

S-03-003 Targeting synaptic and neural plasticity to develop novel, improved, therapeutics for severe mood disorders

H. Manji. *Johnson & Johnson, Titusville, USA*

Objective: In recent years, significant advances have been made in our understanding of serious neuropsychiatric illnesses, including severe mood disorders. Typically, these common disorders start early in life, making them chronic diseases of the young. Here, we review the underlying mechanisms of serious neuropsychiatric disorders and discuss the clear need to develop improved treatments for these devastating illnesses.

Methods: Public and private resources devoted to research in this area are diminishing. In the face of these challenges, a host of cutting-edge approaches-from genomics to data mining, proteomics to biomarkers, pathway modeling to protein engineering, neuroimaging to optogenetics-is revolutionizing how we study these illnesses and develop novel treatments for them. Mood disorders are multifactorial, resulting from both genetic vulnerability and environmental stressors. They are characterized by dysfunction in diverse biological systems, including the intricate network of limbic, striatal, and fronto-cortical circuits that mediate mood state, cognition, self-awareness, and insight.

Results: Recent progress has been made in understanding the underlying molecular and cellular basis of mood disorders. In particular, there is a growing appreciation that impaired signaling pathways may be involved in these disorders, and that targeting neural plasticity and resilience pathways may lead to novel therapeutics. Furthermore, recent evidence suggests that mood stabilizers significantly affect the signaling pathways that regulate neural and synaptic plasticity. Abnormalities in cellular plasticity cascades likely also underlie impaired structural plasticity. Many of these pathways are critical to both synaptic plasticity and long-term cellular resilience. In turn, these changes in structural plasticity appear to regulate resilience as well as long-term course of illness. Based on these findings, a number of targeted strategies are being investigated that hold promise for developing improved therapeutics to treat severe mood disorders.

Conclusion: Ongoing research may help to reconceptualize diagnostic classifications and, ultimately, help design treatment approaches tailored to illness stage and patient subpopulations.

Policy of full disclosure: Dr. Manji is an employee of Janssen Pharmaceuticals/Johnson & Johnson.

S-03-004 Ebselen as a novel IMPase inhibitor as a lithium mimetic

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Objective: To identify a drug-like inhibitor of the enzyme inositol monophosphatase for treating bipolar disorder with the efficacy of lithium with less toxicity and fewer side effects.

Methods: Known experimental and approved drugs (National Institutes of Health Clinical Collection) were screened for their ability to inhibit bacterially expressed human and mouse forms of the enzyme inositol monophosphatase type 1, the possible therapeutic target of lithium underlying the inositol depletion hypothesis. Screening hits were validated by determining the mechanism of inhibition of the enzyme, intact cell assays monitoring the metabolism of tritiated inositol, and brains from mice injected intraperitoneally with ebselen in ex vivo assays of enzyme activity and inositol levels. A validated inhibitor was then tested in mouse behavioural tests of mania (exploratory behaviour and amphetamine-induced mania) and depression (forced-swim test).

Results: Ebselen inhibits inositol monophosphatase, both in vitro with isolated enzyme and ex vivo in homogenized brains of mice after intraperitoneal injection. Inhibition is dependent on a covalent selinium-sulfur bond between ebselen and a cysteine near the enzyme's active site. Ebselen increased inositol 1-phosphate in cell cultures stimulated with acetylcholine and decreased inositol in the brains of mice after intraperitoneal injection. Ebselen was lithium-like in several mouse behavioural tests as it increased exploratory behaviour and decreased hyperlocomotion induced by amphetamine, which were reversed by intracerebraventricular injection of inositol.

Conclusion: Ebselen may be a lithium mimetic with less toxicity and fewer side effects compared to lithium itself that is blood-brain barrier permeant and acts through inhibition of inositol monophosphatase, supporting Berridge's inositol depletion hypothesis. As ebselen has a known safety profile (it reached Phase 3 trials for stroke but was not marketed), it can be rapidly progressed into man. Indeed, we are currently conducting a proof-of-concept study for lithium-like effects in healthy volunteers.

Policy of full disclosure: Certain authors hold a patent on the use of ebselen for treating bipolar disorder.

S-04. Paediatric disorders characterised by aggression and/or social impairment: From preclinical research to clinical subtyping

S-04-001 Gene-by-environment interaction and epigenetic mechanisms in aggression: Lessons from animal models

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Objective: Although converging evidence links exposure to stressful life events with increased risk for disorders of emotion regulation, including aggression and antisocial behavior, there is extraordinary interindividual variability in vulnerability to adversity. The environmentally moderated penetrance of genetic variation is thought to play a major role in determining who will either develop dysfunctional and maladaptive behavior or remain resilient.

Methods: Research on genetic factors in emotion regulation and related disorders has, nevertheless, been complicated by a discrepancy between high heritability estimates and a scarcity of replicable gene-trait/disorder associations. One explanation for this incongruity is that at least some specific gene effects are conditional on environmental cues, i.e. gene-by-environment interaction (GxE) is present. For example, a number of studies reported an association of variation in human serotonin (5-HT) system-regulating genes with emotional and cognitive traits as well as increased risk for disorders of emotion regulation in interaction with psychosocial adversity.

Results: The results from investigations in non-human primate and mouse support the occurrence of GxE by showing that variation of 5-HT gene function is associated with a vulnerability to adversity across the lifespan leading to unfavourable outcomes resembling various emotional disorders. The neural and molecular mechanisms by which environmental adversity in early life increases disease risk in adulthood are not known but may include epigenetic programming of gene expression during development. Epigenetic mechanisms, such as DNA methylation, histone modification and chromatin remodeling, are dynamic and reversible. Animal models amenable to genetic manipulation are useful in the identification of molecular mechanisms underlying epigenetic programming by adverse environments and individual differences in resilience to stress.

Conclusion: Therefore, deeper insight into the role of epigenetic regulation in the process of neurodevelopmental programmes is likely to result in prevention or early diagnosis and will contribute to the design of innovative treatments targeting the epigenetic machinery that foster resilience.

Policy of full disclosure: None.

S-04-002 Screening for novel aggression therapeutics in zebrafish

W. Norton. *University of Leicester, United Kingdom*

Aggression is common side effect of psychiatric disorders including attention-deficit/hyperactivity disorder (ADHD) and conduct disorder. However, our knowledge about the aetiology of aggression is limited and current treatment strategies are insufficient. The zebrafish is an ideal model organism to address this issue. Zebrafish display aggression from around one month of age and agonistic behaviour can be reliably measured by recording the interaction of a fish with its own mirror image. Furthermore, aggression is controlled by similar genes and neurotransmitters in zebrafish and other vertebrates allowing the translation of data to other species. Finally, drugs can be administered by immersion (dissolving the drug in the tank water) thus speeding up their application. Work in our laboratory has already established protocols to measure aggression and used them to characterise fish lacking the function of a single gene in the brain. As part of an EU-wide project called Aggressotype we are now undertaking a screen to identify novel drugs that can modulate aggression levels. We will start by investigating the ability of existing aggression therapeutics (methylphenidate, risperidone, valproate and lithium) to reduce aggression levels in fish. We will then choose novel drugs with similar chemical properties and examine their behavioural function. Our screen will investigate a minimum of one hundred novel drugs in the first year, and will test further compounds time permitting. Promising drugs will be validated in aggressive mouse strains in order to demonstrate a conserved behavioural function across species. This approach represents an excellent opportunity to identify novel aggression therapeutics, with the global aim of improving treatments options for patients suffering from psychiatric disorders.

Policy of full disclosure: No financial conflicts of interest.

S-04-003 Genetics of adult ADHD and antisocial personality disorder

A. Reif. *University of Wuerzburg, Wuerzburg, Germany*

Objective: Attention deficit/hyperactivity disorder (ADHD) is amongst the most common childhood neuropsychiatric disorders, often is co-morbid with conduct disorder (CD) and syndromal aggression. Regarding its etiology, ADHD is highly genetic and also CD has genetic components. Despite being the candidate phenotype in several GWAS and CNV studies, still only few risk genes have emerged for both ADHD, CD, as well as symptomatic aggression. In 30–60% of cases, childhood ADHD persist into adult ADHD and also CD can develop into antisocial personality disorder (APD). Especially childhood ADHD with co-morbid CD can take the trajectory towards adult ADHD with co-morbid APD. Only few studies however have addressed the genetic basis of adult ADHD and APD.

Methods: Review of the literature, case-control studies, genome-wide association studies.

Results: Still, no targeted GWAS have been published for adult ADHD apart from a small pooled GWAS, although these are expected for spring 2014. Nevertheless, some candidate gene studies were published on reasonably large samples and provided evidence for at least a few risk genes. These mainly overlap with childhood ADHD risk genes (such as DAT), however, there are also some risk genes that seem to be exclusive for adult ADHD, e.g. NOS1. The latter genes therefore do not seem to increase the risk for ADHD as such but rather its persistence into adulthood. Studies on APD ofter suffer from small sample sizes, while studies on symptomatic aggression or criminality have the drawback of phenotype heterogeneity. Amongst the best replicated candidate genes in these phenotypes is MAOA, acting in a gene x environment manner.

Conclusion: Despite being strongly genetic, present data still falls short to explain the molecular architecture of adult ADHD and ASD. Larger and well-controlled studies therefore are urgently needed that take into account the developmental trajectory of these phenotypes, previous life events, and psychophysiological endophenotypes.

Policy of full disclosure: None.

S-04-004 Overlap and differences between ADHD and conduct disorder: Imaging genetics approaches

B. Franke. *Radboud University Medical Centre, Department of Human Genetics & Psychiatry, Nijmegen, Netherlands*

Objective: ADHD and conduct disorder (CD) are highly common neurodevelopmental disorders and often co-occur. Both disorders have a strong societal impact – through health care costs, but, especially in the case of conduct disorder, also as a direct result of social maladjustment and crime. Pathological aggression is regularly observed in both disorders. This trait can be subdivided into two main subtypes, reactive impulsive and low-emotional instrumental aggression, which facilitates research into the underlying mechanisms.

Methods: As part of the EU project 'Aggressotype' we are investigating the neural correlates of aggression in ADHD and CD. People with ADHD often show impulsive aggression while those with CD more often display instrumental aggression. Since both disorders show a strong influence of genetic factors, our main question is how aggression risk genes influence the brain in its structure, connectivity and function using imaging genetics approaches.

Results: ADHD and CD are characterized by altered brain structure, connectivity and function in cortical and subcortical structures. Implicated in aggression traits in these disorders are mainly structures in the limbic system (amygdala, hippocampus, ventral striatum) and subregions of prefrontal cortex. Especially the amygdala and striatum and their connections with prefrontal cortex are the subject of our research investigating overlap and differences between ADHD and CD and between impulsive and instrumental aggression. We show that genetic variation in NOS1, a gene for ADHD and other impulse control disorders,

indeed alters the activity of the ventral striatum during reward anticipation, while variants in the archetypical ADHD gene DAT1 do not show this effect. Results of our consortium also implicate MAOA in altered connectivity between amygdala and prefrontal cortex.

Conclusion: Genes with a role in ADHD indeed influence neural substrates of aggression. The results for NOS1 and MAOA both fit with a role of these genes in impulsive aggression.

Policy of full disclosure: None.

S-05. Alcohol dependence: Neuroimaging and pharmacology

S-05-001 Mapping of functional brain activity in alcohol drinking rats using manganese-enhanced magnetic resonance imaging

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Objective: Development of compulsive drug seeking is hypothesized to involve neural adaptations in brain circuits mediating motivation and reward. Although these circuits have been identified by previous work, alterations in global functional brain activity in these circuits by long-term use of abused drugs remain to be described. Therefore, in these experiments, we used manganese-enhanced magnetic resonance imaging (MEMRI) for measuring functional activity changes induced by voluntary alcohol drinking in alcohol-preferring AA (Alko Alcohol) rats, one of the best characterized animal models of high alcohol consumption.

Methods: The usefulness of MEMRI for functional brain imaging is based on the ability of manganese ions to enter excitable cells via voltage-gated calcium channels and to accumulate into neurons in proportion to neural activity. The accumulation of manganese in active brain regions can be seen as enhanced signal intensity in T1-weighted scans. Because high acute systemic manganese doses are toxic, we used 7-day subcutaneous osmotic minipumps for manganese chloride administration. The pumps were implanted following 6 weeks of voluntary alcohol drinking, and the rats were then scanned at the end of the 7-day manganese chloride infusion using a 4.7 T Bruker scanner.

Results: Compared to water-drinking controls, voluntary alcohol drinking produced a widespread region-specific increase in MEMRI signal both in cortical and subcortical brain regions. Increased signal was observed also at the end of the alcohol-free period in animals with a previous history of long-term alcohol drinking. Many specific brain regions showing altered activity were largely overlapping with the reward circuitry established previously by other methods, including regions of the mesolimbic and nigrostriatal dopamine pathways.

Conclusion: Collectively, our data suggest that MEMRI is a sensitive method for detecting alterations in neuronal activity caused by long-term voluntary alcohol consumption. Future experiments are designed to examine the effect of potential medications on alcohol-induced brain activation.

Policy of full disclosure: None.

S-05-002 Increased brain activity during protracted abstinence as a predictor for relapse behaviour in alcohol dependent rats

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Objective: Bringing novel medications from preclinical to clinical development is challenging, especially when efficacy predictors are based on subjective assessments. Neuroimaging methods such as magnet resonance imaging (MRI) may allow for objective human-animal comparisons by identifying brain imaging signatures that are comparable between patients with alcohol use disorders (AUD) and animal models. Such signatures may represent "AUD-networks" that should be positively modulated (i.e. towards normal states) by effective pharmacological treatments.

Methods: Here, we used resting state functional MRI (rsfMRI) and manganese enhanced MRI (MEMRI) for global mapping of brain activity in an established rat model of abstinence from alcohol dependence.

Results: The combined analysis of rsfMRI and MEMRI data identified abstinence related changes in cortical and subcortical brain regions known to be involved in the addiction circuitry, but also regions currently not in the focus of alcohol research. These results from neuroimaging corroborate recent molecular findings from this model.

Conclusion: We expect that by integrating data from animal neuroimaging with respective human findings, it will be possible to increase the translational value of all MRI modalities and the power of our strategy to identify relevant neuronal networks in AUD and potential therapeutic targets.

Policy of full disclosure: None.

S-05-003 Alcohol use disorder: Structural and functional brain changes in abstinence and effects of naltrexone

A. J. Greenshaw. *Department of Psychiatry, University of Alberta, Edmonton, Canada*

We are examining brain functional connectivity as part of the ERA-NET NEURON and CIHR project TRANSALC. Using a 4.7 T MRI scanner to measure resting state fMRI in patients with alcohol use disorder, patients (5–10 days abstinent) and healthy controls were scanned and re-scanned after three weeks. Patients underwent treatment during the three week period with care as usual (participation in a residential addiction treatment program involving groups and behaviour therapy) or naltrexone plus care as usual. Seed region correlation analysis was used to investigate functional brain networks. Using first scan data, with an anterior cingulate cortex (ACC) seed there were larger correlations (i.e. greater involvement in networks including ACC as a major component) in perigenual ACC for controls compared to patients. With the seed in left anterior insula, first session, there were greater correlations in subgenual ACC and ventral medial prefrontal cortex for controls vs. patients and greater correlations for patients vs. controls in right ventrolateral prefrontal cortex. In the first scan, with the seed in right anterior insula, there were greater correlations in subgenual ACC and ventral medial prefrontal cortex for controls vs. patients and greater correlations for patients vs. controls in right anterior insula. With data from the second scan, these differences were not present. Our interpretation is that newly-abstinent patients had lesser resting state activity compared to controls in the conflict and performance monitoring network involving ACC. Newly-abstinent patients had larger resting state activity in reward and value judgement networks involving right anterior insula and right ventrolateral prefrontal cortex. Patients' functional connectivity patterns normalized during the three week treatment period becoming more similar to those of controls. The results from our studies will be discussed in the context of current and emerging concepts of maladaptive and adaptive brain changes in relation to alcohol and drug abuse.

Policy of full disclosure: None.

S-05-004 NK1 and dopamine D3 antagonists as new approaches to alcohol dependence

D. Nutt. *Imperial College, London, United Kingdom*

The massive prevalence of alcohol dependence and the relatively limited efficacy of interventions means that there is a great unmet need. One area particularly poorly served is that of relapse prevention treatments. To begin to remedy this area we have developed an MRC funded collaborative experimental medicine research 'platform' between Imperial College, Cambridge and Manchester (ICCAM) (with GSK and Imanova as partners). This uses psychological and MRI measures to assess the brain processes underpinning relapse – reward, impulsivity and emotional salience – and their associated brain systems in alcohol, cocaine and opioid addiction. Moreover we studied the modulation of these effects by an opioid receptor antagonist (naltrexone), a dopamine D3 antagonist (GSK598809) and an NK1 antagonist (vofipitant or apipretant) with a view to detecting potential effects that might be predictive of relapse prevention. My talk will present the first data with from these studies in the group of abstinent alcoholics and the implications for using these drugs in relapse prevention.

Policy of full disclosure: I have no interests to declare other than have been a consultant for GSK.

S-06. Emerging neuromechanisms for the treatment of depression: Insights from animal and human studies

S-06-001 Role of mTOR signaling and synaptogenesis in the response to rapid acting antidepressants

R. Duman. *Yale University, School of Medicine, New Haven, USA*

Objective: Currently available medications for depression have significant limitations, including a slow onset of action, low rates of response, and

treatment resistance, emphasizing a major unmet need for more efficacious and faster-acting antidepressants. Recent studies have reported that ketamine produces rapid (~2 hr) antidepressant effects in patients who have failed to respond to conventional antidepressants. The discovery that NMDA receptor blockade produces such profound antidepressant effects represents one of the most important discoveries in the field of depression in over 60 years. Preclinical studies have begun to unravel the cellular mechanisms underlying the rapid actions of ketamine, as well as other rapid acting agents.

Methods: The effects of ketamine and other rapid acting agents on mTORC1 signaling, the number and function of spine synapse in PFC neurons, and behavior in models of depression and antidepressant response were determined.

Results: These studies demonstrate that ketamine rapidly increases the number and function of synapses in the medial prefrontal cortex (PFC) via a burst of glutamate and activation of mTORC1 signaling. Studies of such additional putative rapid agents will be discussed, including selective NR2B and mGlu2/3 receptor antagonists that also increase glutamate transmission and stimulate mTORC1 signaling. In addition, scopolamine, a muscarinic receptor antagonist scopolamine that produces rapid antidepressant effects in humans, also increases glutamate, mTORC1 and synaptogenesis in PFC. Finally, drugs that enhance synapse formation, such as GSK-3b inhibitors, and could thereby enhance or sustain the effects of ketamine will be discussed.

Conclusion: The discovery that different rapid acting agents, but not typical, antidepressants increase glutamate, mTORC1 and synaptogenesis represents a fundamental shift in our understanding of the treatment and pathophysiology of depression, and is informing and guiding current drug discovery and development.

Policy of full disclosure: Dr. Duman is a consultant and/or receives research funds from Taisho, Sunovion, Lundbeck, Forest, Johnson & Johnson, Naurex, and Lilly.

S-06-002 Resilence and susceptibility to stress: Predictors of response to antidepressants and ketamine

A. Markou[1], A. Der-Avakian[1]. [1]*University of California San Diego, La Jolla, USA*

Objective: Anhedonia, or diminished interest or pleasure in rewarding activities, is a core symptom of depression and reflects deficits in brain reward circuitries. Social stress induces anhedonia in a subset of individuals and increases the risk for depression, although the factors predicting this susceptibility are poorly understood. The objectives of the present studies were to characterize resilience and susceptibility to anhedonia in response to chronic severe stress exposure, and investigate the effects of antidepressants on the anhedonic response in susceptible rats.

Methods: Rats trained in the intracranial self-stimulation (ICSS) procedure were exposed to chronic social defeat and subordination. We also evaluated the effects of chronic treatment with fluoxetine or desipramine, or acute treatment with ketamine in susceptible rats.

Results: Exposure to chronic social defeat and subordination induced profound and enduring deficits in brain reward function, reflecting a persistent anhedonic response (i.e, ICSS threshold elevations), in a subset of 'susceptible' rats, while the remaining 'resilient' rats showed no long-term deficits in brain reward function. Social defeat, regardless of susceptibility or resilience, persistently decreased and increased brain-derived neurotrophic factor (BDNF) and phosphorylated AKT protein levels, respectively, in the ventral tegmental area (VTA), whereas only susceptibility was associated with increased phosphorylated mammalian target of rapamycin (mTOR) in the VTA. Chronic administration of fluoxetine or desipramine reversed brain reward deficits in susceptible rats with lower, but not higher, stress-induced threshold elevations. Acute ketamine administration reversed anhedonia only in a very small percentage of susceptible rats exhibiting mild anhedonia.

Conclusion: The differential persistent anhedonic response to psychosocial stress may be mediated by VTA signaling molecules independent of BDNF, and indicate that greater stress-induced anhedonia is associated with resistance to antidepressant treatment. Consideration of these behavioral and neurobiological factors associated with resistance to stress and antidepressant action may promote the discovery of novel targets to treat stress-related mood disorders.

Policy of full disclosure: Research contract support from Bristol-Myers-Squibb, Forest Laboratories and Astra-Zeneca, and consulting fee from AbbVie, Germany during the last 3 year.

S-06-003 Neuropeptide receptors as targets for drug discovery for the treatment of depression

S. Chaki. *Taisho Pharmaceutical Co. Ltd., Discovery Pharmacology, Saitama, Japan*

Objective: Stress has been well recognized as the primary cause of depression and anxiety disorders, and neuropeptides have been suggested to play a pivotal role in stress responses. The expression and secretion of neuropeptides changes upon stress exposure so as to regulate hypothalamus-pituitary-adrenal (HPA) axis activity and monoaminergic neuronal activity. Therefore, the dysregulation of neuropeptide systems may cause stress-related disorders, and neuropeptide receptors provide an opportunity to develop novel treatments for depression and anxiety disorders, in spite of recent failures of drug discovery targeting neuropeptide receptors.

Methods: We investigated antidepressant/anxiolytic potential of antagonists for neuropeptide receptors, which are involved in the regulation of HPA axis activity (vasopressin V1b receptor) and reward activity (melanin-concentrating hormone MCH1 receptor and melanocortin MC4 receptor) in various animal models of depression and anxiety.

Results: V1b receptor antagonists having different scaffolds exhibited antidepressant effects in animal models of depression such as a forced swimming test and an olfactory bulbectomy model. In addition, a V1b receptor antagonist showed an antidepressant effect in a repeated corticosterone treatment model, which severely impaired HPA axis, consistent with a mechanism of V1b receptor antagonism. At doses exerting antidepressant effects, a V1b receptor antagonist attenuated plasma ACTH elevation induced by stimulation of the anterior pituitary V1b receptor, supporting that V1b receptor antagonists may exert the effects through blockade of HPA axis hyperactivity. Moreover, both MCH1 receptor antagonists and MC4 receptor antagonists exerted antidepressant effects in animal models of depression. Of note, these neuropeptide receptor antagonists also showed anxiolytic effects in a variety of animal models with more prominent effects in models which contains highly stressful situation.

Conclusion: Therefore, neuropeptide receptor antagonists may have potential for the treatment of depression and anxiety. Issues of drug discovery approaches aiming at neuropeptide receptors will also be discussed.

Policy of full disclosure: None.

S-06-004 Rewiring faulty circuits: The promise of deep brain stimulation for severe major depression

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Policy of full disclosure: None.

S-07. Allosteric modulators of metabotropic glutamate receptors (mGlu) as novel tools for the treatment of CNS disorders

S-07-001 Therapeutic implications of diverse modes of efficacy and stimulus bias of allosteric modulators of mGlu receptors

P. J. Conn. *Vanderbilt University Medical Center, Drug Discovery, Nashville, USA*

Objective: Allosteric modulators of GPCRs provide a novel approach to modulation of specific GPCR subtypes. Negative allosteric modulators (NAMs) inhibit whereas positive allosteric modulators (PAMs) potentiate responses to endogenous agonists. Allosteric modulators offer high selectivity for targeted receptors and provide an exciting new approach to development of novel therapeutic agents.

Methods: We use a multidisciplinary approach to optimize highly selective allosteric modulators for multiple subtypes of metabotropic glutamate (mGlu) receptors and muscarinic acetylcholine receptors (mAChRs) for treatment of CNS disorders. We evaluate these compounds using molecular, cellular, and in vivo approaches.

Results: The diversity of allosteric modulators now available is allowing us to develop fundamental new insights into the multiple mechanisms by which these compounds regulate GPCR function and are providing new insights into the functional impact of different modes of efficacy of allosteric modulators. Closely related allosteric modulators can display striking differences in their effects on GPCR signaling and subtle chemical changes to convert a PAM to a NAM. In addition, some scaffolds display allosteric agonist activity whereas others are pure PAMs. In addition, we have observed multiple examples in which allosteric modulators confer

"stimulus bias" and selectively regulate agonist effects on some but not all signaling pathways coupled to a given GPCR. Finally, we have identified allosteric modulators that differentially regulate activity of GPCR homomers and heterodimers. Closely related allosteric modulators can have fundamentally different effects in vivo, depending on subtle differences in their effects on GPCR signaling.

Conclusion: Allosteric modulators of GPCRs provide a promising new approach to targeting this important class of neurotransmitter receptors. Subtle differences in modes of efficacy of different allosteric modulators can have a major impact on efficacy and adverse effect liability of closely related compounds.

Policy of full disclosure: Dr. Conn receives research funding from Astrazeneca and Bristol Myers Squibb and is an inventor on multiple patents protecting allosteric modulators of mGlu receptors and muscarinic acetylcholine receptors.

S-07-002 Design, synthesis and evaluation of Novel Group II Metabotropic Glutamate Receptor Allosteric Modulators in rodent models of CNS disorders

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The Group II metabotropic glutamate (mGlu) receptors include the mGlu2 and mGlu3 receptor subtypes and couple via Gi/o proteins to negatively regulate the activity of adenylyl cyclase. Localization studies suggest that mGlu2 receptors act as presynaptic autoreceptors to modulate release of glutamate, whereas mGlu3 receptors exhibit a broad distribution in the brain and have been shown to be present on astrocytes [1]. Recent findings suggest that neuroadaptations in glutamatergic transmission produced by repeated exposure to drugs of abuse such as cocaine or nicotine are likely to contribute to the maintenance of addictive behaviors including drug use, craving, and relapse to drug taking in humans. Repeated cocaine exposure alters the function of mGlu2 and mGlu3 receptors while nicotine increases glutamatergic neurotransmission by activating excitatory nicotinic acetylcholine (nACh) receptors located on glutamatergic terminals. Brain regions implicated in different aspects of drug abuse and drug dependence display high levels of mGlu2 and mGlu3 receptor binding, suggesting a role for mGlu2/3 receptors in the development of drug dependence and as potential targets for therapeutic agents. We recently reported data on selective mGlu2 receptor positive allosteric modulators (PAMs) in models of drug dependence [2–4]. We now report the design and synthesis of novel, systemically active PAMS that selectively modulate both mGlu2 and mGlu3 receptors. Structure-activity relationship (SAR) data on this series will be described in addition to results from behavioral models of self-administration in rats.

Policy of full disclosure: None.

S-07-003 The antipsychotic activity of allosteric vs./orthosteric agonists of mGlu4 receptors

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Objective: Clinical and basic studies suggest that a dysregulation of the glutamatergic system plays an important role in some of the pathologic changes associated with schizophrenia. Modulation of the central glutamatergic system via metabotropic glutamate (mGlu) receptors might lead to novel pharmacological treatments. The objective of this work was to explore, compare and contrast the pharmacological effects of central activation of the mGlu4 receptor through orthosteric and allosteric ligands.

Methods: Two groups of compounds that selectively activate the mGlu4 receptor, the orthosteric agonists LSP1-2111 and LSP4-2022, as well as the positive allosteric modulators (PAM) Lu AF21934 and Lu AF32615, were characterized in terms of their in vivo properties in preclinical models thought to represent different aspects of psychosis, including positive, negative and cognitive disturbances. The role of 5-HT1A receptors in the observed phenotype was also investigated with the use of a selective agonist or an antagonist at this receptor.

Results: Compounds activating mGlu4 receptors through an orthosteric or allosteric mechanism were efficacious in a number of preclinical rodent models reflecting behaviors linked to positive, negative and cognitive schizophrenia-like symptoms. These include dose-dependent inhibition of both MK-801 and amphetamine-induced hyperactivity; antagonism of 2,5-dimethoxy-4-iodoamphetamine (DOI)-induced head twitches in mice; MK-801-induced disruption in the social interaction test and efficacy in the delayed spatial alternation test. The action of the ligands (as shown for LSP1-2111 and Lu AF21934) was 5-HT1A receptor dependent.

Conclusion: The efficacy shown by compounds activating the mGlu4 receptor as assessed by mechanistic and behavioral models provides evidence for a potential role played by this receptor in the pathophysiology of schizophrenia. Regulation of synaptic glutamate concentrations using compounds which activate the functional response of the mGlu4 receptor, and the concomitant regulation of glutamate release by serotonine, may be a promising mechanism for the discovery of novel antipsychotic drugs.

Policy of full disclosure: None.

S-07-004 Metabotropic glutamate and GABA receptors in fragile X syndrome

D. R. Hampson. *University Toronto, Leslie Dan Faculty of Pharmacy, Toronto, ON, Canada*

Fragile X syndrome is a genetic disorder caused by a CGG repeat expansion in the fragile X Fmr1 gene. This syndrome is the most common single gene cause of mental retardation. FXS is a "syndromic" form of autism spectrum disorders (ASDs); about 35% of persons with FXS meet the full criteria for autism while, over 90% have at least some autistic symptoms. Because non-syndromic ASDs have many causes, most of which are unknown, the study of idiopathic autism has been hindered due to a lack of good animal models. In contrast, there are several excellent animal models of FXS. Animal models of FXS, particularly the Fmr1 KO mouse, are widely studied not only to provide insight into FXS, but also as a window into the non-syndromic forms of ASDs. In FXS there is a perturbation of the delicate balance between neuronal excitation and inhibition. Drugs acting at metabotropic glutamate receptors (mGluRs) and GABAB receptors are currently in clinical trials for both FXS and ASD. The results of clinical trials assessing the effects of negative allosteric modulators of mGluR5 receptors, and agonists of the GABAB receptor, will be discussed along with the preclinical findings that led to the initiation of the trials.

Policy of full disclosure: This work was supported by the Fragile X Research Foundation of Canada, Lundbeck Research Inc., and the Canadian Institutes of Health Research. The author has no financial conflict of interest.

S-08. Obsessive-compulsive and related disorders: A translational approach

S-08-001 Coherence between orbitofrontal cortex and nucleus accumbens reflects OCD-like persistent avoidance

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Objective: OCD is characterized by compulsive actions that may result from a failure to use learned information to extinquish events that are no longer salient, leading to inappropriate persistent avoidance. We propose that this is due to deficits in the ability to devalue an avoidance-triggering stimulus; consistent with overactivity in the orbitofrontal cortex (OFC). This circuitry was examined by correlating local field potential (LFP) coherence with OCD-like behavior.

Methods: Food-deprived rats trained to lever press for food were repeatedly exposed to a tone (CS) paired with a footshock; shock could be avoided by stepping onto a nearby Plexiglas platform. Groups were trained to low (60%), normal (90%) or overtrained (90% plus 7 additional sessions) avoidance criteria. A Plexiglas barrier was subsequently inserted into the chamber to prevent access to the platform and the CS was #devalued# with repeated tone alone (without shock) presentation. This approach is believed to model the #extinction with response prevention (Ext-RP) behavioral therapy used in OCD. After three Ext-RP sessions the barrier was removed and animals were tested to see if the #devalued# CS could still elicit avoidance.

Results: Overtrained, but not low or normal criteria rats, failed to devalue the CS during Ext-RP training and continued to avoid excessively during its presentation across test sessions. This finding suggests that OCD-like behavior results from a failure to devalue avoidance-triggering stimuli. LFP analyses suggest that such habitual avoidance behavior correlates with an increase in OFC-NAc and decrease in OFC-BLA and ilPFC-BLA coherence.

Conclusion: Therefore, deficits leading to excessive avoidance may be mediated by a failure to normalize OFC-NAc network activity following

devaluation of an evoking stimulus. This would result in an impairment of the prefrontal cortex to down-modulate amygdala-driven anxiety states in conditions in which the stimulus is no longer behaviorally salient.

Policy of full disclosure: Johnson & Johnson, Lundbeck, Pfizer, GSK, Puretech Ventures, Merck, Takeda, Dainippon Sumitomo, Otsuka, Lilly, Roche, Asubio, Abbott.

S-08-002 The streptococcal model of obsessive-compulsive and related disorders

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Objective: Group A ß-hemolytic streptococcal (GAS) infection is associated with a spectrum of neuropsychiatric disorders, including Sydenham's chorea, pediatric autoimmune neuropsychiatric disorders associated with streptococcus (PANDAS), obsessive-compulsive disorder, and Tourette's syndrome. The leading hypothesis regarding this association proposes that a GAS infection induces the production of autoantibodies, which cross-react with neuronal determinants in the brain through the process of molecular mimicry.

Methods: We have established a novel rat model of GAS-related neuropsychiatric disorders, which mimics behavioral, pharmacological, immunological and neural characteristics of GAS-related neuropsychiatric disorders (Brimberg et al., 2012, Neuropsychopharmacology, 37, 2076–2087).

Results: Using this model we found that exposure of male Lewis rats to GAS antigen leads to induction of antibodies, which react with D1 and D2 dopamine receptors and 5-HT2a and 5-HT2c serotonin receptors, in vitro, and deposit in the striatum, prefrontal cortex and thalamus in vivo. Calcium calmodulin dependent protein kinase II was activated by serum IgG in a human neuronal cell line and dopamine and glutamate levels were altered in the medial frontal cortex and basal ganglia of GAS-exposed rats, supporting functional effects of the autoantibodies. Behaviorally, GAS-exposed rats show increased compulsive-like behavior and motor disturbances, which are attenuated by a selective serotonin reuptake inhibitor and a D2 blocker, respectively, further supporting the link between GAS-exposure, dysfunction of the serotonergic and dopaminergic systems and behavioral abnormalities. Finally, infusion of IgG from GAS-exposed rats to naïve rats led to behavioral and motor alterations partially mimicking those seen in GAS-exposed rats, and to IgG deposits in the striatum of infused rats, which colocalized with dopamine receptors and with the serotonin transporter.

Conclusion: Our results demonstrate the potential pathogenic role of anti-neuronal autoantibodies produced following exposure to GAS in the induction of behavioral and motor alterations, and support a causal role for autoantibodies in GAS-related neuropsychiatric disorders.

Policy of full disclosure: None.

S-08-003 Current perspectives on compulsivity

T. Robbins. *University of Cambridge, Department of Psychology, Cambridge, United Kingdom*

Compulsivity is a burgeoning dimensional construct in neuropsychiatry that can be defined as the maladaptive tendency to repeat behaviour without apparent purpose, often with adverse consequences. It is relevant not only to disorders which explicitly describe compulsive behaviour as a key symptom, such as the prototypical obsessive-compulsive disorder (OCD), and also drug addiction and gambling, but also eating disorders, and elements of autism and schizophrenia. Like impulsivity, compulsivity may have several forms and could be understood for example at the levels of sterotyped motor behaviour at one extreme (e.g. tics) and perseverative and inflexible, rigid thinking at the other. Compulsive behaviours can theoretically be understood as resulting from excessively engaged attentional processing, from aberrant stimulus-response habits, excessively retarded extinction, and perseverative responding in reversal learning tasks or from combinations of these factors. Consequently, such experimental paradigms may be implemented to delineate underpinning psychological processes that contribute to compulsive behaviour, and their precise neural substrates in experimental animals as well as in humans. This talk will illustrate several examples of this translational strategy with respect to OCD and addiction. For example, the balance of competing neural systems mediating action-outcome learning and stimulus-response habit learning appears to be shifted towards the latter in obsessive-compulsive disorder, based on performance of a human associative learning paradigm inspired by neuropsychological experiments on associative learning in rodents. A further approach to establishing a neurobehavioural understanding of compulsivity using such methods as resting state functional connectivity, is to compare directly neural networks affected in such disorders in order to establish whether their apparently different compulsive behaviours are mediated by shared neuroanatomical circuitry, thus further validating a common construct of compulsivity.

Policy of full disclosure: None.

S-08-004 Clinical advances in obsessive-compulsive and related disorders

D. Stein. *University of Cape Town, Cape Town, South Africa*

Objective: To review recent clinical research on obsessive-compulsive and related disorders (OCRDs), and to assess advantages and disadvantages of including this new category in the diagnostic classification system.

Methods: As part of the DSM-5 and ICD-11 process, reviews of obsessive-compulsive and related disorders, including relevant psychobiology, were undertaken. Key findings from these reviews, as well as from DSM-5 field surveys, are summarized here.

Results: There is growing evidence that the psychobiology of obsessive-compulsive disorder (OCD) differs from that of anxiety disorders. There are important overlaps in symptom evaluation and treatment approach across OCDRs characterized by preoccupations and repetitive behaviors (e.g. OCD, body dysmorphic disorder, hoarding disorder), and across OCDRs characterized by body-focused repetitive behaviors (e.g. trichotillomania, excoriation disorder).

Conclusion: The new category of obsessive-compulsive and related disorders may encourage appropriate recognition and treatment of these under-diagnosed disorders. However, it is important for clinicians to be aware of key differences across these conditions. Additional work to consolidate a translational neuroscience approach to these conditions is needed.

Policy of full disclosure: In the past 3 years, Dr. Stein has received research grants and/or consultancy honoraria from Biocodex, Lundbeck, Novartis, Servier, and Sun.

S-09. Neuroimaging vulnerability to neuropsychiatric disorders

S-09-001 Using neuroimaging to identify neural markers of familial vulnerability to depression

P. Cowen. *University of Oxford, Department of Psychiatry, Warneford Hospital, Headington, Oxford, United Kingdom*

Objective: To identify neuroimaging biomarkers of vulnerability to depression in young people at increased familial risk.

Methods: Functional neuroimaging using fMRI with BOLD and structural MR in euthymic young people with a biological parent with recurrent major depression.

Results: Young people at increased familial risk of depression may have smaller hippocampal volumes though the expression of this abnormality may depend on a combination of childhood maltreatment and genetic risk. Young people at risk of depression exhibit impaired neural responses to rewarding and aversive stimuli. There is also behavioural evidence for a conservative approach to risk-taking even when the odds of a good outcome are favourable.

Conclusion: Young people without significant depressive symptoms but at increased familial risk of illness demonstrate a range of abnormal neuroimaging biomarkers. The relation of these abnormalities to the risk of experiencing subsequent depression is unclear and follow-up studies are needed. It is possible that impaired reward mechanisms could be linked to sub-optimal decision-making, thereby increasing psychosocial adversity and the risk of depression.

Policy of full disclosure: The studies of the author were supported by the UK Medical Research Council PJC has been a member of advisory boards for Lundbeck and Servier.

S-09-002 Neuroimaging the vulnerability to depression: The glutamate system

G. Hasler. *University of Bern, Psychiatric University Hospital, Bern, Switzerland*

Objective: To review the current evidence for a glutamatergic vulnerability to depression based on molecular neuroimaging studies in humans.

Methods: Magnetic resonance spectroscopy, positron emission tomography.

Results: Glutamate is the major excitatory neurotransmitter in the brain, playing an important role in neuronal plasticity, learning, and memory. Reduced prefrontal and subcortical glutamate/glutamine, as determined by magnetic resonance spectroscopy, has been found to be a specific marker of unipolar depression. In bipolar disorder, glutamate/glutamine has been shown to be consistently increased in all mood states (1). Moreover, there is increasing evidence demonstrating abnormalities in glutamate receptors in depressed individuals. The metabotopic glutamate receptor 5 (mGluR5) has been found to be decreased in depression in both a positron emission tomography study and in a postmortem study on mGluR5 protein expression (2). In some depressed patients, increased levels of N-Methyl-D-Aspartate (NMDA) receptor antibodies (epitope: Nr1a/NR2b) have been detected.

Conclusion: Taken together, neuroimaging and possibly neuroimmune measures of the glutamate system may provide promising mood disorder subtype-specific biomarkers for the vulnerability to clinical depression.

Policy of full disclosure: None.

S-09-003 What underlies the onset of psychosis? Multi-modal and longitudinal imaging data from people at risk of psychosis

O. D. Howes. *Imperial College – Hammersmith, Cyclotron Building, Hammersmith Hospital, London, United Kingdom*

Objective: It is not known when dopaminergic overactivity first occurs in the development of psychotic disorders such as schizophrenia or the relationship between dopaminergic dysfunction and the neural substrates of cognitive impairment.

Methods: The following age-matched groups have received longitudinal [18F]-DOPA PET imaging: A) individuals with at risk mental states (ARMS, n=54) who show prodromal signs of developing psychosis; B) individuals with persistent sub-clinical symptoms who have not developed psychosis (psychosis continuum, n=14); C) healthy controls (n=36). The ARMS subjects received follow-up to determine who developed psychosis and repeat PET scans to determine change in [18F]-DOPA influx constants (Ki) values. The neural substrates of cognitive impairments seen in the ARMS were investigated using functional magnetic resonance imaging whilst subjects performed tasks involving working memory and executive function.

Results: There was a significant group effect on Ki values at baseline for the whole striatum ($F=3.7$, $df=2,42$, $p=0.035$), and the AST striatal subdivision ($F=6.5$, $df=2,42$, $p=0.004$); and this was replicated in a second independent cohort ($p=0.001$). The elevation in the ARMS group was seen in the nine ARMS subjects who developed psychosis but was not evident in those who have not developed psychosis to date, or in the psychosis continuum group. Furthermore there was a longitudinal increase in Ki value as subjects developed psychosis ($t=3.01$, $df=7$, $p=0.020$). ARMS subjects showed greater activation during the cognitive task, and this was directly correlated with striatal dopamine function ($r=0.732$, $p<0.001$).

Conclusion: These findings indicate that i) elevated dopamine synthesis capacity predates the onset of psychosis in people with prodromal symptoms, ii) is related to the neural substrates of neurocognitive dysfunction; iii) increases further over time with the development of psychosis; and iv) is specific to the risk of a psychotic disorder.

Policy of full disclosure: Funded by MRC UK.

S-09-004 PET studies of dopamine responses in subjects at risk for substance use disorders

M. Leyton. *McGill University, Montreal, Canada*

Objective: Only some people who try drugs of abuse develop a substance use disorder. Here, we tested whether people at elevated risk for addictions have disturbed drug-induced activations of the dopamine reward system.

Methods: Striatal dopamine release was measured in two studies using positron emission tomography (PET) with [11C]raclopride. In Study 1, d-amphetamine (0.3 mg/kg, p.o.), given in the absence of drug-related cues, was administered to three groups: (1) high-risk young adults with a multigenerational family history (FH) of substance use disorders (FH+, n=16), (2) stimulant drug-naïve healthy controls with no known risk factors for addiction (Ctls_naive, n=17), and (3) subjects matched to the high-risk group on personal drug use but without a FH of substance use problems (Ctls_exposed, n=15). In Study 2, an alcohol beverage was ingested with cues present (sight, smell, taste & touch, 0.75 *g* ethanol/kg, p.o.) by two groups (n=13/group) differentiated by reward-sensitivity related personality traits and the Subjective High Assessment Scale index of risk for alcohol use disorders.

Results: Study 1: When given encapsulated d-amphetamine, the high-risk FH+ subjects exhibited significantly smaller [11C]raclopride responses, as compared to both control groups. Past drug use correlated negatively with the [11C]raclopride response, but including it as a covariate increased the group differences. Study 2: High-risk subjects exhibited significantly larger [11C]raclopride responses than low-risk subjects after drinking alcohol.

Conclusion: These studies provide the first evidence that young adults at high-risk for substance use disorders have disturbed dopamine responses to drug challenges, the exact direction of which may depend upon conditions of the study, such as the presence vs. absence of drug-related cues. Since the participants were non-dependent, the perturbation expresses itself well before extensive drug exposure, potentially reflecting a trait marker for addictions.

Policy of full disclosure: None.

S-10. Coming of age for phosphodiesterase inhibitors as central nervous system therapeutics

S-10-001 Role of PDE-mediated signaling and its crosstalk in brain function

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Objective: Dopamine neurotransmission is mainly mediated through cAMP/PKA signaling. Phosphodiesterases (PDEs) that inactivate cAMP and/or cGMP are involved in dopamine neurotransmission. PDE inhibitors have therapeutic potential in treating neuropsychiatric disorders, but development of therapeutic drugs has not successful because of the complexity of CNS PDE systems. Multiple PDEs with different substrate specificity and subcellular localization control cAMP and cGMP signaling in a neuron-type specific manner. We have screened the effect of various PDE inhibitors on cAMP/PKA signaling in brain slices, and found that inhibitors of PDE2A, PDE4 and PDE10A are useful to dissect the role of each PDE.

Methods: We used in vitro biochemical techniques to dissect the role of PDEs in dopamine neurotransmission. The ability of selective PDE inhibitors to regulate phosphorylation of presynaptic (e.g., tyrosine hydroxylase) and postsynaptic (e.g., DARPP-32 and GluA1) PKA substrates was monitored in mouse brain slices from striatum, prefrontal cortex and hippocampal dentate gyrus.

Results: In the striatum, the PDE10A inhibitor, papaverine, and the PDE2 inhibitor, BAY 60-7550, activated cAMP/PKA signaling in both striatonigral and striatopallidal neurons, and potentiated dopamine D1 receptor signaling. The PDE4 inhibitor, rolipram, mainly acted at dopaminergic terminals and increased dopamine turnover. Nitric oxide/cGMP signaling counteracted cAMP/PKA signaling via activation of PDE2A, demonstrating a mechanism for interaction of cAMP and cGMP signaling. In the prefrontal cortex, PDE4 and PDE2A, but not PDE10A, activated cAMP/PKA signaling, and the inhibition of PDE4 or PDE2A potentiated dopamine D1 receptor signaling. Furthermore, actions of PDE4 and PDE2A inhibitors were synergistic. In the hippocampal dentate gyrus, PDE4, PDE2A and PDE10A are involved in the regulation of cAMP/PKA signaling. The roles of these PDEs in antidepressant effects are under investigation.

Conclusion: These data suggest that PDE inhibitors, acting at multiple PDEs, have the potential to regulate cAMP/PKA signaling efficiently in a neuron-type specific manner, and may be a useful therapeutic approach to neuropsychiatric disorders.

Policy of full disclosure: None.

S-10-002 Role of cyclic nucleotides in cognitive function in the brain

L. Wennogle. *Intra-Cellular Therapies, Drug Discovery, New York, USA*

Objective: The objective of this work is to test the effectiveness of phosphodiesterase inhibitors for disorders of the central nervous system involving cognitive dysfunction, and in particular cognitive impairments associated with schizophrenia (CIAS).

Methods: Potent and selective phosphodiesterase 1 (PDE1) inhibitors have been evaluated in various models of cognition.

Results: We have developed potent, selective and safe small molecules with good oral bio-availability. The lead compound for CIAS, ITI-214, is active in animal models of cognition including the rat novel object recognition with a broad time course of effectiveness.

Conclusion: In view of the well-established hypo-functionality of the dopamine D1 receptor in pre-frontal areas of the brain associated with cognitive function in schizophrenia and the close association of PDE1 with the signaling of the D1 receptor, we have been evaluating PDE1 inhibitors, together with our collaborators at Takeda Pharmaceuticals, for cognitive impairment associated with schizophrenia (CIAS). The background to this work as well as the status of development will be reviewed. We have potent, selective and safe small molecules with good oral bio-availability. The lead compound for CIAS, ITI-214, is active in animal models of cognition including the rat novel object recognition with a broad time course of effectiveness.

Policy of full disclosure: Lawrence Wennogle is a full-time employee of Intra-Cellular Therapies, Inc.

S-10-003 PDE4 and PDE5 inhibitors in cognition enhancement: From animals to humans and back again

J. Prickaerts. *Maastricht University, Maastricht, Netherlands*

Objective: Phosphodiesterases (PDEs) are enzymes that differ in their substrate, i.e. cyclic adenosine monophosphate (cAMP) and/or cyclic guanosine monophosphate (cGMP), being hydrolyzed. Since these cyclic nucleotides have been suggested to play specific roles in processes of cognition, selective PDE inhibitors preventing the breakdown of cAMP and/or cGMP could improve cognition. Our objective is to elucidate the putative procognitive effects of PDE inhibitors in a translational approach.

Methods: Rodents and monkeys were treated with different inhibitors of PDE2, PDE4, or PDE5 and tested in cognitive tasks. In a translational approach we also investigated the effect of PDE5 inhibition on cognition in humans.

Results: Animal studies with different timing of treatment with specific PDE inhibitors indicated that distinct underlying signaling pathways for early and late consolidation processes exist corresponding to specific time-windows for memory consolidation. We also explored other cognitive domains including acquisition processes/short-term memory and information processing. It was found that elevation of central cGMP levels as well as cAMP levels after treatment with a specific PDE inhibitor improves acquisition processes/short-term memory. Further, the effects of specific PDE inhibitors on information processing by using a sensory gating paradigm indicate that elevation of cGMP as well as cAMP with a specific PDE inhibitor improves sensory gating, whereas elevation of cGMP alone has no effect. We also investigated the effect of PDE5 inhibition on cognition in humans. In contrast to animal studies, PDE5 inhibition had no effect on memory processes in humans. Yet sensory gating was also not affected underlying the translational value of this measure.

Conclusion: Obviously, the transition of a drug from preclinical to clinical creates translational hurdles. This has to be taken into consideration and minimized in order to be able to select a specific PDE inhibitor (e.g. PDE2, PDE4 or PDE5) as a promising drug to enhance cognitive function in humans.

Policy of full disclosure: None.

S-10-004 Differential effects of PDE2, 4, 9 and 10 inhibition on biochemical and behavioral markers of striatal function

C. Schmidt. *Pfizer, Groton, USA*

Objective: The complexity of cyclic nucleotide phosphodiesterases in the striatum underscores the importance of second messenger signaling in this nucleus. This presentation will focus on the use of selective inhibitors of four enzyme families: two dual substrate enzymes, PDE2A and PDE10A, the cGMP-specific PDE9A and the cAMP selective PDE4 family.

Results: PDE10A is the most highly expressed PDE in the striatum and its inhibition elevates activity in both the cAMP and cGMP signaling cascades to amplify striatal output. Behaviorally, PDE10A inhibition mimics the effects of D2 receptor blockade. The cGMP pool regulated by PDE10A is generated by the soluble guanylyl cyclase (sGC)/nNOS/NO system and play a role in regulating the response of striatal neurons to cortical input. In contrast to PDE10A inhibition, PDE2A inhibition results in only modest changes in cGMP and cAMP signaling and behavior under basal conditions. However, during D1 receptor stimulation, cGMP derived from the sGC/NO/nNOS pathway activates PDE2A to regulate striatal cAMP signaling. Although PDE9A has one of the lowest expression levels of any striatal PDE, inhibition of this enzyme elevates levels of cGMP throughout the brain. Significantly, PDE9 appears to regulate a pool of cGMP independent of NO/nNOS and therefore distinct from that regulated by PDE10A and from that involved in the regulation of PDE2A activity. The activity of PDE4 inhibitors in models linked to striatal function such as CAR and catalepsy has been well-described. Despite this behavioral similarity to PDE10A inhibition, the neurochemical effects of PDE4 inhibition are modest by comparison. Yet, while the administration of rolipram does not affect basal cAMP or pCREB levels or other elements of cAMP cascade, pharmacological manipulations decreasing cAMP signaling are reversed by PDE4 inhibition.

Conclusion: These studies, using selective PDE inhibitors, reveal the presence of functionally overlapping but biochemically distinct pools of both cAMP and cGMP in the striatum.

Policy of full disclosure: In am a full time employee of Pfizer, Inc.

JS-01. Japanese Session: Current research topics in schizophrenia and future perspectives

JS-01-001 Cognitive impairment and response to antipsychotic drug treatment as intermediate phenotypes in schizophrenia: Integrating animal model, genetic and clinical trial approaches

H. Meltzer[1], Y. Oyamada[1], L. Rajagopal[1], J. Li[1]. [1]*Psychiatry and Behavioural Science, Northwestern Feinberg School, Chicago, USA*

Objective: Cognitive impairment in schizophrenia (CIS) and persistent psychotic symptoms in patients not responsive to antipsychotic drugs (APDs) other than clozapine are endophenotypes and treatment targets. Deficiencies in glutamate, GABA, dopamine (DA), and acetylcholine (Ach) neurotransmission in cortex and hippocampus are hypothesized causes of CIS.To clarify which neurotransmitters enable atypical APDs to be more effective means of preventing or treating cognitive impairment due to subchronic PCP treatment and to identify a genetic biomarker and treatment target for treatment resistant schizophrenia (TRS).

Methods: Rodents treated sub-chronically with the N-methyl-D-aspartate (NMDAR) antagonist phencyclidine (PCP) were administered serotonin (5-HT)1A, 5-HT2A, 5-HT2C and 5-HT7 receptor agentss, or D1, D2, and GABA A receptor agents, to determine which prevent or restore cognitive function in subchronic PCP- treated rodents. A GWAS study of TRS and NonTRS patients was used to identify a potential biomarker for TRS

Results: 5-HT1A partial agonism, 5-HT2A, 5-HT7 antagonism, GABA A agonism, and weak D2 antagonism will be shown to impact PCP induced cognitive impairment in rodent. The SNP rs2237457, located in 7p12.2, had the lowest p value to discriminate RS and NRS, and is 70 kb upstream from dopa decarboxylase (DDC), the rate limiting enzyme for trace amine synthesis. Animal model studies have shown that the trace amine associated receptor 1 (TAAR1) is a target for developing novel antipsychotic drugs (Revel et al. 2013 Mol Psychiatry 18:543–565). An agonist for TAAR1 is also effective in the subchronic PCP model of CIS noted above.

Conclusion: These results suggest animal models and genetic studies based upon endophenotypes can be of great value in developing novel treatments for specific dimension of the schizophrenia syndrome. Prevention of development of CIS by early treatment with tolerable neuroprotective agents may be the best way to minimize cognitive impairment of schizophrenia.

Policy of full disclosure: Financial disclosure for Dr. Meltzer-Ownership/Investment Interests-Suregene, ACADIA, GlaxoSmithKline Industry activities (such as speaking, advising, consulting, providing educational programs)- Janssen Pharmaceuticals, Lundbeck Inc., Sunovion Pharmaceuticals Inc, Dainippon Sumitomo Pharma Co., Ltd, TEVA, BiolineRx, BI (Boehringer Ingelheim Pharma GmbH & Co. KG, Envivo, Companion Diagnostics, ACADIA Grant Support (in last 3 years)-Bioline Rx,Cephalon, Eli Lilly,Janssen,Pfizer, Sunovion Novartis, Dainippon Sumitomo, Envivo NeuroTherapeutics Pharma, Inc, Otsuka, Takeda Alkermes, Naurex, Inc, Reviva Pharmaceuticals, Inc, Astellas Research Institute of America.

JS-01-002 Identification of chromosomal segments and individual genes critical for schizophrenia in mouse models of 22q11.2 copy number variants

N. Hiroi. *Albert Einstein College of Medicine, USA*

Objective: Hemizygosity of 22q11.2 is associated with extraordinarily high rates of schizophrenia and autism spectrum disorders (ASDs). The critical barrier to understanding precise genotype-phenotype relationship

is that this chromosomal deletion is minimally 1.5Mb in size and includes at least 30 genes. We and others previously demonstrated, using genetic mouse models, that a 200 kb region is responsible for many behavioral phenotypes of 22q11.2 hemizygosity. We have further evaluated the role of Tbx1, one of the genes encoded in the 200 kb region, in behavioral and neuronal phenotypes.

Methods: Male, congenic Tbx1 heterozygous (HT) mice and their wild-type (WT) littermates, at 2 months of age, were evaluated for behavioral phenotypes in a battery of behavioral tests. Moreover, because Tbx1 protein is enriched in postnatal neural progenitor cells (pNPCs), we examined the role of this gene in proliferation of pNPCs using Tbx1 HT mice and Tbx1 siRNA in culture of pNPCs derived from postnatal day 0 (P0) C57BL/6J pups.

Results: Tbx1 HT mice exhibited deficits in prepulse inhibition, social interaction and communication, behavioral alternation, working memory and anxiety-related behavior. Tbx1 HT mice had less pNPCs in the hippocampal dentate gyrus, compared to WT mice. Tbx1 siRNA suppressed the proliferation of pNPCs in vitro.

Conclusion: Tbx1 deficiency contributes to 22q11.2-assoicated behavioral phenotypes and defective proliferation of pNPCs in mice. Given that some of the behavioral phenotypes of Tbx1 HT mice mimic symptomatic elements of 22q11.2-associated neuropsychiatric disorders, Tbx1 deficiency and defective proliferation of pNPCs could be exploited as potential therapeutic targets of schizophrenia and ASDs.

Policy of full disclosure: Dainippon Sumitomo Pharma Co., Ltd.

JS-01-003 Intermediate phenotype studies in schizophrenia

R. Hashimoto[1], K. Ohi[1], H. Yamamori[1], Y. Yasuda[1], M. Fujimoto[1], S. Umeda-Yano[1], M. Takeda[1]. [1]*Osaka University, Osaka, Japan*

Objective: The effects of schizophrenia susceptibility genes would be more penetrant at the level of biologically based intermediate phenotypes than at the level of a complex and phenotypically heterogeneous psychiatric syndrome. Intermediate phenotype concept is that the association between intermediate phenotypes (neurocognition, neuroimaging, neurophysiology, etc.) and genetic variations such as SNP (single nucleotide polymorphism) shows stronger evidence for association between the disease itself and genetic variants. Intermediate phenotypes should be heritable, have good psychometric properties, be related to the disorder and its symptoms in the general population, be stable over time, show increased expression in unaffected relatives of probands, cosegregate with the disorder in families, and have common genetic influences with the disorder.

Methods: We developed human brain phenotype consortium in Japan, which is a database of intermediate phenotypes with research resource (DNA, blood RNA, serum and lymphoblastoid cell line) in patients with schizophrenia, mood disorder, autism spectrum disorders and healthy controls: total of more than 2000. Using data in human brain phenotype consortium, we present several new data of intermediate phenotype analysis.

Results: Using data in human brain phenotype consortium, we present several intermediate phenotype analysis of genes identified by recent case control GWAS (genome wide association study) as well as GWAS of intermediate phenotypes.

Conclusion: Although these studies should be replicated with a larger sample size, our results show that intermeadiate phenotype analysis (in conjunction with GWAS) could be a gene discovery tool. We should note, however, that we cannot rule out an interaction of our gene variants with the affect of antipsychotic drugs on intermeadiate phenotypes.

Policy of full disclosure: There is no financial conflict of interest. This work was supported by research grants from KAKENHI, 22390225-Grant-in-Aid for Scientific Research (B), 23659565-Grant-in-Aid for Challenging Exploratory Research and Grant-in-Aid for Scientific Research on Innovative Areas (Comprehensive Brain Science Network) from the Japanese Ministry of Education, Culture, Sports, Science and Technology (MEXT), and the Japan Foundation for Neuroscience and Mental Health. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. Dr. Hashimoto reports having received support from Dainippon Sumitomo Pharma Co., Ltd. and Novartis Pharma K.K for a project unrelated to this research and speaker's fees from Eli Lilly Japan K.K., GlaxoSmithKline plc, Hisamitsu Pharmaceutical Co., Inc. , Janssen Pharmaceutical K.K., Nippon Zoki Pharmaceutical Co., Ltd., Novartis Pharma K.K., and Otsuka Pharmaceutical Co., Ltd.

JS-01-004 The research and development of aripiprazole

T. Kikuchi. *Otsuka Pharmaceutical Company, Japan*

Otsuka Pharmaceutical firstly initiated research on dopamine autoreceptor agonists in the late 1970s. This research evolved into developing novel compounds that exhibit agonistic activity at presynaptic dopamine autoreceptors and antagonistic activity at postsynaptic dopamine D2 receptors. The result of this research was aripiprazole, a novel antipsychotic with dopamine D2 receptor partial agonistic activity. Today's presentation will review the history of the research and development of aripiprazole and present the pharmacological data of aripiprazole.

Policy of full disclosure: None.

Tuesday 24 June 2014

S-11. The potential of high-risk studies to inform early intervention in bipolar disorder

S-11-001 Use of genetic and clinical variables for clinical intervention in subjects at risk for bipolar disorder

J. Nurnberger. *Indiana University, Indianapolis, USA*

Objective: Childhood precursors of adult bipolar disorder (BP) are still a matter of controversy. Our objective was to identify early clinical predictors of psychiatric disorders in offspring from families of probands with DSM-IV Bipolar Disorder compared to offspring of controls.

Methods: Participants were offspring ages 12–21 in families with a BP proband (n=141, designated as cases) as well as similarly aged offspring of control parents (n=91). The outcome measure was lifetime DSM IV diagnosis of major affective disorder (BPI, SABP, BPII, or Major Depression) determined by a best estimate diagnostic process that included information from the K-SADS-BP and also medical records. We have now added genetic data from 33 SNPs identified by the PGC Bipolar Working Group (2011) as reflecting BP vulnerability.

Results: At an average age of 17, cases showed 23.4% lifetime prevalence of major affective disorder compared to 4.4% in controls (p=0.002, adjusting for age, gender, ethnicity, and correlation between siblings). Prevalence of bipolar disorder in cases was 8.5% vs. 0% in controls (adjusted p=0.007). In cases but not controls, a childhood diagnosis of an anxiety disorder (Relative Risk (RR)=2.6 (1.1 # 6.3), p=0.039) or an externalizing disorder (RR=3.6 (1.4 # 9.0), p=0.007) was predictive of later onset of major affective disorder. These results were published (Nurnberger et al., 2011). We have found that a risk allele score derived from the 33 SNPs separates affected BP cases (N=243) from controls (N=403) (p<0.0001); the same SNP panel separates high risk subjects from controls as well.

Conclusion: An expanded sample with follow-up now includes 241 cases and 158 controls (unpublished data). We have confirmed the predictive value of early anxiety diagnoses and early externalizing disorder diagnoses in this larger sample (p<0.0005 for each). We are also analyzing risk score data in this larger sample.

Policy of full disclosure: None.

S-11-002 The clinical trajectory into bipolar disorder: Targeting early intervention in high-risk youth

A. Duffy. *University of Calgary, Calgary, Canada*

Bipolar disorder is largely a familial illness with an estimated heritability of 85 % and typically onsets starting in adolescence. However it takes many years before the disorder is accurately identified. As a result there is substantial morbidity and premature mortality associated with the illness. Therefore, longitudinal investigation of the offspring of a parent with confirmed well-characterized bipolar disorder is an important research strategy to describe the early natural history of the developing illness and to identify targets for early intervention and prevention. In this talk we will review the latest findings regarding the early clinical stages of evolving bipolar disorder based on high-risk research and highlight critical junctures in the early illness trajectory important for intervention. In addition, new findings highlighting promising underlying neurobiological correlates of illness risk and progression will be presented.

Policy of full disclosure: None.

S-11-003 What interventions can be used in high risk offspring? An evidence map of currently available therapies, and their potential for preventing disease onset or progression

J. Scott. *Newcastle University, Newcastle-upon-Tyne, United Kingdom*

Objective: The goal of this study is to produce an evidence map of the emerging literature on prevention and treatment interventions for the early stages of Bipolar Disorder (BD) and to use this strategy to highlight the strength of and gaps in the available evidence-base.

Methods: Given that there are few randomized controlled trials (RCTs) targeting interventions at individuals at risk of or with early onset BD, it was not realistic to apply the gold standard approaches to data synthesis such as a systematic review. Therefore we used a process termed 'evidence mapping' which is emerging as a means of systematically identifying the 'extent, distribution and methodological quality' of evidence in a clinical or research field.

Results: The search strategies identified only 203 potentially relevant records, whilst another 32 were obtained from hand searches, known experts, conference proceedings and grey literature. Of the 92 publications screened, 30 were included in the final map: 15 papers for the narrative review and 15 studies for the review of outcomes.

Conclusion: The evidence map demonstrates that therapies for the early stages of BD are emerging and that the models being developed draw on a range of clinical and research fields, especially adaptations of adult BD therapies, and from those employed in first episode psychosis. The time lag in the translation of research models for early intervention and clinical staging from psychosis and depression to BD is frustrating, but we anticipate a significant expansion in the BD literature in the next decade. The additional prize in BD is that, even if a young person has previously experienced depression or sub-threshold manic symptoms, it is conceivable that we could use psychological interventions to prevent a first episode of mania- offering opportunities to understand the interplay between psychological and biological mechanisms, and risk and protective factors.

Policy of full disclosure: None.

S-11-004 Using brain imaging and genetics to identify those at high risk for bipolar disorder

P. Mitchell[1], G. Roberts[1], A. Frankland[1], M. Breakspear[2], P. Schofield[3], J. Fullerton[1]. *[1]University of New South Wales, Randwick, Australia; [2]QIMR, Brisbane, Australia; [3]NeuRA, Randwick, Australia*

Objective: It is becoming increasingly apparent that young people at high genetic risk of bipolar disorder evidence changes in brain function (Whalley et al., 2011; Roberts et al., 2013) and structure (Sprooten et al., 2011). Furthermore, there is some suggestion that such changes may predict those who later develop major depressive disorder (Whalley et al., 2013). In this paper we report on our functional studies, elaborating upon our 2013 finding of reduced inferior frontal gyrus (IFG) activation in a facial-emotion go/no-go task using fMRI.

Methods: Two studies were undertaken: i) using dynamic causal modelling (DCM) to model effective dysconnectivity in the fMRI data previously reported (Roberts et al., 2013) in at-risk and control subjects; and ii) resting state functional connectivity of the IFG using 3 complementary approaches in at-risk, bipolar disorder and control subjects.

Results: First, the DCM study demonstrated significant dysregulation in the relative salience of emotion over inhibitory control in the at-risk subjects. Second, the functional connectivity study found that the left IFG was functionally dysconnected in the BD group from a network of regions including bilateral insulae, dorsal anterior cingulate cortex, superior temporal gyri and the putamen. Compared to healthy controls, unaffected at-risk participants showed a functional dysconnection intermediate in strength to the BD group. The dysconnected constellation of regions overlapped with fronto-limbic regions that predicted group membership with significant accuracy.

Conclusion: Functional dysconnectivity of the IFG from regions involved in emotional regulation may represent a trait abnormality for BD which may potentially distinguish such subjects from normal controls. Future studies will explore the capacity of functional and structural imaging to predict future onset of bipolar disorder and MDD.

Policy of full disclosure: None.

S-12. Targeting the endocannabinoid system to treat psychiatric disorders: Clinical and pre-clinical evidence

S-12-001 CB1 receptor imaging provides a model for evidence-based treatment development in post-traumatic stress disorder

A. Neumeister. *New York University School of Psychiatry and Radiology, New York, USA*

Objective: Central clinical features of PTSD are the persistence of a heightened salience of traumatic memories (i.e., experience of alarm and distress) and a failure of the extinction process to diminish the impact of traumatic memories. Cannabinoid type 1 (CB1) receptor-mediated eCB signaling plays a key role in normal fear extinction and impaired CB1 receptor function leads to chronic anxiety-like and depression-like symptoms in animals.

Methods: Untreated individuals with PTSD with non-combat trauma histories, and TC and HC participated in a magnetic resonance (MR) imaging scan and a resting PET scan with the CB1 receptor antagonist radiotracer [11C]OMAR, which measures volume of distribution (VT) linearly related to CB1 receptor availability. Peripheral levels of anandamide, 2-arachidonoylglycerol (2-AG), oleoylethanolamide (OEA), palmitoylethanolamide (PEA), and cortisol were also assessed.

Results: In the PTSD group, relative to the HC and TC groups, we found elevated brain-wide [11C]OMAR VT values ($F(2,53)=7.96$, $p=0.001$; 19.5% and 14.5% higher, respectively). Anandamide concentrations were reduced in the PTSD relative to the TC (53.1% lower) and HC (58.2% lower) groups. Cortisol levels were lower in the PTSD and TC groups relative to the HC group.

Conclusion: These data suggest a deficit of eCB signaling in PTSD and suggest pathways for novel, mechanism based discoveries of the next generation of PTSD treatments.

Policy of full disclosure: None.

S-12-002 A homeostatic role for the endocannabinoid system in schizophrenia

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Objective: The endocannabinoid system represents a major homeostatic system of the central nervous system. It has been shown to play an adaptive role in schizophrenia. We therefore aimed to further elucidate the therapeutic potential of this system in acute psychosis.

Methods: We performed a randomized, double-blind, placebo-controlled, cross-over clinical trial in acute, antipsychotic-naive, first-break paranoid schizophrenia patients, fulfilling diagnostic criteria of DSM-IV. 29 patients were treated after written informed consent with either cannabidiol (600 mg per day) or placebo for 14 days and than switched to the corresponding cross-over condition. Drop-out patients were replaced to gain a total of 18 patients treated per protocol.

Results: Cannabidiol significantly improved psychotic symptoms in the cannabidiol-placebo condition during the first 14 days of treatment when compared to baseline. A MMRM analysis of all randomized patients ($n=29$) yielded an mean improvement of 2.4 points (standard error 3.0) on PANSS total in favor of cannabidiol (vs. placebo), albeit not statistically significant. Only one patient on sequence cannabidiol-placebo terminated treatment early (last seen at visit 3) whereas 10 patients terminated early on sequence placebo- cannabidiol. The most frequent reason given was worsening of symptoms (5/11 patients). In addition, cannabidiol was detectable in serum of almost all patients in the cannabidiol-placebo group. Side-effects of cannabidiol were on the level of placebo.

Conclusion: Although limited by design issues (cross-over), duration of treatment (14 days), carry-over effects (serum levels of cannabidiol), and relevant placebo-response rates, this is the second study to provide evidence for antipsychotic properties of cannabidiol accompanied by a superior side-effect profile. Future placebo-controlled parallel-group trials studying the antipsychotic properties of cannabidiol in acute schizophrenia are necessary to provide further evidence for its efficacy in the treatment of this devastating disease.

Policy of full disclosure: None.

S-12-003 Cannabinoid receptors in the human CNS: Changes in psychotic disorders

B. Dean. *Molecular Psychiatry Lab., FINMH, Howard Florey Laboratories, Melbourne, Australia*

Objective: It is still debated whether cannabis use constitutes an environmental factor that increases the risk of developing schizophrenia and worsens the severity of symptoms or is used by people with the disorder as a self-medication1. This presentation will review a growing body of research seeking to determine if the cannabis 1 receptor (CB1), the predominant cannabis receptor in the human CNS2, is affected by the pathophysiology of schizophrenia and whether this information may be informative as to whether cannabis use may constitute self-medication.

Methods: The notions presented will be from review of studies in the literature that have involved both the use of neuroimaging techniques and post-mortem tissue3. This approach was taken to look for any form of consensus across these two approaches to studying the human CNS.

Results: Neuroimaging ligands are being developed that allow the visualisation of CB1 receptors in the human CNS. Using one such ligand, [11C] OMAR, it has been reported that CB1 receptor trend to being higher in many CNS regions in people with schizophrenia with that increase reaching significance (23%) within the pons. Two CNS regionally focussed studies using postmortem CNS have reported higher CB1 receptors in people with schizophrenia whilst one study has reported the receptor levels to be no different and one study has reported lower levels of the receptor in people with the disorder.

Conclusion: These results will be reviewed and discussed more intensely in this presentation where it will be argued that further study of the CB 1 receptor in the CNS of subjects with schizophrenia is necessary but that current data would favour higher levels of CB1 receptors in people with schizophrenia.

References

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Policy of full disclosure: None.

S-12-004 What do CB1 knockout mice tell us about the endocannabinoid system

E. Scarr. *University of Melbourne, Melbourne, Australia*

Objective: Cannabis or rather its major psychoactive ingredient, (#6aR,10aR)-delta-9-tetrahydro-cannabinol (THC), can cause psychosis, anxiety and short term memory deficits. The effects of cannabinoids are predominantly mediated by CB1 receptors in the brain, which constitute a part of the endocannabinoid system. Although CB1 receptors have been shown to dampen synaptic input (1) and a number of neurotransmitter systems have been shown to interact with the endocannabinoid system (2), we still don#t understand the mechanisms behind the unwanted psychoactive effects. In order to better understand the consequences of altering transmission via the CB1 receptor, we examined tissue from cb1 knockout mice.

Methods: mRNA from cb1 knockout and wildtype mice was hybridised to an Affymetrix# GeneChip® (Mouse Exon 1.0 ST Array) overnight. Following post-hybridization washes, the chips were scanned and the fluorescent signals used to generate subsequent cell intensity (CEL) and chip (CHP) files for analysis. Data from the CEL files were imported into JMP Genomics 6.1, using the relevant Affymetrix library files, and summarised at the gene level. The data was analysed to determine variance between the two genotypes.

Results: The expression profiles of over 11,000 genes were altered by knocking out the cb1 receptor, with over 90 canonical pathways disrupted. Exploration of the gene expression changes revealed that a significant proportion of the molecules interacted with other neurotransmitter systems.

Conclusion: The effect of knocking out one G-protein coupled receptor was far-reaching. The pathways and interactomes that are affected provide possible mechanisms by which the endocannabinoid system influences disparate aspects of brain chemistry.

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Policy of full disclosure: None.

S-13. The epigenetic embedding of early life stress in humans and animal models

S-13-001 Epigenetic signature of life adversities in utero and long-term consequence for mental illness

M. A. Riva. *University of Milan, Milan, Italy*

Objective: Perinatal life is a period of high plasticity and vulnerability to adverse life conditions, which may reshape the normal developmental trajectory of several structures, leading to enhanced risk for psychiatric disorders. Epigenetic modifications have been proposed to translate environmental cues into persistent cellular memories that are responsible for behavioral and functional alterations.

Methods: We used the rat prenatal stress (PNS) model and characterized persistent behavioral and neuroplastic alterations produced by the early life manipulation. We next analyzed genome-wide promoter methylation profiles of the hippocampus and prefrontal cortex from adult PNS rats. Methylation profiles were created using the method MeDIP with microarray hybridization.

Results: PNS rats show a region- and time-specific reduction in the expression of the neurotrophin BDNF, a marker of neuronal plasticity that has an important role in mood and cognitive function. Using the epigenome-wide analysis an overlap of 893 differentially methylated genes was observed between the hippocampus and prefrontal cortex of adult male and female rats that were exposed to PNS. Interestingly, the list includes several genes previously associated with schizophrenia and other psychiatric conditions, such as calcium and potassium voltage operated channels as well as GABA and glutamate receptor subunits. Cross-species analyses of human and non-human samples exposed to early life adversities allowed us to restrict the list of genes that may hold psychopathologic implications.

Conclusion: These results highlight the importance for the identification of methylation signatures through which stress exposure early in life could engrave on the outcome of the adult phenotype, and may allow the identification of novel genes and pathways that are affected as a consequence of early life adversities.

Policy of full disclosure: M.A. Riva has received honoraria or research support from Bristol-Myers Squibb, Dainippon Sumitomo Pharma, Eli Lilly, Servier and Sunovion.

S-13-002 Early life stress and genome wide adaptation

M. Szyf[1], R. Masart[1], S. Suomi[2], N. Provencal[1], C. Yi[1]. [1]*McGill University, Department of Pharmacology and Therapeutics, Montreal, Canada;* [2]*NIH/NICHD, Laboratory of Comparative Et., Bethesda, MD , USA*

Objective: Early life social adversity is known to have long-lasting impact on the phenotype of the offspring. What are the mechanisms that mediate between exposure to adversity during early life and long-term changes in the phenotype?

Methods: Models of non-primate maternal deprivation were previously examined (Suomi et al.,). We tested whether maternal deprivation will affect the methylome in T cells which provide a noninvasive tissue source.

Results: Early life maternal separation in monkeys is associated with a DNA methylation signature that is seen at 14 days. A large fraction of these differentially methylated regions remains to adulthood and there is gender specificity in the stability of the differentially methylated signatures associate with early life maternal deprivation.

Conclusion: These data support the hypothesis that system wide DNA methylation changes early in life in response to social stress occur in both humans and animals in a genome wide and system wide manner. These are proposed to be 'adaptive genomic' mechanisms that prepares life-long genome programming to the anticipated life-long environment based on stress signals received during gestation and early life. We will discuss the hypothesis that stress hormones might be mediating the genome wide and system wide response of the methylome to stress. Glucocorticoids might act as 'integrators' that translate the social stress signals during gestation to genome wide methylation changes across multiple systems.

Policy of full disclosure: None.

S-13-003 Activation of the glucocorticoid receptor: A possible mediator of genome-wide changes in DNA-methylation following early trauma

E. Binder. *Max Planck Institute for Psychiatry, Munich, Germany*

Objective: A number of studies point to the fact that the biological embedding of the longterm effects of early trauma can be mediated by epigenetic effects. This talk will highlight several lines of evidence suggesting that glucocorticoid-receptor (GR) activation induced changes in DNA-methylation may be one of the mechanisms contributing to these longterm effects.

Methods: Genome-wide DNA methylation has been investigated in a human hippocampal neuron progenitor cell line treated with the GR agonist dexamethasone during as well as after hippocampal differentiation. In a sample of 394 African American individuals, expression (eQTL) and methylation quantitative trait loci (mQTL) moderated by exposure to early trauma were investigated using peripheral blood cells.

Results: In the neuronal progenitor cell line, we observed differentiation-depedent differences in the longterm effects of GR-administration. Over 450 CpG showed significant changes in methylation with administration of dexamethasone during prolifration and early differentiation that remained stable after 20 days of washout. These CpG were not affected by treatment after differentiation of the cells and 43% were located in the opean sea and not within CpG islands. In analyses investigating the effects of early trauma exposure on eQTLs and mQTLs, we identified 598 cis eQTLs showing significant SNP × early trauma interaction on gene expression. Of these eSNPs, over 20% were also associated with mQTLs in the same cis window, suggesting that the early trauma × SNP interaction on gene expression could be mediated by changes in DNA methylation. The SNPs sequences were enriched for brain-relevant enhancer regions as well as for GR response elements. In addition, the differentially methylated CpGs within the mQTLs showed significant overlap, with the CpGs differentially methylated following GR agonist treatment in the neuronal cell lines.

Conclusion: Our data suggest that a combined approach using in vitro and in vivo data can help to elucidate the role glucocorticoids and DNA methylation changes in the longterm effects of early trauma.

Policy of full disclosure: None.

S-13-004 Prenatal exposure to a natural disaster and life long health risks

S. King. *Department of Psychiatry, McGill University, Douglas Mental Health University Institute, Verdun, Quebec, Canada*

Objective: Prenatal maternal stress (PNMS) is challenging to study in humans using experimental methods. The goal of our PNMS research program is to increase understanding of the effects of PNMS on the unborn child as well as the biopsychosocial mechanisms of these effects. In particular, we wish to disentangle the effects of objective levels of maternal hardship from subjective levels of maternal distress, and to determine moderating effects of child sex and timing of stress in pregnancy. Natural disasters offer the possibility of quasi-random assignment of stress exposure from an independent stressor.

Methods: We have three studies of pregnant women exposed to natural disasters. In each, we assessed objective exposure and subjective distress shortly following the disaster. We began Project Ice Storm in Quebec in 1998; The Iowa Flood Study in 2008 (adding pre-disaster data from an on-going study of pregnant women); and The QF2011 Queensland Flood Study in Australia in 2011 (including pre-trauma data on pregnant women, a pre-existing RCT of two prenatal care programs, plus placenta, umbilical cords and cord blood samples). We evaluated pregnancy outcomes, and the cognitive, behavioural, motor and physical development of the children.

Results: We demonstrate strong and long-lasting effects of prenatal stress on children's cognitive outcomes (IQ, language, memory); behaviour (anxiety, depression, aggression, autistic-like traits); motor development (coordination, visual-motor integration); and physical development (brain, sexual dimorphisms, body composition, immune function, insulin secretion, obesity).

Conclusion: Using a natural disaster as a platform for studying prenatal maternal stress is a powerful approach for capturing the unique effects of objective and subjective aspects of prenatal stress, as well as precise timing of in utero effects.

Policy of full disclosure: None.

S-14. Prefrontal norepinephrine in arousal and executive function

S-14-001 Functional network effects of selective LC-NE stimulation

G. Aston-Jones. *Medical University of South Carolina, Department of Neurosciences, Charleston, SC, USA*

Objective: The nucleus locus coeruleus (LC) projects widely throughout the CNS and is the primary source of norepinephrine (NE) to cortex. It has been functionally implicated in a range of activities including arousal, mood and executive functions. Electrical or pharmacological manipulations have been used previously to investigate modulation of LC. However, the development of novel tools now allows unprecedented specificity and precision for testing causal roles of LC-NE neuron functions. We have optimised and validated several methods for targeting LC-NE neurons for modulation with both optogenetics and synthetic receptors.

Methods: Using electrophysiologically guided injections and cell-type specific viral vectors in vivo, along with optogenetics or synthetic receptors (DREADDs, Designer Receptors Exclusively Activated by Designer Drugs), we can selectively manipulate LC-NE activity in anesthetized or behaving rats. Use of a synthetic DBH promotor has allowed us to achieve robust expression specifically restricted to noradrenergic LC neurons. Both optogenetic and DREADD tools can be employed across a range of dosing patterns to modify local LC-NE activity, which produce global cortical and behavioral responses.

Results: Our results show that selective activation of LC-NE neurons has a number of functional effects, including cortical EEG activation, modulation of cortical responses to sensory events, acceleration of emergence from anesthesia. These findings are consistent with previous work indicating a role for LC-NE neurons in cortical modulation that regulates executive functions including attention, decision processes and behavioral flexibility.

Conclusion: These new tools that afford selective manipulation of LC-NE neurons open new avenues for therapeutic development to treat a host of mental disorders association with LC-NE dysfunction. Supported by USPHS grants R01MH092868 and R21MH099534, the Parkinson's Disease Foundation, and the Neuroscience Institute of MUSC.

Policy of full disclosure: None.

S-14-002 Monoaminergic regulation of impulsivity and gambling-related decision-making

C. Winstanley. *University of British Columbia, Department of Psychology, Vancouver, BC, Canada*

Objective: Impulse control deficits have been associated with problem gambling behaviour. Drugs which act on monoaminergic systems significantly alter multiple forms of impulsivity. Determining whether such compounds likewise influence gambling-related decision-making could inform our understanding of the degree to which these cognitive processes overlap, and also speak to whether treatments that influence different forms of impulse control would be appropriate for individual with a gambling disorder.

Methods: Rats were trained on distinct operant behavioural paradigms designed to measure different aspects of gambling-related decision-making. Once stable behaviour has been established, the effects of dopaminergic, serotonergic and noradrenergic manipulations were determined, and the results compared to a measurement of impulsive action in the form of premature responses.

Results: While both dopaminergic and serotonergic compounds can influence choice under uncertainty across multiple paradigms, the effects of both acute and chronic administration of D2- family agonists differs drastically across the tasks, with greater effects observed in tasks in which gains rather than losses are emphasised. Noradrenergic compounds in isolation had little effect on tests of gambling behaviour, despite robust changes in impulsivity. Amphetamine, which potentiates the actions of dopamine, serotonin and noradrenaline, increases premature responding and also impairs decision-making on a rat gambling task. Whereas the effects of this psychostimulant on impulsivity can be blocked by dopamine antagonists, the effects on choice could not.

Conclusion: Although broadly speaking the same neurotransmitter systems are implicated in both impulsivity and gambling-related decision-making, different forms of choice under uncertainty vary in the degree to which they can be influenced by dopaminergic compounds. Although analysis is preliminary, noradrenergic compounds do not appear to have such a great effect on models of gambling as compared to tests of impulse control.

Policy of full disclosure: I do not have any financial conflicts of interest.

S-14-003 The dual role of norepinephrine in modulating cognitive flexibility in prefrontal cortex: Acute facilitation and chronic stress-induced attenuation

D. Morilak[1], J. Jett[1], M. Girotti[1], J. Donegan[1]. [1]*University Texas Health Science Center, San Antonio, USA*

Objective: To address the role of the modulatory neurotransmitter, norepinephrine, in facilitating cognitive flexibility in the prefrontal cortex as an adaptive component of acute stress responsivity, and in the beneficial effects of chronic reuptake blockade, but also to address the potential mechanisms by which repeated elicitation of this facilitatory modulation during chronic stress can be detrimental.

Methods: Cognitive flexibility, including cognitive set-shifting and reversal learning, were measured using the rat attentional set-shifting test. Chronic unpredictable stress was applied for 2 weeks, producing a deficit in these measures. Receptor-specific antagonists were applied directly into prefrontal cortex by local microinjection. NE and glutamate release were measured by microdialysis. Prefrontal function was assessed by fos response to activation of GLU afferents in mediodorsal thalamus. Chronic drug treatment was administered by osmotic minipump.

Results: Acute activation of NE in prefrontal cortex facilitates cognitive flexibility through actions at alpha1 receptors. After chronic stress, cognitive flexibility is compromised, but still facilitated acutely by NE in PFC via alpha1 receptors. Glutamate function in PFC is similarly compromised. Tonic NE elevation by chronic reuptake blockade is beneficial. However, blocking adrenergic receptors in PFC during chronic stress protects cognitive flexibility and glutamate function, implying that repeated acute facilitation during chronic stress contributes to a cumulative functional deficit.

Conclusion: The adaptive and acutely facilitatory effects of NE are maintained after chronic stress, contributing to the cumulative compromise of cognitive flexibility and prefrontal function over time. But tonic elevations of NE by chronic reuptake blockade are beneficial in restoring function compromised by chronic stress, suggesting that acute, stress-induced activation of NE function must act convergently with other factors that are also activated by stress, perhaps including glutamate, glucocorticoids or cytokines, to contribute to the deficit. The signaling mechanisms underlying these convergent effects may suggest novel therapeutic targets.

Policy of full disclosure: This work was supported by grants from the National Institutes of Health (MH053851 and MH072672). Dr. Morilak has received research funding from H. Lundbeck A/S in the past year, for work unrelated to the research presented in this symposium.

S-14-004 Noradrenergic modulation of cognitive control and attention in rodents and humans; translational implications

T. Robbins. *University of Cambridge, Department of Psychology, Cambridge, United Kingdom*

The notion that the locus coeruleo-cortical noradrenergic projection has a prominent role in cognitive control in humans and experimental animals has been discussed in various forms by several authors. Cognitive control is a broad term that covers several aspects of executive function including attention and inhibitory response control, there being good evidence of noradrenergic involvement in both of these interacting processes. The stop-signal reaction time (SSRT) task is a useful paradigm for measuring motor inhibitory functions and has been associated with a specified neural network in the human brain including the inferior frontal cortex, striatum, subthalamic nucleus and supplementary motor area, among other regions. Based primarily on the effects of the selective noradrenergic reuptake inhibitor atomoxetine in human volunteers and rodents, there is excellent evidence that noradrenaline released in the prefrontal cortex (PFC) may contribute importantly to improve SSRT performance (by speeding the SSRT), and that this involvement is significant for neuropsychiatric syndromes such as attention deficit hyperactivity disorder (ADHD) where there is excessive impulsive behaviour. Relevant evidence is based on paradigms of pharmacological functional magnetic resonance imaging in human volunteers, intra-cerebral microinfusions in rats, and genomics. Thus for example, the improvement in SSRT performance produced by atomoxetine is correlated with a BOLD response in the right inferior frontal region, an area that is also correlated with (i) the capacity to perform the task (ii) the presence of ADHD symptoms and (iii) the modulatory effect of a single nucleotide polymorphism affecting the noradrenaline transporter. Moreover, when infused into possibly homologous regions of the rat prefrontal cortex, similar improvements in SSRT performance are found that appear to depend on cortical noradrenaline. The translational significance of these parallel effects in humans and rodents are discussed in terms of the treatment of ADHD, stimulant addiction and Parkinson's disease.

Policy of full disclosure: Research funded by the Wellcome Trust, MRC and EU (IMAGEN project). TWR discloses consultancy with Cambridge Cognition, E. Lilly, Shire Pharmaceuticals, Teva, Lundbeck. He has held research grants from Lilly and Lundbeck. He is an editor of Psychopharmacology (Springer Verlag).

S-15. BACE1 in Alzheimer's disease pathogenesis and drug development

S-15-001 GSK3 signaling regulates BACE1 expression and APP processing and its pharmaceutical potential for Alzheimer's disease

W. Song[1], P. Ly[1], Y. Wu[1]. [1]*University of British Columbia, Vancouver, Canada*

Objective: Alzheimer's disease (AD) is the most common neurodegenerative disorder leading to dementia. Deposition of neuritic plaques is one of the characteristic pathologies observed in AD. Abeta, the central component of neuritic plaques, is produced from sequential cleavages of the amyloid beta precursor protein (APP) by the beta- and gamma-secretases. Beta-site APP cleaving enzyme 1 (BACE1) is the beta-secretase in vivo essential for Abeta generation. Inhibition of Abeta generation by targeting BACE1 will have therapeutic implications for AD. Previous studies indicated that glycogen synthase kinase 3 (GSK3) plays an intimate role in APP processing to promote Abeta production. However, the mechanistic action of GSK3 in APP processing has not been thoroughly examined. This study aimed to examine the role of GSK3 signaling in Alzheimer pathogenesis and its pharmaceutical potentials.

Methods: To address this issue, we applied GSK3alpha and beta isoform specific knockdown and highly potent GSK3 inhibitors. APP processing and Abeta production was examined by Western blot analysis and ELISA. Luciferase assay was used to study BACE1 promoter activity. The effect of GSK3 on AD phenotypes was examined using transgenic AD model mice in vivo.

Results: We found that specific inhibition of GSK3beta, but not GSK3alpha reduced BACE1-mediated cleavage of APP and Abeta production by decreasing BACE1 gene transcription and expression. Furthermore, the regulation of BACE1 transcription by GSK3beta is dependent on NFkB signaling. We also demonstrate that specific inhibition of GSK3 signaling markedly reduced Abeta deposition and neuritic plaque formation, and rescued memory deficits in the double transgenic AD model mice.

Conclusion: Our results demonstrate that GSK3beta regulates BACE1 expression and AD pathogenesis and inhibition of GSK3 signaling can reduce Abeta neuropathology and alleviate memory deficits in AD model mice. Our study suggests that interventions specifically targeting the GSK3beta isoform may be a safe and effective approach for treating AD.

Policy of full disclosure: None.

S-15-002 Alteration of BACE1 processing of APP in Alzheimer's disease

K. Stefansson. *deCODE Genetics, Reykjavik, Iceland*

Policy of full disclosure: None.

S-15-003 Inhibition of BACE1 for benefiting AD patients

R. Yan. *Case Western Reserve University, Cleveland, USA*

BACE1, a type I transmembrane aspartyl protease, cleaves amyloid precursor protein (APP) at the ß-secretase site. Following this cleavage, ß-secretase processes the membrane-bound APP C-terminal fragment to release amyloid peptides (Aß). Since Aß aggregation is the major component in amyloid plaques and excessive production of Aß is linked to both familial and sporadic Alzheimer's disease (AD) pathogenesis, inhibition of BACE1 is widely pursued as an important target for AD therapy. A large volume of experimental results has shown that chemical inhibition of BACE1 in both mouse models and humans produces substantial inhibition of Aß generation and amyloid deposition. Because of its important applications in human AD treatment, it is imperative to understand the potential side effects associated with mechanistic inhibition of BACE1. To address this practical question, we have used BACE1-knockout mice to explore the physiological functions of BACE1. We demonstrate that BACE1 can also process other membrane-bound substrates such as neuregulin-1 and Jagged-1 in addition to APP. The abolished cleavage of these two important substrates leads to hypomyelination of both central

and peripheral nerves as well as altered neurogenesis. Collectively, we conclude that BACE1 is an important molecule that plays multiples roles in various neurological processes and that inhibition of BACE1 in the adult requires cautious monition of other neurological functions.

Policy of full disclosure: I have no conflict of interest to declare. For the funding, my research is funded by three NIH grants: R01AG025493, NS074256, and R01AG046929.

S-15-004 MCI and dementia in China

J. Jia. *Capital Medical University, Beijing, China*

Objective: Estimate the prevalence of MCI and dementia including Alzheimer's disease (AD), and vascular dementia (VaD) among elderly Chinese individuals.

Methods: A total of 10,276 community residents (6096 urban, 4180 rural) aged 65 years were evaluated and diagnosed with normal cognition, MCI, or dementia. MCI was further categorized by imaging into MCI caused by prodromal Alzheimer's disease (MCI-A), MCI resulting from cerebrovascular disease (MCI-CVD), MCI with vascular risk factors (MCI-VRF), and MCI caused by other diseases (MCI-O). Dementia, AD, and VaD were diagnosed. The data were analyzed between rural and urban areas.

Results: The prevalences of overall MCI, MCI-A, MCI-CVD, MCI-VRF, and MCI-O were 20.8% (95%CI=20.0#21.6%), 6.1% (95%CI=5.7#6.6%), 3.8% (95%CI=3.4#4.2%), 4.9% (95%CI=4.5#5.4%), and 5.9% (95%CI=5.5#6.4%) respectively. The rural population had a higher prevalence of overall MCI (23.4% vs. 16.8%, P<0.001). The prevalence of dementia, AD, and VaD among individuals aged 65 and older were 5.14% (95%CI =4.71#5.57%), 3.21% (95%CI=2.87#3.55%), 1.50% (95%CI=1.26#1.74%), respectively. The prevalence of dementia was significantly higher in rural than in urban areas (6.05% vs. 4.40%, P<0.001). The same regional difference was also seen for AD (4.25% vs. 2.44%, P<0.001) but not for VaD (1.28% vs. 1.61%, P=0.166). The difference in AD disappeared when the sample was stratified by educational level.

Conclusion: The prevalence of MCI in elderly Chinese is higher in rural than in urban. Vascular-related MCI (MCI-CVD and MCI-VRF) was most common. A notably higher prevalence of dementia and AD was found in rural than in urban areas.

Policy of full disclosure: None.

S-16. New basic and clinical developments for treatment resistant depression

S-16-001 Drug development in treatment-resistant depression: Current progress, major hurdles and future strategies

C. Zarate. *NIMH, CRC, Bethesda, USA*

Objective: Current treatments for patients are generally unsuccessful for a number of patients with severe and recurrent mood disorders. A better understanding of the neurobiology of mood disorders, informed by preclinical research and bi-directionally translated to clinical research, is critical for the future development of new and effective treatments. Recently, diverse new targets/compounds have been specifically tested in preclinical models and in proof-of-concept studies, with potential relevance as treatments for mood disorders.

Methods: This talk will review clinical translational studies conducted at the National Institute of Mental Health (NIMH) on the following candidate targets with the goal of developing novel therapeutics for TRD. These targets include: (1) the glutamatergic system (NMDA receptor complex), (2) the cholinergic system (muscarinic receptor), (3) the opioid neuropeptide system (delta opioid), and (4) the cAMP cascade (PDE4).

Results: Our studies targeting the glutamatergic and cholinergic systems found that the NMDA antagonists ketamine, MK-0657 (oral NR2B antagonist), and AZD6765 (low trapping non-selective NMDA antagonist) and the cholinergic antagonist scopolamine were found to have rapid antidepressant effects in TRD. AZD2327, a delta opioid agonist, showed anxiolytic effects in patients with anxious depression. Finally, by using 11C-(R)-rolipram, an inhibitor of phosphodiesterase 4, we found that the cAMP cascade is downregulated in unmedicated patients with major depressive disorder, and antidepressant treatment normalizes the cascade.

Conclusion: These targets may be of substantial interest in defining future directions in drug development, as well as in developing the next generation of therapeutic agents for the treatment of mood disorders. Overall, further study of these and similar drugs may lead to a better understanding of relevant and clinically useful drug targets in the treatment of these devastating illnesses.

Policy of full disclosure: Dr Zarate is listed as a coinventor on a patent application for the use of ketamine and its metabolites in major depression. Dr Zarate has assigned his rights in the patent to the US government but will share a percentage of any royalties that may be received by the government.

S-16-002 TRD: Results of a European multi-centre study

S. Kasper. *Medical University of Vienna, Department of Psychiatry and Psychotherapy, Vienna, Austria*

Objective: It has been estimated that 30 to 45% of adequately treated major depressive disorder (MDD) episodes in a psychiatric setting fail to achieve an adequate response.

Methods: The Group for the Study of Resistant Depression (GSRD) (Souery et al., 2007; Journal of Clinical Psychiatry 68: 1062–1070), a collaborative project between 8 centers in Europe in Belgium, France, Greece, Italy, Israel, and Austria developed a staging model that distinguishes between 'non-responders' (patients who fail to respond to one form of treatment, administered for 6–8 weeks), a condition which is now termed 'insufficient response' by the European Medicines Agency (EMA), 'treatment resistant depression' (TRD, patients that fail to respond to two or more adequate antidepressant trials of different classes of antidepressants), and 'chronic resistant depression' (CRD, patients being treated with several antidepressants for more than 12 months).

Results: The clinical findings of the GSRD provide a set of 11 variables associated with treatment response, among them comorbid anxiety disorders as well as melancholic features (Souery et al., 2007; Journal of Clinical Psychiatry 68: 1062–1070). The GSRD performed the until now largest candidate gene studies to investigate associations with treatment response phenotypes (Serretti et al., 2011; Journal of Affective Disorders 128: 56–63). Although there is a plethora of hints in textbooks that switching the mechanism of action should be obtained when a patient does not respond to one medication, the results of the GSRD challenge this notion by describing that staying on the same antidepressant mechanism of action for a longer time is more beneficial than switching (Souery et al., 2011; World Journal of Biological Psychiatry 12: 364–375).

Conclusion: The results of the GSRD European multicentre project has recently been summarized by Schosser et al. (European Neuropsychopharmacology, 2012; 22: 259–266) and will be presented in the symposium.

Policy of full disclosure: Prof. Kasper has received grant/research support from Bristol Myers-Squibb, Eli Lilly, GlaxoSmithKline, Lundbeck, Organon, Sepracor and Servier; he has served as a consultant or on advisory boards for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen, Lundbeck, Merck Sharp and Dome (MSD), Novartis, Organon, Pfizer, Schwabe, Sepracor, and Servier; and he has served on speakers' bureaus for Angelini, AstraZeneca, Bristol Myers-Squibb, Eli Lilly, Janssen, Lundbeck, Neuraxpharm, Pfizer, Pierre Fabre, Schwabe, Sepracor, and Servier.

S-16-003 Potential of mGlu2/3 receptor antagonists for treatment-resistant depression: An alternative to ketamine

S. Chaki. *Taisho Pharmaceutical Co. Ltd, Discovery Pharmacology, Saitama, Japan*

Objective: Ketamine, a non-competitive NMDA receptor antagonist, has been demonstrated to exert rapid and sustained antidepressant effects for patients with depression including treatment-resistant depression (TRD). However, a number of adverse effects including psychotomimetic symptoms and neurotoxicity preclude routine use of ketamine, and alternatives to ketamine are needed. Metabotropic glutamate (mGlu) 2/3 receptors are distributed in brain regions related to emotion and affect where they have important roles in regulating glutamatergic tone, suggesting that mGlu2/3 receptors may be implicated in pathophysiology of depression. Therefore, we investigated antidepressant potential of mGlu2/3 receptor antagonists, and compared their effects with those of ketamine.

Methods: The effects of mGlu2/3 receptor antagonists such as MGS0039 and LY341495 were examined in animal models of depression. Moreover, the neuronal mechanisms through which mGlu2/3 receptor antagonists exert antidepressant effects were examined, and compared with those of ketamine.

Results: mGlu2/3 receptor antagonists exerted antidepressant effects in some animal models of depression, which sustained for at least 24 hrs. Antidepressant effects of mGlu2/3 receptor antagonists were attenuated by NBQX (an AMPA receptor antagonist), K252a (a TrkB inhibitor) and rapamycine (an mTOR inhibitor), indicating that mGlu2/3 receptor antagonists exerts antidepressant effects through stimulation of AMPA

receptor-BDNF-mTOR signaling, and shared similar neuronal mechanisms with ketamine. In addition, mGlu2/3 receptor antagonists increased serotonergic and dopaminergic transmission in the medial prefrontal cortex and nucleus accumbens shell, respectively, through AMPA receptor stimulation, which may also be involved in the antidepressant effects of the compounds. Moreover, mGlu2/3 receptor antagonists, like ketamine, exhibited antidepressant effects in animal models, which are refractory to currently used antidepressants. In contrast, mGlu2/3 receptor antagonists, unlike ketamine, did not increase locomotor activity at doses which show antidepressant effects.

Conclusion: These results suggest that mGlu2/3 receptor antagonists may be an alternative approach to treating patients with TRD.

Policy of full disclosure: None.

S-16-004 Neurochemical and behavioral effects of vagal nerve stimulation

A. Frazer[1], A. Shah[1], F. Carreno[1]. [1]*UTHSCSA, San Antonio, USA*

Objective: Therapies for treatment resistant depression include vagal nerve stimulation (VNS), already approved in several countries, and ketamine which blocks glutamatergic N-methyl-D-aspartate (NMDA) receptors and produces rapid effects. The objective of our study was to compare effects produced by VNS and ketamine with those caused by traditional antidepressants such as desipramine (DMI) or sertraline on neurochemical and behavioral parameters.

Results: Traditional antidepressants phosphorylated two sites on Trkb, the receptor for the neurotrophin BDNF. Both VNS and ketamine phosphorylated these sites also as well as an additional site on TrkB that is linked to activation of PI3 K. To examine the role of TrkB phosphorylation in behavioral effects of the antidepressants, use was made of K252a, which prevents the autophosphorylation of TrkB. Chronic intraventricular administration of K252a blocked the phosphorylation of TrkB caused by either VNS or DMI. Its administration also prevented the anxiolytic-like effect of chronic VNS shown using the novelty-suppressed feeding test (NSFT). By contrast, chronic administration of K252a did not prevent either the anxiolytic-like effect of DMI in the NSFT or its antidepressant-like effect in the forced swim test (FST). A single injection of ketamine had antidepressant-like effects in the FST measured either 30 min or 7 days later. Ketamine caused phosphorylation of TrkB, but this effect was relatively transient, seen 30 min after its administration but not after 7 days. K252a, administered directly into the ventral hippocampus (vHipp), was able to prevent the transient increase in TrkB phosphorylation caused by ketamine as well as its positive effects in the FST 7 days later.

Conclusion: Thus, ketamine's prolonged behavioral effect is prevented by blocking its ability to cause an early and transient increase in TrkB phosphorylation in the vHipp. Behavioral effects of VNS and ketamine may be dependent upon activation of TrkB whereas this may not be so for traditional antidepressants.

Policy of full disclosure: Previously, Dr. Frazer has received financial support both as a consultant and in the form of a grant from Cyberonics, Inc., the manufacturer of the VNS stimulation device.

S-17. Novel glutamatergic treatment approaches for schizophrenia: Pharmacology, imaging and clinical trials

S-17-001 Challenges for novel treatment approaches in schizophrenia

G. Gründer. *RWTH Aachen University, Aachen, Germany*

Objective: Drug development for CNS disorders has been in a crisis for more than two decades. New treatments with truly novel mechanisms of action are lacking, and several large pharmaceutical companies stopped their programmes for CNS disorders. A huge number of experimental drugs failed in late stage development. Glutamatergic compounds represent one of the most promising approaches to address the unmet needs of schizophrenia treatment.

Results: Reasons for the lack in innovation might be 1) the search for drugs that are directed against all different psychopathological dimensions (positive, negative, affective, cognitive) of schizophrenia, 2) the lack of biomarkers for subtyping of schizophrenia, 3) study designs that neglect the biological heterogeneity of this group of disorders, and 4) the lack of outcome parameters that are related to long-term outcome.

Conclusion: Here we propose that the goal of drug research should be to develop different compounds for the different dimensions of schizophrenic psychopathology to allow for a "rational polypharmacy". This is directly linked to the establishment of new outcome measures that reflect long-term functional outcome. However, this will only be possible with new study designs that account for patient heterogeneity and the chronic nature of the diseases.

Policy of full disclosure: Gerhard Gründer has been on advisory boards, acted as consultant, has been on the speaker's bureau and received grant support from the following companies: Cheplapharm, Eli Lilly, Gedeon Richter, Lundbeck, Roche, Servier, Takeda.

S-17-002 The pharmacological basis for novel glutamatergic treatments

D. C. Javitt. *Columbia University, New York, USA*

Objective: Disturbances in N-methyl-D-aspartate receptor (NMDAR) function contribute to schizophrenia (Sz) and are indexed by objective neurophysiological disturbances. Agents such as glycine and D-serine bind to an allosteric regulatory site of the NMDA receptor complex and may be therapeutically beneficial in Sz.

Methods: Two recent studies were conducted with 60 mg/kg/d (~4 g/d) D-serine. Study 1 investigated D-serine effects (4–6 wks) on neurophysiological biomarkers including MMN and visual P1 in 35 stabilized, chronic Sz subjects, along with PANSS symptoms and MCCB neurocognitive function. Study 2 investigated D-serine effects (16-wk) on prodromal symptoms in 44 individuals at clinical high risk (CHR) for Sz based on SIPS/SOPS criteria.

Results: Study#1: D-serine patients showed a significant (8.5±13.2%) decline in PANSS symtpoms vs. placebo, along with a small but significant improvement in MCCB composite score. Significant improvements were also observed for MMN ($p=0.044$) and visual P1 ($p=0.043$, $d=0.67$). Study#2: a highly significant ($p=0.03$; $d=0.68$) 35.7±17.8% reduction was observed in effect was observed on SOPS negative symptoms. Furthermore, >20% improvement was observed in 9/10 subjects who completed all 16 weeks of treatment vs. only 5/11 placebo patients ($p=0.023$). A 30.9±14.9% reduction was observed on total symptoms that approached significance ($p=0.07$, $d=0.67$).

Conclusion: These are the first double-blind studies of D-serine at a dose of 60 mg/kg. Although magnitude of symptoms improvement was small in chronic patients, objective effects were observed on brain function including improvements in both auditory and visual neurophysiological measures. Moreover, in prodromal patients, robust improvements in symptoms were observed, suggesting that NMDAR-based interventions may be most effective when applied early in the course of Sz.

Policy of full disclosure: Supported by NIMH grant U01 MH074356. The author holds intellectual property rights for treatment of schizophrenia with D-serine.

S-17-003 Characterization of novel glutamatergic treatments with PET imaging

D. F. Wong. *Johns Hopkins Medical Institute, Baltimore, USA*

Despite the hypotheses of NMDA receptor hypofunction and low cortical glutamate in the pathophysiology and treatment of schizophrenia (SZ); there has been only recent progress in imaging biomarkers and treatment trials. This presentation will describe recent events in imaging and potential treatment of two specific glutamatergic targets, mGluR5 and GlyT1. There has been a confluence of PET imaging potential biomarkers and clinical trials involving mGluR5 drugs primarily Negative Allosteric Modulators (NAM) that inhibits the efficacy and/or affinity of the orthostatic magnet and may have clinical applications in addiction and depression and fragile X. There is also a parallel development in Positive Allosteric Modulators (PAMs) which may have applications in SZ. In parallel a number of PET radioligands labeled [11C] and [18F] have been developed and applied to human imaging. [11C]ABP688 and more recently [18F]FPEB have shown considerable utility in imaging studies of various neuropsychiatric disorders. Occupancy studies using NAMs in current clinical trials will be demonstrated. The second focus of imaging and therapeutic interest is the glycine transporter (GlyT1) with inhibitors that are currently in clinical trials for SZ. This is an attractive target because it is an alternative way of increasing glutamate in cortex which may be much more effective than the direct administration of glutamatergic drugs. We will document the development of human GlyT1 PET radioligands developed for non-human primate and human studies and show how one in particular was used for occupancy studies in pre-clinical and Phase I. These studies will demonstrate that there is a good correlation between pre-clinical animal models and early SZ efficacy studies with a mid-range of occupancy of one particular GlyT1 compound using a specific human PET radioligand, in healthy humans. Thus, the development of

PET radioligands for neuropsychiatric and occupancy studies for target engagement, together with the growing number of mGluR5 and GlyT1 inhibitors, opens new opportunities for SZ treatment.

Policy of full disclosure: Dean F. Wong, M.D., Ph.D. Disclosure of the existence of any significant financial interest or other affiliation with a funding organization or with a commercial supporter of the session and/or provider of commercial services. Below is the declaration of relationship to the funding agencies: Roche Investigator Research funding through JHU contracts Novartis Investigator Fenoban drug received for research studies Merck Investigator Radiopharmaceutical precursor received for research studies NIH Investigator Research grants.

S-17-004 Clinical results with novel glutamatergic treatments

D. Umbricht. *F. Hoffmann La Roche Ltd., Basel, Switzerland*

Despite progress in our understanding of the genetics and the neurobiology of schizophrenia, an array of psychosocial interventions and effective antipsychotic pharmacotherapy, the long-term disability of patients with schizophrenia remains high. Over the last two decades the search for alternative therapeutic approaches beyond D2 antagonists has focused on the glutamate system. Several lines of evidence implicate N-methyl-D-aspartate (NMDA) receptor hypofunction as a factor underlying many symptoms of schizophrenia, in particular negative symptoms. In recent years various pharmacological approaches to normalizing NMDA receptor function have been tested including glycine reuptake inhibitors (GRI) and N-acetyl cysteine (NAC). GRIs are assumed to increase NMDA function by increasing intrasynaptic concentrations of glycine – a mandatory coagonist at the NMDA receptor. Two GRIs – bitopertin and ORG25935 – have recently been tested in proof-of-concept studies in which patients with predominant negative symptoms of schizophrenia received adjunctive treatment with the respective GRI for 8 and 12 weeks, respectively. While 8 week treatment with bitopertin led to a significant amelioration of negative symptoms, ORG25935 treatment was not associated with a significant improvement over placebo. However, closer inspection of the results indicate that the magnitude of observed effects were comparable to the effects of bitopertin lending support for glycine reuptake inhibition as a viable treatment of negative symptoms. In addition, two proof-of-concept studies evaluated adjunctive treatment with NAC in patients with schizophrenia. NAC is assumed to increase deficient glutathione levels which can induce NMDA hypofunction in preclinical models. In both studies treatment with NAC was associated with significant improvement, in particular of negative symptoms. Thus, the available evidence supports the hypothesis that normalizing NMDA hypofunction leads to an amelioration of negative symptoms in schizophrenia. In the presentation the results of these studies will be reviewed in detail. Challenges and promises of these therapeutic approaches will be discussed.

Policy of full disclosure: I am an employee of F.Hoffmann-La Roche, Ltd.

S-18. Breakthroughs in psychopharmacology for prevention and treatment of PTSD

S-18-001 Three decades of research in circuits and receptor systems in PTSD

E. Vermetten. *University Medical Center Utrecht, Utrecht, Netherlands*

Objective: Three decades of PTSD research have placed it well on the map. PTSD is a young disorder that started being properly understood only from 1980 with incorporation in DSMIII in which it was acknowledged that exposure to traumatic events can lead to long term psychopathology.

Methods: The biological framework is based on the concepts of stress sensitization, fear conditioning as well as failure of inhibition. After the decade of the hippocampus we have seen a shift to the decade of the amygdala in the new milennium. Given the specific role of the prefrontal cortex in (neuro) psychological functions in patients with PTSD (i.e. attention and cognitive interference), the interest in the role of the prefrontal cortex has increased significantly.

Results: Evidence for neurobiological dysfunction in PTSD, such as dysregulation of both main arms of the stress response system, the HPA axis and the LC-norepinephrine system, as well as dysfunctional responses of other neurotransmitter systems, including serotonergic, GABA, and glutamate, suggest an opportunity for pharmacotherapeutic interventions; however, data obtained from RCTs thus far suggest limited efficacy.

Conclusion: There are no specific drugs for PTSD, except for the treatment of irritability and depressive features with SSRI. Atypical neuroleptics have been more recently been introduced as well as mood stabilizers. Other options are specific serotonergic agents such as 5-HT 1A antagonists, NA-blockers, CRF antagonists, GC-receptor antagonists, prazosin and α1-adrenergic blocker with nightmares, use of β-blockers early after trauma exposure are investigated. The last few years two windows of opportunity to reduce fear memories can be defined as 'golden hours' in treatment of PTSD symptoms: event-based golden hours and exposure-based golden hours. New treatment options such as D-cycloserine and cortisol seem to offer opportunities to influence memory consolidation of traumatic experiences in timed relation to exposure.

Policy of full disclosure: None.

S-18-002 New insights into secondary prevention in PTSD

J. Zohar. *Sheba Medical Center, Tel Aviv, Israel*

Objective: Current psychopharmacological interventions in PTSD are administrated to the patients once PTSD diagnosis is well established (i.e. at least several months after the exposer to the traumatic event). The well-established medical concept of "Golden Hours" is increasingly became a focus in PTSD research since the time the symptoms have unset (the exposure to trauma) could be clearly detected. Data from animal study suggests that hypo-reactive hypothalamic–pituitary–adrenal (HPA) axis may be associated with increased venerability to PTSD. The objective of the present study was to examine early intervention with a single shot of hydrocortisone in the "Golden Hours" in humans.

Methods: 25 patients with acute stress symptoms were administered a single intravenous bolus of high-dose hydrocortisone (100–140 mg) or placebo within 6 hours of a traumatic event in a prospective, randomized, double-blind, placebo-controlled pilot study. They have followed up at 2 weeks, one month, and 3 months.

Results: The hydrocortisone and placebo groups did not differ significantly on any of the demographic measures such as age, gender, marital status, education or on any clinical characteristics. Early single high doze hydrocortisone intervention attenuated the core symptoms of both the acute stress and of subsequent PTSD in patients, as measured by clinicians administrated PTSD scale (CAPS). (Using the CAPS total scores, participants treated with hydrocortisone exhibited significantly lower total CAPS score than those treated with placebo at the 2-week and 3-month follow-up assessments).

Conclusion: The results of these studies highlight the potential therapeutic value of an initial bolus of endogenous corticosteroids in the normative response to stress as a key to a return to homeostasis. The data provides initial evidence that a single dose of hydrocortisone administered in the acute aftermath of trauma promotes recovery. The current finding suggests that a further evaluation of a single high dose hydrocortisone treatment as a potential option for secondary intervention of stress related clinical disorders is warranted.

Policy of full disclosure: Joseph Zohar has received grant/research support from Lundbeck, Servier and Pfizer, has served as a consultant or on advisory boards for Servier, Pfizer, Abbott, Lilly, Actelion, AstraZeneca and Roche, and has served on speakers' bureaus for Lundbeck, Roch, and Abbott.

S-18-003 Update on the use of alpha-1 adrenoreceptor antagonists for PTSD

M. Raskind. *University of Washington, VA Puget Sound Health Care Sys., Seattle, USA*

Objective: Increased CNS noradrenergic activity contributes to the pathophysiology of PTSD, possibly by increased postsynaptic adrenoreceptor (AR) responsiveness to norepinephrine. Prazosin, a CNS active alpha-1 AR antagonist, has been demonstrated effective for treatment refractory trauma nightmares and sleep disruption in several placebo controlled trials. Here we evaluated prazosin in active duty US combat soldiers with PTSD and frequent trauma nightmares. The authors conducted a 15-week randomized controlled trial of the alpha-1 adrenoreceptor antagonist prazosin for combat trauma nightmares, sleep quality, global function, and overall symptoms in active-duty soldiers with posttraumatic stress disorder (PTSD) returned from combat deployments to Iraq and Afghanistan.

Methods: Sixty-seven soldiers were randomly assigned to prazosin or placebo for 15 weeks. Drug was titrated based on nightmare response over 6 weeks to a possible maximum dose of 5 mg midmorning and 20 mg at bedtime for men and 2 mg midmorning and 10 mg at bedtime for women. Mean achieved bedtime doses were 15.6 mg of prazosin

(SD=6.0) and 18.8 mg of placebo (SD=3.3) for men and 7.0 mg of prazosin (SD=3.5) and 10.0 mg of placebo (SD=0.0) for women. Mean achieved midmorning doses were 4.0 mg of prazosin (SD=1.4) and 4.8 mg of placebo (SD=0.8) for men and 1.7 mg of prazosin (SD=0.5) and 2.0 mg of placebo (SD=0.0) mg for women. Primary outcome measures were the nightmare item of the CAPS, the Pittsburgh Sleep Quality Index, and the CGIC. Maintenance psychotropic medications and supportive psychotherapy were held constant.

Results: Prazosin was effective for trauma nightmares, sleep quality, global function, total CAPS score and hyperarousal cluster. Prazosin was well tolerated.

Conclusion: Prazosin is effective for combat-related PTSD with trauma nightmares in active-duty soldiers, and benefits are clinically meaningful.

Policy of full disclosure: None.

S-18-004 Does the endocannabinoid system provide a new avenue for treatment development in PTSD?

A. Neumeister. *New York University, School of Psychiatry and Radiology, New York, USA*

Objective: To date, drug development in posttraumatic stress disorder (PTSD) has been opportunistic, building almost exclusively on empirical observations with drugs approved for other indications. there have been increasing efforts to unravel the neurobiological mechanisms that underlie the symptom development in PTSD in order to provide an evidence-based approach in generating the next generation of PTSD treatments and possible PTSD prevention.

Methods: Patients with PTSD and controls with (TC) and without (HC) trauma histories participated in a single magnetic resonance imaging scan and a positron emission tomography (PET) study under resting conditions with the novel, CB1 receptor-specific radiotracer [11C]OMAR. Peripheral levels of anandamide and cortisol levels were collected on the day of the imaging studies in all participants.

Results: In PTSD, we found brain-wide upregulation of CB1 receptors in a stress circuit that is routinely involved in PTSD. These alterations were associated with increased stress sensitivity and increased anxiety. Peripheral reductions in anandamide levels suggest a lower endocannabinoid tone in PTSD.

Conclusion: Despite their potential therapeutic value, direct-acting CB receptor compounds have very limited medical applications, mainly because of their undesirable psychotropic side effects and liability to cause addiction. In contrast, blocking eCB deactivation or eCB uptake may lead to a more circumscribed and beneficial spectrum of biological responses than those produced by direct CB1 receptor activation.

Policy of full disclosure: None.

S-19. The psychopharmacology of aggression: From biomarkers to therapeutics

S-19-001 Genetic determinants in aggression

K.-P. Lesch. *School of Mental Health and Neuroscience (MHENS), Department of Neuroscience, Maastricht, Netherlands*

Objective: The expression of aggressiveness, which constitutes many facets of behavior, is influenced by a complex interaction of biologic, psychologic, and social variables. Even though individual differences in impulsivity and the behavioral consequences, including externalized or inwardly directed aggression are substantially heritable, they ultimately result from an interplay between genetic variation and environmental factors. The molecular mechanisms by which e.g. early-life adversity increases impulsive/aggressive behavior in adolescence and adulthood is likely to include epigenetic programming of risk gene expression in conjunction with modulation of neural plasticity.

Methods: While formation and integration of multiple neural networks is dependent on the actions of neurotransmitters, such as serotonin (5-HT), converging lines of evidence indicate that (epi)genetically determined variability in 5-HT system-regulating gene expression influences impulsivity and inappropriately violent behavior. Based on the remarkable progress in technologies that allow the alteration or elimination of individual genes to create transgenic animal models, gene modification strategies further increase our knowledge about which genes are involved in behavioral traits.

Results: This overview focuses on mouse models which have been modified by deletion of genes coding for key players of 5-HT neurotransmission. In particular, phenotypic changes in mice bearing inactivation mutations of 5-HT1A and 5-HT1B receptors, 5-HT neuron-specific transcription factor Pet1, tryptophan hydroxylase-2, 5-HT transporter, and monoamine oxidase A, and genes related to 5-HT signaling will be discussed and major findings highlighted.

Conclusion: Although special emphasis is given to the molecular psychobiology of 5-HT in aggression-related behavior in rodents, nonhuman primates, and humans, relevant conceptual and methodological issues in the search for candidate genes for impulsivity and aggression and for the development of mouse models of aggressive and antisocial behavior in humans are also considered.

Policy of full disclosure: None.

S-19-002 Biomarkers in aggressive behavior

S. Comai[1], A. Bertazzo[2], J. Vachon[3], G. Côté[3], G. Gobbi[4]. [1]*Department of Psychiatry, McGill University, Montreal, Canada;* [2]*University of Padua, Padua, Italy;* [3]*Institut Philippe-Pinel, Montreal, Canada;* [4]*McGill University, Montreal, Canada*

Objective: Aggressive behavior is a major concern in social and criminal justice settings and also in mental health. To date it is known that impairments in the serotonin (5-HT) system, but also imbalances in the levels of trace elements are implicated in the neurobiology of aggression. However, it is still unknown at which level the 5-HT metabolic pathway is impaired in aggression as well as how trace elements are linked to aggression and mental disease.

Methods: Between January 2007 and March 2012, we collected a unique databank of 360 male prisoners from a federal penitentiary in Montreal in which we evaluated Axe I and Axe II disorders (SCID I and II), levels of impulsivity and aggression toward others and themselves, attention-deficit/hyperactivity disorder (ADHD) indices, and some biological correlates of aggressive behavior such the serum concentration of tryptophan (Trp), 5-hydroxytryptophan (5-HTP), 5-HT, kynurenine (Kyn), zinc, copper and cadmium

Results: Our preliminary results showed that aggressive prisoners had significant higher prevalence of mood disorders, drug abuse/dependence, and borderline, conduct and antisocial behaviors. In addition, they exhibited higher levels of impulsivity and CAARS indices, lower serum levels of Trp and Kyn but higher serum levels of 5-HT. A logistic regression analysis using psychiatric/psychological and biological variables indicated that antisocial behavior and the ratio 5-HT/Trp were predictors of prisoners with aggressive behavior. Moreover, we found that zinc was linked to personality disorders and addictions, but not directly to aggression.

Conclusion: This study suggests that not only impulsivity but also adult ADHD indices are related to aggressive behavior. Noteworthy, it shows that peripheral markers related to the 5-HT pathway are significantly altered in aggressive behavior and discriminate aggressive vs. non-aggressive prisoners.

Policy of full disclosure: None.

S-19-003 Mood stabilizers in aggression: Basic and clinical research

G. Gobbi. *McGill University, Montreal, Canada*

Objective: In the last ten years a major change has occurred in the treatment of aggression. The introduction of novel atypical antipsychotics/mood stabilizers into the market and the prevalent use of anticonvulsants and lithium in clinical psychiatry have completely changed the therapeutic approach used to treat aggressive patients. The purpose of this study has been to examine the recent advancements in the treatment of aggression by integrating pharmacological findings on mood stabilizers from clinical research with neurobiological knowledge gained from basic science research. This translational approach is necessary, as the results of clinical trials alone are limited in utility by the complexity of aggressive behavior.

Methods: Relevant clinical studies were identified by searching PubMed using the names of the putative drugs (belonging to the family of atypical antipsychotics and anticonvulsants as well as lithium) along with the keywords "aggression," "hostility," and "agitation". Studies were selected if they reported on the effects of the target drugs on measures of aggression, hostility, or agitation. Dementia-associated aggression was excluded, as its etiology has a distinct neurobiological basis. Basic research studies focusing on the pharmacological targets of mood stabilizers, mainly serotonin, dopamine, norepinephrine, GABA, glutamate and ion channels, and their role in the etiopathogenesis of aggressive behavior were also collected using PubMed.

Results: The neurobiology of aggressive behavior is complex and multifactorial including different neurotransmitters and a large spectrum of membrane receptors, ion channels, intracellular elements and epigenetic/genetic mechanisms. Consequently, the association of atypical antipsychotics with antiepileptics and/or lithium which allows targeting several different cellular and intracellular pharmacological sites might represent the

actual most valid therapeutic strategy for the treatment of aggressive patients.

Conclusion: Additional randomized, double-blind clinical trials are needed to confirm the clinical efficacy of the combination of mood stabilizers in the treatment of aggression.

Policy of full disclosure: Dr Gobbi has been a speaker for Eli Lilly and Merck, and has received grant/honoraria from GlaxoSmithKline, Merck, and AstraZeneca in the past.

S-19-004 Atypical antipsychotics for the management of agitation and aggression: An update

L. Citrome. *New York Medical College, Clinical Professor of Psychiatry & Behavioral Sciences, Suffern, USA*

Objective: To review the current evidence supporting the use of atypical antipsychotics for the management of agitation and aggression.

Methods: Literature review, with emphasis on randomized controlled trials.

Results: The etiology of aggressive behavior is multifactorial and can be driven by psychosis, impulsivity, psychopathy, intoxication, cognitive impairment, or a combination of all of these. Recognition of the different factors behind the aggression can inform medication selection and the relative need for specific environmental and behavioral interventions in hospitals and forensic psychiatric settings. Atypical antipsychotics have supplanted the use of older agents and have substantial advantages in terms of avoiding dystonic reactions and akathisia. Effect sizes for the relief of agitation are comparable with that of intramuscular haloperidol. Using the a priori definitions of response at 2 hours after first administration, NNT for response vs. placebo (or placebo equivalent) in treating agitation for the pooled data at the recommended dose of ziprasidone 10–20 mg was 3 (95% CI=2 to 4), for olanzapine 10 mg was 3 (95% CI=2 to 3), and for aripiprazole 9.75 mg was 5 (95% CI=4 to 8). Similarly, the NNT for response vs. placebo for haloperidol 6.5–7.5 mg was 4 (95% CI=3 to 5). In contrast to agitation associated with schizophrenia or bipolar mania, no agents have yet been approved by regulatory authorities for the treatment of persistent aggressive behavior. However, some atypical antipsychotics, such as clozapine and olanzapine, appear to have specific anti-hostility effects over time, as evidenced in specifically designed randomized controlled trials and in post hoc analyses of large effectiveness studies such as CATIE and EUFEST.

Conclusion: Several atypical antipsychotics have regulatory approval for the treatment of agitation. Although not approved for persistent aggressive behavior, clozapine and olanzapine demonstrate specific anti-hostility effects.

Policy of full disclosure: In the past 12 months, L. Citrome, was a consultant for, has received honoraria from, or has engaged in collaborative research supported by the following: Alexza, Alkermes, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Envivo, Forest, Genentech, Janssen, Lundbeck, Merck, Mylan, Novartis, Noven, Otsuka, Pfizer, Reckitt Benckiser, Reviva, Shire, Sunovion, and Takeda.

S-20. Remodeling synaptic connections in the pathophysiology and treatment of depression

S-20-001 Synaptic plasticity of reward circuitry in stress-related disorders and antidepressant responses

S. Russo. *Mount Sinai School of Medicine, New York, USA*

Objective: Chronic social defeat stress induces changes in nucleus accumbens (NAc) excitatory synaptic plasticity that contributes to the expression of depression- and anxiety-like behavior.

Methods: Using a series of retrograde expressing Cre viruses and conditional channel rhodopsin, we have defined differential roles of prefrontal cortical versus thalamic glutamatergic inputs to the NAc in controlling stress-induced depression-like behavior.

Results: Stimulation of thalamo-striatal glutamate inputs promotes depression-like behavior while stimulation of cortico-striatal inputs has limited effects. Silencing the thalamo-accumbal circuits using genetically encoded pre-synaptic voltage gated Ca+ channel toxins prevents stress-induced depression-like behavior while silencing the cortico-accumbal inputs promotes depression-like behavior.

Conclusion: Our data identifies specific roles for glutamatergic inputs to the NAc, suggesting that there is a very complex relationship between the input and the resulting behavioral and cellular response to stress.

Policy of full disclosure: None.

S-20-002 Cell genesis and dendritic plasticity: A neuroplastic pas de deux in the onset and remission from depression

N. Sousa. *University of Minho, Braga, Portugal*

The ability to set an appropriate response to stimuli through dynamic rearrangements of synapto-dendritic networks, as well as by regulating the generation of new neuronal and glial cells, renders the brain highly mutable. These phenomena, collectively known as neuroplasticity, are critical to promote the neuronal adaptations; its failure is now increasingly considered to be a major component in many neuropsychiatric conditions. Among these, depressive spectrum disorders are a paradigmatic example of the importance of neuroplastic alterations in the adult brain. In this talk a comprehensive picture of the effects of stress, a major trigger factor in depression, in the (de)regulation of neuroplasticity will be provided; the latter is, in turn, related to the emergence of physiological and behavioral alterations comprised in the symptomatic profile of depressive disorders. While these molecular and physiological mechanisms regulating neuroplastic processes are relevant for the onset of depressive symptoms, they also proved to be implicated in the action of antidepressants. So far, and although there is still much to be elucidated, it is becoming increasingly evident that the triad stress-neuroplasticity-depression constitutes ground for new findings and discoveries.

Policy of full disclosure: The author has no conflict of interest.

S-20-003 TRKing the neurobiological mechanisms of conventional and rapid-acting antidepressants

T. Rantamäki. *University of Helsinki, Neuroscience Center, Helsinki, Finland*

Previous studies show that conventional monoaminergic antidepressant drugs slowly reactivate developmental-like of plasticity in the adult brain. Long-term molecular and functional alterations in interneuron maturation and subsequent changes in excitation-inhibition balance are thought to critically underlie this antidepressant-induced plasticity. Most importantly, when combined with appropriate rehabilitation, this induced plasticity allows rewiring of neuronal networks with functional and behavioral consequences. Remarkably, some medications that primarily target brain excitation-inhibition mechanisms have been shown to produce rapid amelioration of depressive symptoms. Interestingly, activation of BDNF (brain-derived neurotrophic factor) receptor TrkB is associated with the neuroplastic and therapeutic actions of both conventional – gradually acting – antidepressants (e.g. fluoxetine) as well as rapid-acting antidepressants (ketamine, isoflurane). Understanding the short- and long-term neurobiological effects of diverse antidepressant treatments on TrkB signaling, synaptic plasticity and neuronal network function is important for future attempts to develop novel rapid-acting and more effective antidepressant therapies with sustained clinical benefits.

Policy of full disclosure: T.R. has received research support from Orion Pharma, Hermo Pharma and Ono Pharmaceuticals.

S-20-004 Synaptic homeostasis in the etiology and treatment of depression

R. Duman. *Yale University, School of Medicine, New Haven, USA*

Objective: Basic research studies have demonstrated that stress causes neuronal atrophy, characterized by decreased dendrite branching and reduced numbers of spine synapses in brain regions implicated in depression, notably the prefrontal cortex (PFC) and hippocampus. These effects of stress could contribute to the reduced volume of PFC and hippocampus that has been observed in depressed patients. Recent studies have examined the molecular mechanisms underlying these effects, as well as the ability of rapid acting antidepressants (i.e., ketamine) to increase synaptic connections and block the effects of stress.

Methods: The mTORC1 signaling pathway controls translation of synaptic prorteins and plays a role in synaptogenesis. We have examined tthe effects of chronic stress and ketamine on mTORC1 signaling, the number and function of spine synapse in PFC neurons, and behavior in models of depression.

Results: We have found that ketamine causes a rapid induction of synaptogenesis and spine formation in the PFC via stimulation of mTORC1 signaling and increased synthesis of synaptic proteins. This effect is driven by stimulation of glutamate-AMPA receptors and activity dependent release of BDNF. These effects rapidly reverse the atrophy of PFC neurons caused by chronic stress and underlie the rapid antidepressant behavioral responses to ketamine. We have also found that the neuronal atrophy caused by stress occurs, in part via inhibition of mTORC1 and synaptogenesis, and is mediated by increased expression of REDD1, an inhibitor of mTORC1 signaling.

Conclusion: The results demonstrate that neuronal atrophy is caused by inhibition of synaptic protein synthesis. Conversely the rapid acting antidepressant ketamine stimulates activity dependent induction of protein synthesis, increases synapse formation, and rapidly reverses the deficits caused by chronic stress. This remodeling of synaptic connections restores homeostatic balance of depression related circuits that are essential for control of mood and emotion, and thereby underlies the rapid antidepressant responses to ketamine.

Policy of full disclosure: Dr. Duman is a consultant and/or receives research funds from Taisho, Sunovion, Lundbeck, Forest, Johnson & Johnson, Naurex, and Lilly.

KS-01. Korean Session: Neural basis of poor social functions in schizophrenia

KS-01-001 Mismatch negativity, theory of mind, neurocognition, and functional outcomes in patients with schizophrenia

S.-H. Lee. *Inje University Ilsan Paik Hospital, Republic of Korea*

Objective: Mismatch negativity (MMN) is known to be associated with neurocognition, social cognition, and functional outcomes. The present study explored the relationships of MMN with neurocognition, theory of mind, and functional outcomes in patients with schizophrenia, the first-degree relatives of patients with schizophrenia, and healthy controls.

Methods: Twenty-five patients with schizophrenia, 21 first-degree relatives of patients with schizophrenia, and 29 healthy controls were recruited. We examined symptom severity, neurocognition, theory of mind, functional outcomes, and the MMN.

Results: Mismatch negativity amplitudes decreased in order of patients with schizophrenia, then first-degree relatives, then healthy controls. Mismatch negativity amplitude was significantly correlated with measures of neurocognition, theory of mind, and functional outcome measurements in patients with schizophrenia. However, the most powerful correlations were those between MMN in the frontal region and measures of functional outcomes. The power and frequency of the correlations were weaker in first-degree relatives and healthy controls than in patients with schizophrenia.

Conclusion: Hierarchical regression analysis revealed that functional outcomes (relative to measures of neurocognition and theory of mind) constituted the most powerful predictor of mismatch negativity. Our results suggested that mismatch negativity reflects functional outcomes more efficiently than do measures of neurocognition and theory of mind in patients with schizophrenia.

Policy of full disclosure: None.

KS-01-002 Neural basis of deficits in emotional experience and expression in schizophrenia

J. S. Lee. *Bundang Jesaeng Hospital, Republic of Korea*

Objective: Previous researches have revealed deficits in emotional experience and expression in schizophrenia. Neuroimaging studies in patients with schizophrenia indicate regional brain activation abnormalities are related to the deficits in emotional experience and expression.

Methods: Data from our laboratory and other research groups using neuroimaging will be presented.

Results: For emotional experience, neuroimaging studies about current pleasant feelings in schizophrenia demonstrated deficient activation in limbic/paralimbic regions (e.g., nucleus accumbens, amygdala and hippocampus), while studies about non-current feelings showed additional deficits in the default-mode network (e.g., medial prefrontal cortex, precuneus and posterior cingulate cortex). For emotional expression, previous neuroimaging studies using indirect approaches like emotional appraisal or experience found that more severe blunted affect was correlated with higher amygdala and parahippocampal activities, whereas a recent study using a direct approach like facial expression showed that functional disturbance of the mirror neuron system was related to the severity of blunted affect.

Conclusion: An underrecruitment of limbic/paralimbic regions, accompanied by limited activations in the default-mode network or mirror-neuron system may play an important role in deficits in emotional experience and expression in patients with schizophrenia.

Policy of full disclosure: None.

KS-01-003 Cortical thinning and disrupted structural connectivity in medial prefrontal region associated with theory of mind and social functioning in first-episode psychosis

T. Y. Lee[1], J. S. Kwon[1], W. H. Jung[2], J. W. Hur[1], J.-Y. Yun[1], S. N. Kim[1], J. H. Jang[1], D.-H. Kang[1]. *[1]Seoul National University, Seoul, Republic of Korea; [2]University of Pennsylvania, Philadelphia, USA*

Objective: Decreased performance in theory of mind, the ability to attribute mental states to oneself and others, is considered as the core contributor of the poor psychosocial functioning in patients with schizophrenia. Recent evidence suggests that the medial prefrontal cortex (mPFC) has a special role in social cognition. However, relationship between theory of mind, social functioning, and the cortical thickness and structural connectivity in the mPFC has not been fully understood.

Methods: This study included 34 first-episode psychosis (FEP) patients and 34 age and gender-matched healthy controls (HCs). False-belief, story task and social functioning scale were employed to assess theory of mind performance and social functioning, respectively. For investigate the white matter (WM) connectivity, the seed regions of interest was given in the medial orbitofrontal cortex (mOFC) and rostral anterior cingulate cortex (rACC) of mPFC. Differences in cotical thickness and WM connectivity between the two groups were assessed. Further correlational analyses were examined between measures of false-belief, story task and social functioning scale and cortical thickness and WM connectivity in regions showing significant differences.

Results: Patients with FEP showed lower scores of false-belief, story task and social functioning scale than HCs. The bilateral mOFC and left rACC thickness, left mOFC and bilateral rACC WM track numbers, and bilateral rACC WM track volume were decreased in patients with FEP compared with HCs. The scores of story task were positively correlated with the left rACC thickness and right rACC WM track numbers, respectively. There were positive correlations between scores of the all domains of social functioning scale and left rACC thickness, WM track volume, right rACC WM track number, respectively.

Conclusion: Our results suggest that decreased theory of mind performance and social functioning in FEP may reflect dysfunction of mPFC, which likely stems from both cortical thinning and disrupted WM connectivity.

Policy of full disclosure: None.

KS-01-004 Neurocognitive components of social impairments in schizophrenia

S. Park[1], K. Thakkar[2]. *[1]Vanderbilt University, Nashville, USA; [2]USA*

Objective: In the past two decades, cognitive impairments such as working memory deficits have become central to our understanding of the nature of this disorder but surprisingly little is known about the origins and consequences of these problems.

Methods: In a series of experiments, we examined generation, inspection and manipulation of mental representations (imagery) to identify the loci of difficulties that may contribute to working memory deficits. In another series of studies, we investigated one's ability to simulate and model other people's behavior to understand the role of mental representation and perspective taking in social understanding.

Results: The results from these studies indicate that in contrast to stable deficits in cognition overall, there exist surprising pockets of enhanced abilities in schizophrenia. Individuals with schizophrenia appear to show superior mental imagery generation, inspection and manipulation abilities in spite of their permanent working memory deficits. Moreover, their enhanced imagery ability extends to perspective taking and is related to a porous sense of the body boundary and self. Individuals with schizophrenia can put themselves in other people's shoes with ease and speed. Further investigation revealed that about half of outpatients with schizophrenia have experienced out-of-body phenomenon and that these disturbances of self may be associated with reduced social interactions and increased social isolation.

Conclusion: Taken together, these results depict a complex and richly contoured internal landscape of schizophrenia. Severe cognitive deficits coupled with superior abilities may lead to misperception, misinterpretation and miscalculation of the internal and external worlds and contribute to a subjective experience of unreality. This brings us back to the core nature of schizophrenia as the disorder of self, and highlights the importance of integrating the methods of cognitive neuroscience with the subjective phenomenology of the psychosis experience.

Policy of full disclosure: None.

Wednesday 25 June 2014

S-21. Personalized medicine in mood and anxiety disorders

S-21-001 Neurobiological consequences of child abuse

C. Nemeroff. *University of Miami, Miami, USA*

Genetic, brain imaging and neurotransmitter studies have revealed the long-term consequences of child abuse and neglect. These changes increase vulnerability to mood and anxiety disorders in adulthood. Exposure to trauma during childhood increases the risk of certain psychiatric disorders beyond the risk associated with adult violence exposure. We have demonstrated a number of long term neurobiological consequences of child abuse and neglect including structural and functional brain imaging changes, neuroendocrine and immune alterations. In particular, alterations in the hypothalamic-pituitary-adrenal (HPA) axis, a major mediator of the stress response, contribute to the long standing effects of early life trauma. However, not all exposed individuals demonstrate altered HPA axis physiology, suggesting that genetic variations influence the psychiatric consequences of trauma exposure. Variants in the gene encoding the CRF R1 receptor, FKBP5, PAC1 and others interact with adverse early environmental factors to predict risk for stress-related psychiatric disorders. These studies suggest molecular targets for new drug development, biological risk factors, and predictors of treatment response. In addition, the effect of abuse may extend beyond the immediate victim into subsequent generations as a consequence of epigenetic effects transmitted directly to offspring and/or behavioral changes in affected individuals. Recognition of the biological consequences and transgenerational impact of trauma has critical importance for both treatment research and public health policy.

Policy of full disclosure: Charles B. Nemeroff, M.D., Ph.D. Declaration of Financial/Propriety Interest 2011–2014 Monday, February 03, 2014 Research/Grants: National Institutes of Health (NIH) Consulting: Xhale, Takeda, SK Pharma, Shire, Roche, Lilly, Allergan, Mitsubishi Tanabe Pharma Development America, Taisho Pharmaceutical Inc., Lundbeck Stockholder: CeNeRx BioPharma, PharmaNeuroBoost, Revaax Pharma, Xhale, Celgene, Seattle Genetics, Abbvie Scientific Advisory Boards: American Foundation for Suicide Prevention (AFSP), CeNeRx BioPharma (2012), National Alliance for Research on Schizophrenia and Depression (NARSAD), Xhale, PharmaNeuroBoost (2012), Anxiety Disorders Association of America (ADAA), Skyland Trail Board of Directors: AFSP, NovaDel (2011), Skyland Trail, Gratitude America, ADAA Income sources or equity of $10,000 or more: PharmaNeuroBoost, CeNeRx BioPharma, NovaDel Pharma, Reevax Pharma, American Psychiatric Publishing, Xhale Patents: Method and devices for transdermal delivery of lithium (US 6,375,990B1) Method of assessing antidepressant drug therapy via transport inhibition of monoamine neurotransmitters by ex vivo assay (US 7,148,027B2) Speakers Bureau: None Honoraria: Various Royalties: Various Expert Witness: Various.

S-21-002 Advances in genomics and epigenetic biomarkers for vulnerability and treatment response in mood and anxiety disorders

E. Binder. *Max Planck Institute for Psychiatry, Munich, Germany*

Objective: Our current efforts in identifying reliable markers to stratify patients with mood and anxiety disorders into biologically relevant categories have so far not been highly successful. Here we will highlight approaches that combine genetic and environmental risk factors and epigenetic measures to identify subsets of patients that are likely biologically more homogeneous and may profit from similar treatment strategies.

Methods: DNA methylation, gene expression and genotyping, combined with endocrine and neuroimaging measures as well as information on antidepressant treatment response from different studies will be presented.

Results: Interaction of a specific functional polymorphism in the FKBP5 gene together with exposure to early trauma leads to epigenetic changes that further derepress the transcription of that gene. This interaction of two risk factors is on the one hand associated with a number of distinct psychiatric diagnoses, including depression, PTSD and psychosis. On the other hand, patients with this specific epigenetic profile represent a subgroup of patients with unique endocrine, gene expression and neuroimaging biomarkers. Preliminary evidence suggest that depressed patients with the FKBP5 risk allele and exposure to early trauma may preferentially respond to cognitive behavioral therapy (CBT). We will also present data from genome-wide genetic and epigenetic studies investigating pattern associated with differential antidepressive response to CBT vs. medication.

Conclusion: This series of studies highlights that identifying subgroups of patients using epigenetic measures and integrating genetic and environmental factors could be useful for more targeted treatment approaches that make use of pathophysiologic findings that can transcend current diagnostic categories.

Policy of full disclosure: None.

S-21-003 The role of inflammation in the pathophysiology of depression: Treatment implications

C. Pariante. *King´s College London, London, United Kingdom*

Objective: To review the evidence linking increased inflammation with (lack of) treatment response in major depression.

Methods: An overview of the most recent studies in this field, from us and others, with an emphasis on studies using inflammatory biomarkers as predictors of response to conventional antidepressants (SSRIs, tricyclics) as well as anti-inflammatory strategies (COX-inhibitors, cytokines blockers, omega-3 PUFAs).

Results: Consistent evidence across clinical trials and naturalistic studies confirms that increased inflammation is associated with a lack of response to conventional antidepressants. Suggestive evidence indicates that increased inflammation is associated with a better response to anti-inflammatories strategies.

Conclusion: Anti-inflammatory strategies are a promising therapeutic strategy in patients who have high inflammatory biomarkers and fail to respond to conventional antidepressants.

Policy of full disclosure: Professor Pariante has received research funding from companies interested in the use of anti-inflammatories in psychiatric disorders, such as Janssen; this amounts to approximately 5% of all of his research funding, which comes predominantly from governmental agencies and charities.

S-21-004 The contribution of HPA axis alterations in defining subtypes in depression: Genetic, endocrine and treatment studies

A. F. Schatzberg. *Stanford University, Stanford, USA*

Objective: To assess the role of HPA axis activity and genetic variation in the development of psychosis and cognitive impairment in the context of major depression.

Methods: Approximately 135 subjects (1/3rd each major depression severe without psychotic features – NPMD, major depression with psychotic features – PMD, and healthy controls) were assessed for neuropsychological impairment, cortisol activity from 6pm to 9am. In approximately 80%, blood samples were collected for allelic variation for genes that encode for components of the HPA axis. Patients were allowed to be on stable medication for at least one week prior to study but were excluded if they were on substances with clear HPA effects – e.g., estrogen.

Results: PMD patients demonstrated significantly elevated cortisol activity from 6pm-1am (the nadir) than did the other two groups. They also demonstrated poorer performance on a number of measures of attention, response inhibition, and working and verbal memory than did healthy controls, often performing significantly worse than NPMD patients. Mean cortisol levels from 6pm-1am were significantly and negatively correlated with most neuropsychological measures, particularly strongest with verbal memory as measured with the CVLT. The contribution of variation for SNP's of genes that encode for specific components of the HPA axis (CRH, CRH-R1, CRH-R2, NR3C1 (GR), MR, and FBP-5) to mean cortisol from 6pm–1am was assessed using linear regression with each gene explored separately with its alleles after controlling for the effects of age, measures of psychosis/depression, and medication status. Only GR contributed significantly to cortisol levels. Using similar analyses performed to predict depression severity and psychosis severity, GR predicted psychosis and CRH-R1 predicted psychosis significantly. Data on genetic prediction of cognitive measures indicate GR also predicts performance on some measures, even after controlling for cortisol.

Conclusion: Elevated cortisol is associated with psychosis and cognitive impairment in depression. GR variation predicts cortisol levels, psychosis and cognitive performance.

Policy of full disclosure: Disclosure of Financial Interest – 1 Year Alan F. Schatzberg, MD 2013-Present Consultant Bay City Capital CeNeRx Cervel Eli Lilly Genentech Gilead Lunbeck/Takeda McKinsey Merck MSI Naurex Neuronetics PharmaNeuroBoost Xhale Equity Amnestix

Cervel Corcept (co-founder) Delpor Forest Merck Neurocrine Pfizer Titan Xhale Honoraria Merck Intellectual Property Named inventor on pharmacogenetic and antiglucocorticoid use patents on prediction of antidepressant response.

S-22. Is schizophrenia a progressive disease?

S-22-001 Early course of cognitive impairment in schizophrenia: Effects and influences

E. Joyce. *University College London, London, United Kingdom*

Objective: To understand the course of neurocognitive impairment in schizophrenia and how this relates to clinical outcome and brain structure and function.

Methods: Patients with schizophrenia or schizoaffective disorder were recruited at first-onset of psychosis, aged 16–55 years. They were assessed at presentation and twice more over the first 4 years of illness on tests of cognitive function including IQ, memory and executive function. A subset underwent structural MRI twice over the same period. Healthy controls were assessed at similar time points. A subset also underwent magnetoencephalography (MEG) while performing a change detection task.

Results: In two separate cohorts, cognitive function showed no evidence of deterioration over the first 4 years of illness. There was improvement in several domains but, when compared to changes in controls, were attributable to practice effects. A subgroup showed evidence of having undergone cognitive decline by the time of psychosis onset. Cognition at onset predicted functional outcome 3–4 years later. MRI measures of cortical thickness and area at psychosis onset showed reduced frontotemporal area compared to controls and the degree of area reduction was related to current and premorbid IQ. A mean of 2 years later there was a reduction in the thickness of frontal and parietal cortex. Although there was no concomitant deterioration in cognitive function over this period, IQ and working memory at psychosis onset predicted the degree of thinning of frontal and parietal cortex in patients two years later. MEG analysis was consistent with functional disconnection in the frontoparietal network.

Conclusion: Cognitive impairment is generalised and present at the time of psychosis onset. Despite progressive changes in cortical pathology following the first episode, cognitive impairment does not progress further. This suggests that cognitive impairment may be longstanding in some and, in others, deteriorate around the time of psychosis onset. Generalised cognitive impairment is related to structural and functional abnormalities of frontal-temporal-parietal association cortex supporting the dysconnectivity hypothesis of schizophrenia.

Policy of full disclosure: None.

S-22-002 Schizophrenia is not progressive: The clinical evidence

R. Murray. *Institute of Psychiatry, King´s College London, London, United Kingdom*

Objective: Although schizophrenia is frequently said to be progressive, there is little evidence that this is so. Indeed, 40 years ago Manfred Bleuler indicated that there was little deterioration after 5 years. Subsequently, many follow-up studies have come to a similar conclusions.

Methods: In the epidemiologically-based AEESOP study we followed up 480 patients with their first episode of psychosis for 10 years.

Results: Over 40% had not had significant psychotic symptoms in the two years before the re-assessment. A small proportion (13%) met criteria for treatment-resistance; however, 80% of these had always responded badly.

Conclusion: This suggests that the majority of patients have an illness which responds to dopamine blockers but a minority may have a different disorder which does not and in whom the pathogenesis may be non-dopaminergic; there are some suggestions that glutamatergic abnormalities may be more important in this sub-group.

Policy of full disclosure: None.

S-22-003 Explaining progressive brain changes in schizophrenia. The role of drugs, stress and inflammation

C. Pantelis. *University of Melbourne, Melbourne Neuropsychiatry Centre, Melbourne, Australia*

Objective: Recent studies demonstrate that brain changes in schizophrenia are progressive particularly at earliest illness stages. While such changes would be consistent with the clinical picture of psychosis, the functional relevance of such changes and the mechanisms underlying them has been unclear. In particular, it has been proposed that neurocognitive function does not show evidence of deterioration. It is suggested that the observed progressive changes may be due to imaging methodology, diagnostic heterogeneity, or secondary to antipsychotic drug treatment, the impact of illicit drugs (e.g. cannabis), or the influence of stress and HPA-axis function. Our recent studies have examined these factors in detail.

Methods: We have undertaken a series of longitudinal imaging studies across the stages of illness from pre-psychosis onset and examined these potential confounds. In particular, recent studies have detailed the effects of antipsychotic medication, differences across psychotic diagnoses and examined the extent of brain structural changes caused by cannabis. We have also examined the impact of neuroinflammation in a PK-11195 PET study assessing activated microglia at the earliest stages of psychosis.

Results: I will present the findings from our series of studies investigating progressive brain changes in psychosis from before illness onset and examine confounds that may explain these changes (esp. cannabis, stress and medication). I will present preliminary data on neuroinflammation as a possible mechanism for progressive brain change.

Conclusion: Progressive brain changes begin from before illness onset and are most apparent over the first few years of illness. Factors such as drug use, the impact of stress and medication need to be taken into account in understanding these changes. Neuroinflammation may underpin the changes observed and help to reconcile the heterogeneity of findings (Cropley et al., Int Clin Psychopharmacol, 2013).

Policy of full disclosure: The studies were funded by National Health and Medical Research Council (NHMRC) of Australia and Australian Research Council (ARC). Additional support was provided by University of Melbourne, Melbourne Health, Jack Brockhoff Foundation, Ian Potter Foundation, AE Rowden White Foundation, Ramaciotti Foundation, Pratt Foundation, Woods Family Trust, Rebecca L Cooper Medical Research Foundation, Australian Computing & Communications Institute, Wellcome Trust, NARSAD, Stanley Foundation. Prof Christos Pantelis was supported by a NHMRC Senior Principal Research Fellowship (ID: 628386), NHMRC Program Grant (ID: 566529) and NARSAD Distinguished Investigator Grant.

S-22-004 Expecting recovery not progression in schizophrenia

R. Zipursky. *St. Joseph's Healthcare, Hamilton, Canada*

Objective: For more than a century, progressive decline has been considered to be an intrinsic feature of schizophrenia. The development of early intervention programs has provided new opportunities to investigate clinical outcomes from schizophrenia as well as the course of brain structure and function over time.

Methods: Longitudinal studies are reviewed to determine whether clinical outcomes worsen over time. Magnetic resonance imaging (MRI) and cognitive testing have been carried out in many samples of individuals who have been studied longitudinally following a first episode of non-affective psychosis. A systematic review was undertaken to investigate the risk of recurrence when medications are discontinued following a remission from a first episode of non-affective psychosis in order to determine the extent to which recurrences can be explained by medication discontinuation.

Results: Longitudinal MRI studies have found evidence of progressive decrements in brain tissue volumes over time. However, the change detected over time may be best explained by factors other than schizophrenia per se such as exposure to antipsychotic medication. Cognitive deficits are also apparent at the first episode of psychosis but do not on average worsen over time. The majority of individuals are able to achieve a remission of psychotic symptoms and to sustain remission over the longer term. Individuals who have achieved a clinical remission and then discontinue antipsychotic medication have a weighted mean 1-year recurrence rate of 77%; by the 2-year point, the cumulative risk of recurrence approaches 95%.

Conclusion: Longitudinal outcome studies do not support the view that schizophrenia is associated with progressive functional or cognitive decline. It is essential that researchers, clinicians, patients and family members have a shared understanding that progressive deterioration is not an inherent feature of schizophrenia. Helping individuals to achieve the fullest degree of recovery should be the objective of current treatments and services.

Policy of full disclosure: Dr. Zipursky has received grant support from Roche and served as a consultant to Amgen, Sunovion, Otsuka, Lundbeck and Roche.

S-23. Psychiatric disorders, 24-hour circadian rhythms: Clock genes and new treatment implications

S-23-001 Clock genes in control and major depressive disorder brain tissue: Possible mode of action of the rapid-acting antidepressant low-dose Ketamine

W. Bunney. *University of California, Irvine, USA*

Objective: This presentation will focus on clock genes and their role in controlling consistently reported abnormal circadian rhythms (sleep, temperature, hormonal secretion, and mood) in major depressive disorder patients (MDD). A further objective involves the evaluation of the hypothesis that the rapid antidepressant effects of low-dose Ketamine may involve the alterations of clock genes.

Methods: Study 1: Analyzed highest quality brain tissue, all with rapid death, accurate time of death high pH and RIN values, next-of-kin interviews and short PMI. Microarray results (12,000 transcripts) were screened for genes having a significant sinusoidal 24-hour cycle. We evaluated the statistical significance of the findings by permutation, randomly reassigning time-of death data across subjects 1,000 times and determined peak times of gene expression. Study 2: Test the effects of Ketamine on clock genes in neuronal cell culture. A reporter constituted by the mPer1 gene promoter fused with the luciferase gene was expressed in neuronal cells. E-boxes which drive CLOCK/BMAL1 transcription of PER and CRY genes were mutated to determine a site of action.

Results: Study 1: Our findings provide the first direct evidence of clock gene sinusoidal rhythms which vary in synchrony over 24 hrs across 6 regions of normal human brain. These rhythms are disrupted in MDD. Study 2: This is the first study to provide evidence that Ketamine inhibits the function of the core clock gene complex, CLOCK/BMAL1, and that e-box elements are critical for Ketamine's actions.

Conclusion: Study 1: Clock genes in control subjects show significant circadian patterns based on time of death over 24 hours, while MDD patients show a marked disruption. Study 2: Ketamine's inhibition of CLOCK/BMAL1 could potentially provide a mechanism by which 'resetting' clock gene machinery could normalize dysregulated rhythms and treat mood disorders.

Policy of full disclosure: None.

S-23-002 Clock gene expression in schizophrenia; and effect of chronic stress on molecular rhythmicity

G. Lundkvist[1], A.-S. Johansson[1], B. Owe-Larsson[2], M. Bartlang[3], S. Reber[4], C. Förster[5]. *[1]Karolinska Institutet, Department of Neuroscience, Stockholm, Sweden; [2]Huddinge Hospital, Stockholm, Sweden; [3]University of Wuerzburg, Wuerzburg, Germany; [4]University of Ulm, Ulm, Germany; [5]Wuerzburg, Germany*

Objective: 1) To analyze clock gene expression in cells obtained from patients diagnosed with schizophrenia. 2) To investigate the role of the circadian clock on the body response to stress.

Methods: 1) We sampled mononuclear cells from whole blood obtained from psychotic patients, and cultured fibroblasts from skin biopsies obtained from patients with chronic schizophrenia. The fibroblasts cultures were serum-schocked and sampled every 4 hr during 3 days in order to analyze rhythmic patterns in clock gene expression. Clock gene and protein expression was analyzed with qRT-PCR and Western blot. 2) We exposed PERIOD2::LUCIFERASE mice to repetitive psyschosocial stress in the morning (inactive phase) or in the evening (active phase) and analyzed the PER2::LUC molecular rhythm in the suprachiasmatic nucleus and adrenal glands.

Results: 1) Cells from psychotic patients expressed lower levels of Cry1, Per2 and Clock. Serum-schocked fibroblasts from schizophrenic patients showed less rhythmicity in clock gene expression. In particular, Cry1 rhytmicity could only be detected in 20% of the cells from schizophrenic patients, whereas cells from healthy controls expressed Cry1 rhythmicity in 100% of the cases. 2) Psychosocial stress in the evening, but not in the morning, altered the PER2::LUC rhythm in the SCN. Psychosocial stress in the morning phase advanced the adrenal PER2::LUC rhythm.

Conclusion: Expression patterns of some clock genes, in particular Cry1, are altered in cells from schizophrenic patients. Psychosocial evening stress affects the central molecular clock, whereas morning stress appears to have more impact on peripheral clocks.

Policy of full disclosure: None.

S-23-003 Effects of clock gene variants and chronotherapeutics on hopelessness and suicidality in drug-resistant bipolar depression

F. Benedetti. *Instituto Scientifico, University Ospedale San Raffaele, Department of Clinical Neurosciences, Milan, Italy*

Previous researches by our group showed that clock genes can bias non-clock brain functions in patients with Bipolar Disorder, such as neural responses to positive and negative moral stimuli. Some components of the molecular machinery of the clock also participate in signal transduction pathways regulating core neuronal and glial metabolic functions, and we showed that their genetic variants bias integrity and function of grey and white matter in the brain. Focusing on genetic mutations of CLOCK, we showed that they bias core psychopatological symptoms such as instability of circadian rhythms, insomnia, recurrence of illness. Now we studied the core negative cognitive biases associated with bipolar depression and found that CLOCK mutants have a worse tendency toward the generalization across time of negative distortions, with worse hopelessness, higher ratings on the suicide item of the Hamilton rating scale, and a dimished resilience as shown by a stroger relationship between early life stress and current suicidality. The effects of external stimuli on circadian rhythms, with clock resetting or perturbing action, may become more apparent when the circadian timing system is compromised. Perturbations of sleep-wake and dark-light exposure cause minimal effects in healthy people, but can produce major clinical effects in patients with mood disorders. Chronotherapeutic antidepressant interventions that directly target the clock, such as the combined administration of sleep deprivation and light therapy, cause an immediate decrease of depression and suicidality thus being able to provide an immediate therapeutic effects for the patients. Alltogether, these findings sustain a central role for the biological clock as a target for the treatment of mood disorders, and of factors affecting the molecular machinery of the clock as core biological components in the gene-environment interaction which shapes the depressive psychopatology.

Policy of full disclosure: None.

S-23-004 Circadian transcriptional network in mammals

J. Takahashi. *Howard Hughes Medical Institute, University of Texas, Southwestern Medical Center, Dallas, USA*

Objective: The circadian clock mechanism in animals involves an autoregulatory transcriptional feedback loop in which CLOCK and BMAL1 activate the transcription of the Period and Cryptochrome genes. The PERIOD and CRYPTOCHROME proteins then feedback and repress their own transcription by interaction with CLOCK and BMAL1.

Methods: We have studied the biochemistry of the CLOCK:BMAL1 transcriptional activator complex as well as the genomic targets of CLOCK and BMAL1 using ChIP-seq methods.

Results: We describe the dynamics of the core circadian clock transcriptional system. CLOCK and BMAL1 interact with the regulatory regions of thousands of genes. The gene network and dynamics of the system will be discussed.

Conclusion: A mechanistic description of the core circadian clock mechanism should promote our understanding of how the circadian clock system influences complex behavior and behavioral disorders such as mood disorders.

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Policy of full disclosure: None.

S-24. Gut microbiota and brain function: Relevance to psychiatric disorders

S-24-001 The gut microbiota and neuroendocrine function

M. Lyte. *Texas Technical University, Health Science Center, Abilene, USA*

Objective: To identify common, evolutionary-based, mechanism(s) by which the microbiota and brain interface in the determination of behavior as part of the microbiota-gut-brain axis.

Methods: 1. In vitro: Examination of the capacity of microbes to respond to and produce neurochemicals that are more commonly associated with mammalian neurophysiology. 2. In vivo: (a) Ability of neurochemicals released during stress to influence growth of gut microbiota. (b) Ability of gut microbiota to directly alter behavior.

Results: The ability of microorganisms, whether present as commensals within the microbiota or introduced as part of a therapeutic regimen, to influence behavior has been demonstrated by numerous laboratories over the last few years. Our understanding of the mechanisms that are responsible for microbiota-gut-brain interactions is, however, lacking. The complexity of the microbiota is, of course, a contributing factor. Nonetheless, while microbiologists approaching the issue of microbiota-gut-brain interactions in the determination of behavior well recognize such complexity, what is often overlooked is the equal complexity of the host neurophysiological system, especially within the gut which is differentially innervated by the enteric nervous system. As such, both in vitro and in vivo work has demonstrated that a common mechanism by which the microbiota may influence behavior is through the production and recognition of neurochemicals which are shared by both host and microbiota. The study of host neuroendocrine-microbiota interactions has been termed microbial endocrinology.

Conclusion: The examination of the microbiota from the vantage point of host-microbiota neuroendocrine interactions can not only identify new microbial endocrinology-based mechanisms by which the microbiota can influence host behavior, but also lead to the design of interventions in which the composition of the microbiota may be modulated in order to achieve a specific microbial endocrinology-based profile beneficial to overall host behavior.

Policy of full disclosure: None.

S-24-002 Gut-brain axis: How the microbiome influences anxiety and depression

J. Foster[1], K.-A. Neufeld[1]. [1]*McMaster University, Hamilton, Canada*

Objective: The human gut contains an enormous number of microorganisms referred to as commensal bacteria, or gut microbiota. Research in the gut-brain field has demonstrated that microbiota are important to the development of brain systems that are important to stress reactivity and behaviour.

Methods: In the past 5 years, our lab and other groups have studied the gut-brain axis in germ-free mice, raised in a sterile microisolator and lacking all gut microbiota. Our first experiments followed on the observation that germ-free mice showed enhanced stress-reactivity (Sudo et al., 2004) and we sought to determine if this resulted in changes in stress-related behaviours.

Results: Surprisingly, our results revealed that germ-free mice showed reduced anxiety-like behaviour in the elevated plus maze, a well established behavioural test that examines approach and avoidance behaviour in mice, in comparison to specific pathogen free (SPF) mice. These findings suggest that gut-brain interactions are important to development of stress systems. The low anxiety-like behavioural phenotype observed in germ-free mice was accompanied by long-term changes in plasticity-related genes in the hippocampus and amygdala (Neufeld et al., 2011a). In addition, the low anxiety-like behavioural phenotype in germ-free mice persisted after colonization with normal intestinal microbiota demonstrating that gut-brain interactions influence CNS wiring early in life (Neufeld et al., 2011b). Our recent results show that the developmental trajectory of CNS stress circuits is altered in GF mice. Interestingly, both microbiota and sex influenced the changes observed.

Conclusion: Research in the last decade has established the link between gut microbiota and brain function. We have learned that gut microbiota are numerous and are important to healthy brain function. Our findings demonstrate that gut microbiota are important during early development and can influence the wiring of stress circuitry in the brain.

Policy of full disclosure: None.

S-24-003 Probiotics as regulators of brain and behavior

J. Cryan[1], T. Dinan[1]. [1]*University College Cork, Cork, Ireland*

Objective: There is a growing appreciation of the relationship between gut microbiota, and the host in maintaining homeostasis in health and predisposing to disease. Bacterial colonisation of the gut plays a major role in postnatal development and maturation of key systems that have the capacity to influence central nervous system (CNS) programming and signaling, including the immune and endocrine systems. Individually, these systems have been implicated in the neuropathology of many CNS disorders and collectively they form an important bidirectional pathway of communication between the microbiota and the brain in health and disease. Over the past 5 years substantial advances have been made in linking alterations in microbiota to brain development and even behaviour and the concept of a microbiota-gut brain axis has emerged. Animal models have been essential in moving forward this frontier research area.

Methods: In order to assess such a role we use studies involving, germ free mice and early-life microbiota manipulations and finally probiotic administration in adulthood. We assess neurochemical, molecular and behavioural effects following these manipulations.

Results: Our data show that the gut microbiota is essential for normal stress, antidepressant and anxiety responses. Moreover, microbiota is essential for both social cognition and visceral pain. Finally, there are critical time-windows early in life when the effects of microbiota on brain and behaviour appear to be more potent. Our data also demonstrates that these effects may be mediated via the vagus nerve, spinal cord, or neuroendocrine systems.

Conclusion: Such data offer the enticing proposition that specific modulation of the enteric microbiota by dietary means may be a useful "psychobiotic"-based strategy for both stress-related and neurodevelopmental disorders ranging from depression to autism.

Policy of full disclosure: The authors are supported in part by Science Foundation Ireland in the form of a centre grant (Alimentary Pharmabiotic Centre Grant Number SFI/12/RC/2273); by the Health Research Board of Ireland (Grant Numbers HRA_POR/2011/23 and HRA_POR/2012/32) and received funding from the European Community's Seventh Framework Programme Grant MyNewGut under Grant Agreement No. FP7/2007–2013. The Centre has conducted studies in collaboration with several companies including GSK, Pfizer, Cremo, Suntory, Wyeth and Mead Johnson. The authors have spoken at meetings sponsored by food and pharmaceutical companies.

S-24-004 Imaging the brain-gut-microbiome axis in humans

E. Mayer[1], K. Tillisch[1], J. Labus[1]. [1]*UCLA, Los Angeles, USA*

Objective: Previous studies in rodents have shown changes in brain neurochemistry and behavior in rodents in response to changes in the gut microbiota. The current study aimed to test the hypothesis that perturbation of the normal human gut microbiome by regular ingestion of probiotics will result in measurable changes in the brain as indexed by resting state and evoked brain responses.

Methods: Healthy women with no gastrointestinal or psychiatric symptoms were randomly assigned to groups given the test product (fermented milk product with probiotics [FMPP] (n=12), a control condition (nonfermented milk product) (n=11), or no intervention (n=13) twice daily for 4 weeks. The FMPP was a consortium of probiotics containing Bifidobacterium animalis subsp Lactis, Streptococcus thermophiles, Lactobacillus bulgaricus, and Lactococcus lactis subsp Lactis. Participants completed questionnaires to assess subjective symptoms and underwent functional magnetic resonance imaging (fMRI) before and after the intervention to measure brain response to an emotional recognition attention task and resting brain activity. Multivariate and region of interest analyses were performed.

Results: No effect of the FMPP on subjective or behavioral measures were observed. FMPP intake was associated with reduced task-related response of a distributed functional network (49% cross-block covariance; P=0.004) containing affective, viscerosensory, and somatosensory cortices. Alterations in intrinsic activity of the resting brain indicated that ingestion of FMPP was associated with changes in midbrain connectivity, which could explain the observed differences in activity during the task.

Conclusion: Four-week intake of an FMPP by healthy women affected the responsiveness of brain regions that control emotion recognition and sensation. This pilot study provides the first demonstration in humans for a gut microbiome brain communication.

Policy of full disclosure: None.

S-25. The expanding roles of microglia in chronic pain: Implications for therapy

S-25-001 Gene regulation in microglia in neuropathic pain

K. Inoue. *Kyushu University, Fukuoka, Japan*

Objective: Neuropathic pain is a debilitating chronic pain that occurs after peripheral nerve injury (PNI). We reported that activated microglia overexpressed P2X4 receptors after PNI evoking the pain (Nature, 2003 & 2005). However, the mechanism of microglia is poorly understood. We wanted to know this by gene regulation.

Methods: Methods are as usual.

Results: The expression the transcription factor interferon-regulatory factor 8 (IRF8) was markedly upregulated only in microglia after PNI. IRF8 overexpression in cultured microglia promoted the transcription of genes of molecules related the pain. IRF8 deficiency prevented the expressions of these genes in the spinal cord and the pain following PNI.

Conclusion: IRF8 may activate a program of gene expression that transforms microglia into a reactive phenotype.

Policy of full disclosure: None.

S-25-002 Microglia-neuron signalling mediates chronic pain-induced alterations in reward pathways

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Objective: It is known that neuronal-glia interactions, particularly products released from activated astrocytes and microglia are proposed to underlie synaptic plasticity pertinent to the development and persistence of NP pain. In the present study we sought to determine whether microglial activation in brain structures responsible for reward may contribute to neuropathic pain as pain and reward are processed within overlapping brain structures and are interacting processes.

Methods: Male C57Bl/6J mice were subjected to peripheral nerve injury or sham surgery. At 14 days post surgery, when pain hypersensitivities are clearly established, animals were subjected to either: (1) in vivo microdialysis for determination of opioid-evoked release of dopamine in the nucleus accumbens, (2) fresh tissue extracted from specific brain structures to measure levels of BDNF and the K/Cl co-transporter KCC2, (3) cardiac perfusion of formaldehyde for immuohistochemical labeling of glia, BDNF and KCC2, and (4) MQAE fluorescent lifetime measurements of Cl- in live tissue slices from the ventral tegmental area.

Results: In the present study, we identify microglial activation in the mesolimbic reward circuitry following peripheral nerve injury. This microglial activation causes release of BDNF within the ventral tegmental area, which in turn disruptions chloride (Cl-) transport in GABAergic neurons. The result is an exaggerated inhibitory tone on dopaminergic neurons projecting to the nucleus accumbens. Morphine-evoked release of dopamine is significantly blunted in neuropathic pain animals and this is recovered by treatment with a microglial inhibitor.

Conclusion: In conclusion, we present a novel mechanism that is responsible for dysfunction of mesolimbic dopaminergic transmission in chronic neuropathic pain that may account for the co-morbidities of mood disorders in chronic pain. Moreover, the blunted analgesic effect of opioids in chronic pain maybe due to alterations in neural systems responsible for reward as their analgesic effects are strongly linked to their rewarding capacity.

Policy of full disclosure: None.

S-25-003 The P2X4+ state of microglia is critical for neuropathic pain

M. Salter. *SickKids Hospital, Toronto, Canada*

Neuron-microglial interactions are increasingly recognized as being key for physiological and pathological processes in the central nervous system. Microglia have been found to play a causal role in neuropathic pain behaviours resulting from peripheral nerve injury, and a core neuron-microglia-neuron signaling pathway has been elucidated. Within the dorsal horn, microglia suppress neuronal inhibition by a cascade involving activation of microglial P2X4 receptors causing the release of brain derived neurotrophic factor (BDNF). BDNF acts on trkB receptors which leads to a rise in intracellular chloride concentration in dorsal horn nociceptive output neurons, transforming the response properties of these neurons. In addition to suppressing inhibition, peripheral nerve injury causes activity-dependent facilitation at dorsal horn glutamatergic synapses which enhances nociceptive transmission. This enhancement is mediated by intracellular signaling networks involving serine/threonine and tyrosine kinases within nociceptive transmission neurons. Key for this enhancement is facilitation of NMDA receptor function by Src family tyrosine kinases. Recently we have discovered that microglia-to-neuron signaling is not only critical for pain hypersensitivity after peripheral nerve injury but also for the paradoxical hyperalgesic effect of morphine and other opioids. We anticipate that by targeting microglia-neuron signaling pathways new therapeutic strategies for chronic pain as well as its comorbid sequelae may be developed.

Policy of full disclosure: None.

S-25-004 Microglia-mediated disruption of neuronal Cl-homeostasis mediates morphine hyperalgesia

Y. De Koninck. *Université Laval, Québec, Canada*

Objective: Morphine, and other opiates, are indispensable in the treatment of moderate to severe postoperative and chronic pain, but use of these drugs is plagued by the development of a particularly debilitating side effect: the development of paradoxical hyperalgesia. Knowing that morphine treatment causes microglial activation, we sought to determine whether morphine-induced hyperalgesia would involve similar mechanisms as those we previously found to underlie neuropathic pain.

Methods: Rats and mice were treated repeatedly with morphine to 5–7 days and nociceptive withdrawal threshold were measured every morning before morphine injection to test for a change in baseline response. A multidisciplinary approach was used involving immunocytochemistry, immunoblotting, patch clamp electrophysiology, cellular imaging, pharmacological interventions and conditional gene deletion to identifying the underlying mechanisms at the level of the spinal dorsal horn, namely those that were previously implicated in neuropathic pain: microglial activation, P2X4 receptors, Brain-Derived Neurotrophic Factor (BDNF), TrkB receptors and the K-Cl-cotransporter KCC2.

Results: We found that hyperalgesia-inducing treatment with morphine caused a downregulation of KCC2, impairing Cl– homeostasis in spinal lamina 1 neurons. Restoring Eanion reversed the morphine-induced hyperalgesia without affecting tolerance. The hyperalgesia was also reversed by ablating spinal microglia. Morphine hyperalgesia, but not tolerance, required μ opioid receptor-dependent expression of P2X4 receptors (P2X4Rs) in microglia and μ-independent gating of the release of brain-derived neurotrophic factor (BDNF) by P2X4Rs. Blocking BDNF-TrkB signalling preserved Cl– homeostasis and reversed the hyperalgesia. Gene-targeted mice in which BDNF was deleted from microglia did not develop hyperalgesia to morphine. Yet, neither morphine antinociception nor tolerance was affected in these animals.

Conclusion: Our findings dissociate morphine-induced hyperalgesia from tolerance and unveil the microglia-to-neuron P2X4-BDNF-KCC2 pathway as a therapeutic target to prevent hyperalgesia without affecting morphine analgesia.

Policy of full disclosure: None.

S-26. Depression in pregnancy and postpartum: A treatment dilemma?

S-26-001 Antidepressant treatment in a model of post-partum depression age- and gender-dependently alter offspring's CNS development

M.-C. Pardon[1], A.-A. Hidayah[1], A. Trist[1]. [1]*University of Nottingham, Nottingham, United Kingdom*

Objective: Gestational chronic mild stress in mice induces hormonal and behavioural changes reminiscent of post-partum depression and produces developmental effects in offspring which appear in an age and sex dependent manner, with females being more vulnerable. We investigated whether antidepressant exposure (via breast milk) reversed the developmental effects of gestational chronic mice stress, or whether it induced adverse behavioural consequences in offspring.

Methods: Chronic mild stress was applied to pregnant B6D2F1 dams after until delivery. Antidepressants (fluoxetine, 10 mg/kg/day and clomipramine, 20 mg/kg/day) were administered through drinking water from post-partum day (PD) 1 until weaning (PD22). Offspring belonged to one of four groups: Control group (no prenatal stress), S group (prenatally stressed and not treated), CL group (prenatally stressed and treated postpartum with clomipramine) or FL group (prenatally stressed and treated postpartum with fluoxetine). On PD7, each litter was subjected to the pup retrieval test during which ultrasonic vocalisations were recorded. Cognitive function, locomotor and anxiety-related behaviour

were then assessed in juvenile (PD23 to PD28) or adults (PD52 to PD58) offspring.

Results: During the pup retrieval test, S offspring emitted more chevron calls in the absence of the dams, and this was reversed by both antidepressants. Dams treated with fluoxetine were more likely to retrieve the pups back to the nest, but there was no effect of either treatment on the number or type of calls. The behaviour of juvenile offspring and of adult female was not affected by maternal exposure to antidepressants. Adult male from the CL group, however, exhibited reduced anxiety-like behaviour in the open-field, increased object recognition memory and decrease contextual fear memory. Adult male from the FL group were hyperactive in the open-field and exhibited reduced anxiety-like behaviour.

Conclusion: Thus, antidepressants administered during breastfeeding can alter maternal behaviour as well as offspring central nervous system function in an age and gender dependent manner.

Policy of full disclosure: None.

S-26-002 Maternal antidepressant exposure and CNS development in the rat offspring

J. Kelly[1], S. O'Brien[2]. [1]*NUI Galway, Galway, Ireland;* [2]*University of Limerick, Limerick, Ireland*

Objective: Assessing the risks of antidepressant exposure clinically during pregnancy and lactation is extremely challenging due to logistical and ethical reasons. Laboratory animals provide an alternative; however, studies evaluating antidepressant exposure have often employed doses and routes of exposure which are not clinically relevant, examined teratogenic effects without exploring behavioural consequences and confined endpoint evaluation to the early life period. Thus the objective of this study was to examine whether prenatal and/or postnatal exposure to the SSRI fluoxetine affected anxiety-related behaviour in the resulting offspring, from early life extending to adulthood.

Methods: Female Sprague-Dawley rats received daily injections of fluoxetine (5 mg/kg by oral gavage) from gestational day (GD) 7 until littering and throughout the neonatal period, i.e. from postnatal day (PND) 1 to 21. Other groups received fluoxetine either only during the prenatal or postnatal period, whilst control animals received distilled water alone. The elevated plus maze and open field test were examined in separate groups of rats either at 1, 2, 3 or 4 months of age. All results were analysed using TwoWay ANOVA, followed by post-hoc Student Newman Keuls tests, where appropriate, $p<0.05$ denoting statistical significance.

Results: Fluoxetine treatment was well tolerated, with no significant effects on maternal weight gain, nor any effect on the weight of the offspring in the neonatal period. A significant reduction in % open arm time in the elevated plus maze for male groups that had received prenatal fluoxetine ($p<0.05$ vs. controls) was observed at 2 months of age, with no significant drug-induced changes in open field behaviour.

Conclusion: It can be concluded that prenatal (but not postnatal) fluoxetine exposure results in selective anxiogenic effects that are transient and confined to male offspring, and indicates the value of using a clinically relevant exposure regime that enables a better extrapolation to the human situation.

Policy of full disclosure: None.

S-26-003 What are the molecular and psychological mechanisms underlying the impact of maternal depression and antidepressant use on the offspring?

C. Pariante. *King´s College London, London, United Kingdom*

Objective: To review our research on the effects of depression in pregnancy on offspring neurobiology and psychopathology.

Methods: We will present data from our current study on women who are depressed in pregnancy, and their offspring who have been followed-up until 1 year of age (Psychiatric and Motherhood – PRAM study), as well as from our ongoing longitudinal cohort of young adults born from mothers who were depressed in pregnancy in 1986 (South London Child Development Study).

Results: Women who are depressed in pregnancy have high levels of cortisol and of pro-inflammatory cytokines, and their offspring have increased stress responses and more immature behaviour. In the longitudinal study, offspring of women who were depressed in pregnancy appear more at risk of developing depression in adulthood, and to be exposed to life stressors; moreover, they have disrupted inflammation even in the absence of depression. Across the two studies, maternal childhood trauma is a very strong risk factor for mothers developing depression specifically in pregnancy.

Conclusion: Depression in pregnancy has specific biological and clinical effects that could participate to the transmission of psychopathology from one generation to the next.

Policy of full disclosure: None.

S-26-004 Impact of in utero exposure to antidepressants on the foetus

M. Reis. *National Board of Forensic Medicine, Linköping, Sweden*

An update of the Swedish Medical Birth Register (1996–2011) will be presented. During these years 1,552,382 women gave birth in Sweden and antidepressant use in early pregnancy was reported by 23,342 women (23,658 infants). The register contains information on nearly all births in the country and is based on standardized medical records: information from the first antenatal visit (gestation weeks 10–12); information from further antenatal care; data from the delivery; and finally data from the paediatric examination of the newborn. Further, neonatal as well as maternal diagnosis from women who got prescriptions for an antidepressants during the 2nd or 3rd trimester (7,940 women; 8,053 infants) will be presented. Few drug categories have been studied as extensively as antidepressants and notably SSRI. Some of the studies which seem to demonstrate teratogenic effects are retrospective case-control studies which may introduce methodological errors. In prospective studies little evidence of teratogenicity is found but the use of clomipramine or paroxetine may have a specific effect on cardiovascular defects, notably cardiac septum defects. Relatively little is known about other antidepressants than tricyclic or SSRI drugs but no major risk appears to exist. Use of antidepressants during the 2nd or 3rd trimester is associated with a number of pregnancy and neonatal complications which usually are of temporary nature but will increase the need for neonatal intensive care. Data in the literature indicate that these effects may only partly be due to the drugs but partly is a result of underlying disease, a confounding by indication. There is a tendency that TCA causes stronger effects than SSRI at least for preterm birth, low birth weight and neonatal diagnoses which supports a drug effect but there may exist differences in underlying pathology.

Policy of full disclosure: None.

S-27. A new nomenclature proposal for psychotropic drugs

S-27-001 Introduction and antidepressants

J. Zohar. *Sheba Medical Center, Tel Aviv, Israel*

Objective: Current psychopharmacological nomenclature remains wedded to earlier period of scientific understanding, failing to reflect contemporary developments and knowledge, does not help clinicians to select the best medication for a given patient, and tending to confuse patients as they are being given a drug with a different name compared to their identified diagnosis (e.g. "Antipsychotic" for depression). A five-axis pharmacology based nomenclature template as a potential system which refresh current nomenclature by using contemporary scientific concepts of Neurospsychopharma- cology will be presented.

Methods: Four major colleges of Neuropsychopharmacology (ECNP, ACNP, Asian CNP, and CINP) proposed a new template comprising a multi-axial pharmacologically-driven nomenclature. The template comprises of five axes: 1) class and Relevant mechanism; 2) sub-class; 3) neurobiological activity; 4) Efficacy (including major side effects); and 5) Indications (FDA or EMA approved, or as stated). Several surveys in four different continents were conducted in order to examine satisfaction with the current psychopharmalogical nomenclature, as well as test the five-axis template.

Results: A significant proportion of the participants in the surveys were in favour of the proposed system, a similar number wanting to consider the idea further, and only a small proportion were against it.

Conclusion: The results of the surveys suggest that clinicians found the available nomenclature system dissatisfactory and at times even confusing for them and the patients. The proposed 5 axis template seeks to up-end current usage by placing pharmacology rather than indication as the primary axes. Based on the results the authors envision that the primary usage would relate to Axis 1—the class—Axis 4 – Efficacy, Axis 5 – Indications. The other Axis 2—sub-class and 3 – neurobiological activity – being optional and largely depending upon the extent to which the clinician seeks to dig into the scientific base.

Policy of full disclosure: Joseph Zohar has received grant/research support from Lundbeck, Servier and Pfizer, has served as a consultant

or on advisory boards for Servier, Pfizer, Abbott, Lilly, Actelion, AstraZeneca and Roche, and has served on speakers' bureaus for Lundbeck, Roch, and Abbott.

S-27-002 Anxiolytics and hypnotics

D. Nutt. *Imperial College, London, United Kingdom*

My talk will focus in the new approach to nomenclature for anxiolytics that is being developed by the ECNP ACNP CINP AsCNP groups – I shall show how a focus on pharmacology can help understand the actions and adverse effects of these medicines.

Policy of full disclosure: None.

S-27-003 Antipsychotics

S. Stahl. *NEI, Carlsbad, CA, USA*

Objective: To illustrate the confusion in classifying antipsychotics and to propose nomenclature based upon pharmacologic action rather than simply reduction of psychosis

Methods: Literature review and consensus panel

Results: Antipsychotics are not merely effective in psychosis, but many are effective in mania, in bipolar depression, in unipolar depression and as adjuncts to antidepressants in treatment resistant depression. This has created confusion in classifying these agents, compounded by notions of whether the antipsychotic is first generation or 'conventional, versus second generation and 'atypical.'

Conclusion: A nomenclature based upon principle and secondary pharmacologic actions is proposed and will be presented and discussed.

Policy of full disclosure: None.

S-27-004 A view on the new nomenclature from the perspective of the drugs developed in Japan

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There is a growing consensus in Asia as well as in Western world that the current nomenclature for psychiatric drugs is outdated and new nomenclature based on scientific evidence by the up-to-date Neuropsychopharmacology is anticipated. Recently some members of Japanese Society of Neuropsychopharmacology (JSNP), with the cooperation of 3 Japanese pharmaceutical companies, reviewed the new Nomenclature proposal introduced by ECNP. As well as presenting overall comments on the format, we have created our experimental proposals of the 3 representative drugs developed in Japan (Aripiprazol, Lurasidone and Donepezil) on the assumption that the new Nomenclature will be presented in a 2-step approach, a simplified version for clinical practice and a more detailed one for reference. General comments on the format are: 1) 5-Axes format provides appropriate elements required for the Nomenclature, 2) The information described in Axes 4 (Efficacy and Side effects) and 5 (Indications) should be reviewed periodically to keep accuracy. Especially, the information in Axis 5 increases over time and it is necessary to consider frequency of updating the contents in both Axes, 3) Axis 3 (Neurobiological description) contains several items but it is difficult to classify data and information into these items, and 4) for Axis 4, criterion for listing information should be developed. It may be practically feasible to include adverse events with more than 5% incidence rate. In addition there was a comment that original 5-axes format is too much for clinical doctors for daily practice, but in the latest version, it is improved properly by dividing the format into 2 pages # 'front page' for the bedside clinicians with Axes 1, 4 and 5 and the committee note and the 'back page' providing details including Axes 2 and 3. In this symposium, our proposals on the 3 drugs developed in Japan will be presented.

Policy of full disclosure: None.

S-28. Serotonin, stress and depression: Genetic and epigenetic factors

S-28-001 Genetic mechanisms for longterm alterations in serotonin in depression

P. Albert. *University of Ottawa, Ottawa, Canada*

Objective: This symposium focuses on new findings that strengthen the long-held link between serotonin, early life stress and depression. Evidence will be presented to demonstrate that genetic and stress-induced epigenetic alterations in the expression of the serotonin regulatory serotonin (1A) receptor gene (HTR1A) that are associated with depression leads to altered serotonin activity, ultimately underlying depression and response to antidepressant treatments.

Methods: Evidence from functional studies of the regulation of serotonin genes focusing on the 5-HT1A receptor gene, from cellular to animal models to clinical imaging studies will be presented.

Results: Dr. Albert has studied the underlying transcription mechanisms that regulate serotonin gene expression, focusing on regulation of the 5-HT1A receptor gene, a critical regulator and transducer of serotonin action. He has identified the rs6295 HTR1A genetic polymorphism that associated with depression and suicide that is located in the promoter of this gene and that alters the activity of specific transcription factors resulting in altered levels of the receptor and reduced serotonin content. Using genetic knockout models, he has shown that the transcription factors that he has identified modify the expression of 5-HT1A receptor and may account for brain region specific alterations in 5-HT1A receptor expression that predispose to depression.

Conclusion: The evidence presented will identify specific gene regulatory mechanisms that lead to dys-regulation of the 5-HT1A receptor and ultimately to increase in susceptibility to depression. Targeting these regulatory mechanisms may provide novel and multimodal new treatments for depression.

Policy of full disclosure: None.

S-28-002 Brain serotonin 1A receptor binding in major depressive disorder

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Objective: The serotonin 1A (5-HT1A) receptor has been implicated in the pathophysiology of MDD. We previously reported higher 5-HT1A receptor binding in two cohorts of subjects with MDD during a major depressive episode (MDE) using PET imaging with [11C]WAY-100635. This is a state phenomenon, not trait, as we have demonstrated that the effect persists in subjects who are remitted and off of medication. We have also shown that 5-HT1A binding is also associated with treatment outcome after non-standardized antidepressant treatment. Most recently, we examined whether pre-treatment 5-HT1A binding is associated with treatment outcome following standardized escitalopram treatment in MDD. We also compared 5-HT1A binding between all MDD subjects in this cohort and a sample of healthy controls.

Methods: 24 MDD subjects in a current MDE underwent PET scanning with [11C]WAY-100635, acquiring a metabolite-corrected arterial input function and free-fraction measurement to estimate 5-HT1A binding (BPF=Bmax/KD, where Bmax=available receptors and KD=dissociation constant). MDD subjects then received eight weeks of treatment with escitalopram. Remission was defined as a post-treatment 24-item HDRS <10.

Results: 46% of subjects achieved remission following eight weeks of escitalopram. Remitters to escitalopram had 33% higher baseline 5-HT1A binding in the raphe nuclei than non-remitters ($p=0.047$, $p=0.033$ with covariates). Across 12 cortical and subcortical regions, 5-HT1A binding did not differ between remitters and non-remitters ($p=0.86$). 5-HT1A binding was higher in MDD than historical controls across all regions ($p=0.0003$), a triplication of our finding. Remitters did not differ from non-remitters in several relevant clinical measures.

Conclusion: Elevated 5-HT1A binding in raphe nuclei is associated with subsequent remission with the SSRI escitalopram; this is consistent with data from a separate cohort receiving naturalistic antidepressant treatment. We confirmed our previous findings of higher 5-HT1A binding in current MDD compared to controls.

Policy of full disclosure: None.

S-28-003 Stress and depression: A vicious cycle?

C. Belzung. *INSERMUMR930, Tours, France*

Objective: Major depression has been much related to chronic stress, particularly in subjects having a low diathesis for depression. In fact, chronic stress induces chronic exposure to glucocorticoids, which elicits a decrease of glucocorticoid receptors in granule cells located in the dentate gyrus of the hippocampus and, later on, to a loss of hippocampal granule cells that can be counteracted by the generation of new granule cells via increased adult hippocampal neurogenesis. Interestingly, all available antidepressant drugs stimulate cell proliferation in the hippocampus and accelerate the maturation of these cells. However, the mechanisms underlying this action are still poorly understood. The objective of this study is to investigate the mechanisms underlying the antidepressant-like action of selective serotonin reuptake inhibitors (SSRIs).

Methods: We combined unpredictable chronic mild stress as a model of depression in mice with chronic SSRIs, focal irradiations of the hippocampus, genetic strategies, immunohistochemistry and hormonal dosages.

Results: We show that newborn neurons of the hippocampus are necessary and sufficient to elicit therapeutic effects in an animal model of depression. This then enables the recruitment of projection areas of the hippocampus, particularly of the anteromedial nucleus of the bed nucleus of stria terminalis, the inhibition of the paraventricular nucleus of the hypothalamus, and thus remission. Resistance to SSRIs is associated with poor aptitude of SSRIS to stimulate neurogenesis.

Conclusion: Drugs of the future could treat depression by targeting directly adult hippocampal neurogenesis or the stress axis.

Policy of full disclosure: None.

S-28-004 The role of SLC6A4 DNA methylation in stress-related changes in hippocampal volume: A study in depressed patients and healthy controls

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Objective: Serotonin (5-HT) plays an important role in the etiology of depression. Serotonin is also crucial for brain development. For instance, animal studies showed that early 5-HT disruptions affect brain development and emotion regulation in later life. We found that childhood trauma in humans interacting with the short allele of the 5-HTTLPR polymorphism was associated with smaller hippocampal volumes in depression (Frodl et al., 2010). However, specific mechanisms of this interaction are not known. A plausible mechanism is that environmental stressors reprogram the 5-HT system through epigenetic processes by altering 5-HT system gene expression. This in turn may affect brain development, including the hippocampus, a region with dense 5-HT innervations and important in stress-regulation. Here, we test whether greater DNA methylation in specific CpG sites at the SLC6A4 promoter in peripheral cells is associated with childhood trauma, depression and smaller hippocampal volume. We were particularly interested in those CpGs that had previously been associated with in vivo measures of brain 5-HT synthesis (Wang et al., 2012).

Methods: Thirty-three adults with major depressive disorder and 36 healthy matched controls were included. Symptoms, childhood trauma and high-resolution structural MRI for hippocampal volume were assessed (Frodl et al., 2010). SLC6A4 methylation was assessed using pyrosequencing.

Results: Regression analyses showed that childhood trauma, female gender and smaller hippocampal volume were independently associated with greater SLC6A4 methylation. Greater SLC6A4 methylation in the depressed group was observed only in SSRI-treated patients. Interestingly, associations were primarily observed in CpGs previously being associated with brain 5-HT synthesis (Wang et al., 2012).

Conclusion: SLC6A4 methylation might be a mechanism for physiological gene-environment interaction in the development of stress-related brain alterations. The results provide some indications that site-specific SLC6A4 methylation may be a biomarker for 5-HT-associated stress-related psychopathology.

Policy of full disclosure: None.

S-29. Clinically useful biomarkers in psychiatry: The promise and problem

S-29-001 Progress toward clinically useful biomarkers in psychiatry

B. Dean. *Molecular Psychiatry Lab, FINMH, Howard Florey Laboratories, Melbourne, Australia*

Objective: In psychiatric disorders, the development of neuroimaging and other tools to measure CNS function and the notion that the biology of psychiatric disorders affects whole of body has fuelled efforts to discover biomarkers that would have diagnostic utility or aid in treatment decision making. Focussing on molecular approaches to biomarker discovery, cost considerations strongly suggest that for any biomarker to have widespread utility it would need to use an easily accessible peripheral tissue with a low risk of collection side-effects. Following this logic, this presentation will focus on the approaches, progress and problems in identifying molecular biomarkers for psychiatric disorders. The focus will be on non-DNA sequence biomarkers because levels of such biomarkers are more likely to reflect interactions between genes and environment that are now predicted to play a pivotal role in the genesis of a psychiatric disorder1.

Methods: Data from the presenter and the literature will be presented to highlight possible approaches to biomarker discovery and the problems and pitfalls from discovery to validation and the use across multi-centres.

Results: Available data would suggest that some progress is being made toward biomarkers that can aid in diagnoses and response to treatment. However, interpreting available data is being hampered because of a lack of standardisation across groups undertaking biomarker discovery programs.

Conclusion: This presentation will suggest that there is growing evidence to support the discovery of clinically useful biomarkers. That such tools will likely be based on changes in panels of analytes, rather than on a single analyte, but that progress needs to be made in standardising sample collecting to allow the potential utility of biomarker system as a widely use clinical aids to be assessed.

Reference

1. Uher R (2014) Gene-environment interactions in common mental disorders: an update and strategy for a genome-wide search. Soc. Psychiatry Psychiatr Epidemiol 49: 3–14.

Policy of full disclosure: None.

S-29-002 Biomarkers for psychosis onset: Promising candidates from the genome

C. Bousman. *University of Melbourne, Parkville, Australia*

Objective: Identification of individuals at high risk for psychotic disorder has proven challenging. The development and validation of standardised clinical criteria to detect individuals at high risk of psychosis has improved our ability to identify individuals at the greatest risk for transition from an at-risk state to frank-level psychotic symptoms. However, the majority of individuals meeting high risk criteria do not develop psychosis and as such biomarkers could further refine our ability to detect those most at risk for psychosis transition/onset. The focus of this presentation will be on recent biomarker discovery efforts within this high-risk group with particular emphasis on genotypic makers for psychosis transition/onset.

Methods: Data from prospective cohort studies that have examined the effects of genotypic variation on transition to psychosis will be presented, with particular focus on the presenter's recent research in the area.

Results: To date, studies have identified variation in neuregulin 1 (NRG1), D-amino acid oxidase activator (DAOA), and catechol-o-methyltransferase (COMT) as potential biomarkers for psychosis transition. However, only genetic variation in NRG1 has support from more than one study.

Conclusion: Current tools used for early identification of individuals at risk for transition, although standardized, are dependent on subjective measures (e.g. clinical rating scales) that relative to genotyping are more susceptible to measurement errors and consequently reduced prediction accuracy. Current findings support the addition of measures that are not dependent on state-related changes. However, the temptation to include genetic variation in psychosis risk prediction must be cautioned until replication has been undertaken in much larger samples, and the true effect size of associations can be more accurately determined.

Additional investigation may then determine which genetic markers, in what contexts, and at what costs will provide the most clinically useful genetically informed risk prediction among at-risk populations.

Policy of full disclosure: None.

S-29-003 Measuring oxidative damage to cortical white matter in blood samples from patients with mood disorders: Evolution of biomarkers in psychiatry

T. Young[1], A. Andreazza[1]. [1]*University of Toronto, Toronto, Canada*

Objective: Bipolar disorder (BD) continues to be a leading cause of disability but the etiology is only partly understood. Among the pathophysiological mechanisms which are important in BD, oxidative stress is increasingly well supported. Lipids are particularly abundant in brain, especially white matter, and are targets for oxidative damage. In the present study, we examined the relation between white matter and oxidative stress.

Methods: Several complimentary approaches were used. We examined post mortem brain from subjects with BD, blood samples from subjects with BD including adults and those from an older age group and from patients with brain imaging data examining white matter tracts. The work was done in collaboration with investigators at University of Toronto and University of Pittsburgh and with tissue from the Harvard Brain Bank.

Results: Increased lipid peroxidation was found in the myelin fraction from frontal cortex but not hippocampus of patients with BD. Increased markers of lipid damage were found in both adults and older patients with BD. There was a relationship between serum lipid peroxidation and white matter integrity.

Conclusion: Oxidative stress may be critically important in BD, be measurable in blood and may be related to white matter tracts. Lipid peroxidation is a potentially relevant target for therapeutic intervention which deserves more intensive study.

Policy of full disclosure: None.

S-29-004 Biomarkers for psychiatric disorders: Expectations and problems from a clinical point of view

H.-J. Moeller. *Ludwig-Maximilians-University, Munich, Germany*

There was and is still great hope for biomarkes in psychiatry, both for diagnosis and treatment. Intensive efforts have been made in the recent decades, but so far nothing evolved for clinical use, inspite of all the technical progress in terms of genetics, brain imaging and other methods. The invention of diagnostic biomarkers so far is not fulfilled, although for the diagnoses of Alzheimer dementia it seems more and more realistic. But even in this field DSM-5 did not include biomarkers, not to speak about other diagnostic entities like schizophrenia and depression. When it comes to the term personalized medicine most people think about biomarkers driven clinical decision making and indeed, there was great hope that among others based on pharmacogenetic findings we would be able to fulfill the dream of personalized medicine. Many polymorphisms were described as relevant for treatment outcome, both related to efficacy or tolerability. But the results were often quite unstable and inconsistent and the explained variance by each of this genetic alterations extremely low. There is still hope, that a combination of such polymorphisms might be helpful in predicting the outcome of drug treatment and improve in clinical decision making. But so far, given the low size of explained variance even for such a combination, it is more realistic to think that this will be not in the sense of individualized/personalized medicine, but in the sense of stratified medicine. Probably beside genetics also other parameters like brain imaging results might be helpful in improving the clinical decision making in this sense.

Policy of full disclosure: Conflict of Interest – Financial Disclosure Statement Prof. Dr. Moeller has received grants or is a consultant for and on the speakership bureaus of AstraZeneca, Bristol-Myers Squibb, Eisai, Eli Lilly, GlaxoSmithKline, Janssen Cilag, Lundbeck, Merck, Novartis, Organon, Pfizer, Sanofi-Aventis, Schering-Plough, Schwabe, Sepracor, Servier and Wyeth.

S-30. Brain-Derived Neurotrophic Factor (BDNF) and synaptic plasticity as a drug target for cognitive dysfunction in CNS disorders

S-30-001 Molecular and cellular mechanisms of synaptic plasticity: Role of BDNF

L. Minichiello. *University of Oxford, Department of Pharmacology, Oxford, United Kingdom*

Objective: A recent main aspect of our research is to understand the contribution of different subsets of inhibitory neurons to animal behavior and neurological conditions. Huntington#s disease (HD) is a progressive neurodegenerative disorder characterized by progressive motor impairment and cognitive dysfunction. This is due to the fact that the disease firstly causes degeneration of cells in the basal ganglia, which controls movement, emotion, and cognitive ability. In particular, the subpopulation expressing enkephalin and the D2 dopamine receptor, originating the indirect pathway, are the first to be affected. Brain derived neurotrophic factor (BDNF) is believed to play a pivotal role in HD pathogenesis by decreased cortical Bdnf expression levels, and/or impaired anterograde BDNF transport induced by mutant Huntingtin. This leads to preferential striatal neuron vulnerability and cell death. However, the murine genetic models used to reach the above conclusions were not ideal because the induced alterations of BDNF levels were not confined to the striatum, but also affected cortical physiology.

Methods: To accurately define the protective role of BDNF in striatopallidal neurons we recently performed a selective deletion of the high affinity BDNF receptor, TrkB, from the striatopallidal, enkephalin-positive (ENK+), MSNs defining the indirect pathway, using a Penk-Cre BAC transgene (generating TrkbPenk-KO mice).

Results: Unexpectedly, loss of TrkB signalling in ENK+ MSNs did not lead to neuronal loss, but to age-dependent spontaneous, as well as drug-induced, hyperlocomotion, associated with increased D2R-dependent MAPK/PKC phosphorylation and reduced striatopallidal activation. However, no procedural learning defects were found.

Conclusion: We therefore have demonstrated that BDNF-TrkB signaling in striatal ENK+ MSNs contributes to the inhibitory control of locomotor behavior exerted by the indirect pathway, but is dispensable for their maintenance. This is unexpected, and challenges the widely held view that BDNF-TrkB signaling supports the long-term survival of ENK + MSNs (Besusso et al., Nat Commun 4, 2013).

Policy of full disclosure: None.

S-30-002 BDNF, adult neurogenesis and pattern separation in the hippocampus

T. Bussey. *Cambridge University, Cambridge, United Kingdom*

Objective: Brain-derived neurotrophic factor (BDNF) has been shown to be one of the essential proteins for memory formation in a variety of brain structures. In this presentation I will present some results to illustrate the role of BDNF and hippocampal adult neurogenesis in 'pattern separation', the process of creating less overlapping, less confusable memories.

Methods: This work combines different behavioural and molecular strategies to assess specific features of memory process and pattern separation.

Results: Our findings show that BDNF and adult neurogenesis in the dentate gyrus are required for consolidation of overlapping memories.

Conclusion: BDNF participates in different aspects of memory and therefore may be an interesting target to treat maladaptive memory disorders.

Policy of full disclosure: None.

S-30-003 Effect of BDNF polymorphism on markeres of synaptic activity and cognition in healthy subjects

P. Nathan. *UCB Pharma and University of Cambridge, Brain Mapping Unit, Cambridge, United Kingdom*

Objective: Increasing evidence suggests that synaptic dysfunction is a core pathophysiological hallmark of neurodegenerative disorders. Brain-derived neurotropic factor (BDNF) is key synaptogenic molecule and targeting synaptic repair through modulation of BDNF signalling has been suggested as a potential drug discovery strategy. The development of such synaptogenic therapies depend on the availability of BDNF sensitive markers of synaptic function that could be utilized as biomarkers for examining target engagement or drug efficacy in humans. We utilized the BDNF Val66Met genetic polymorphism in order to examine the effect of the polymorphism and genetic load on markers of synaptic activity.

Methods: 60 healthy subjects (20 val/val; 20 val/met and 20 met/met) were recruited for the study. Synaptic activity and cognition were quantified using Imaging (electrophysiology, fMRI), brain stimulation (TMS) and behavioural (CANTAB tasks) methods.

Results: A number of BDNF sensitive markers of synaptic activity were identified. Compared to val homozygotes, met carries (val/met and met/met) showed evidence of inefficient synaptic activity as demonstrated by impaired EEG activity (i.e. decreased delta/theta power and phase synchrony) during cognitive processing in an error related negativity task of executive function (all $p<0.05$), increased frontal, central, temporal and parieto-occipital relative slow wave EEG power in the theta frequency (all $p<0.05$), and increased hippocampal ($p<0.05$) and inferior frontal ($p=0.004$) and parietal ($p=0.009$) cortical activation during retrieval of an episodic memory task. There was no evidence for a met load effect on any of the markers examined.

Conclusion: Using BDNF val66met polymorphism, we have identified several electrophysiological and functional imaging biomarkers that could sensitively measure synaptic changes in the human brain, using relatively small number of subjects. These endpoints may potentially be used in early Phase 1 or 2 clinical trials in pre-clinical AD to monitor drug effects on synaptic activity or cognitive function.

Policy of full disclosure: This study was funded by GSK. PJN is a former employee of GSK.

S-30-004 BDNF and markers of disease progression in Alzheimer's disease: Findings from the Australian Imaging Biomarkers & Lifestyle Flagship Study of Ageing

P. Maruff. *Cogstate Ltd, Melbourne, Australia*

Objective: Abnormal levels of beta-amyloid (Ab) has consistently been shown to be associated with unremitting memory decline in healthy individuals. However, other genetic factors may moderate the rate of this decline. We investigate the role of apolipoprotein E (APOE) and brain-derived neurotrophic factor (BDNF) Val66Met polymorphisms in the extent to which they moderate A#-related memory decline in the preclinical stages of Alzheimer's disease.

Methods: Healthy adults (HA; n=333) who had undergone PET neuroimaging for Ab were recruited from the Australian Imaging, Biomarkers and Lifestyle (AIBL) Study. Comprehensive neuropsychological assessments were conducted at baseline, and at 18-, 36- and 54-month follow-ups. ApoeE4 and BDNF val66met genotyping was also conducted at baseline.

Results: Relative to Ab-E4 non-carriers, AB+E4 carriers showed significantly greater rates of decline over 54-months across all memory and other cognitive domains (d=0.40–1.22). Relative to Ab-E4 non-carriers, Ab+E4 non-carriers showed significantly greater decline only on verbal episodic memory. No differences in group mean slopes were observed between AB- E4 non-carriers and Ab- E4 carriers within any cognitive domain. Amongst all Ab+ HAs, relative to E4 non-carrier-BDNFVal homozygotes, E4 carriers who were also BDNFMet carriers showed a significantly greater rate of decline on verbal and visual episodic memory, and language over 54-months (d=0.90–1.02).

Conclusion: APOE and BDNFVal66Met were found to moderate clinical manifestation of preclinical AD in different ways.b Possession of the APOE E4 allele increased the severity of A#-related memory decline, while BDNFVal homozygosity increased the ability of the central nervous system to tolerate Ab-related memory decline. These results suggest that while abnormal Ab is central to early AD, the clinical manifestation of cognitive change is complex and moderated by APOE and BDNFVal66Met polymorphisms.

Policy of full disclosure: None.

Thursday 26 June 2014

S-31. Polypharmacy in psychotic and affective disorders: Co-medication with antipsychotic and antidepressant drugs

S-31-001 Treatment of negative vs. other symptoms in schizophrenia

H.-J. Moeller. *Ludwig-Maximilians-University, Munich, Germany*

Although there is a phenomenological overlap between the depressive and the negative symptoms and to a certain degree also with cognitive symptoms of schizophrenia, most psychiatrists feel able to distinguish between the two syndromes under clinical conditions. Also cross-sectional and longitudinal clinical studies using standardised rating procedures demonstrate the differentiation between the negative syndrome, the depressive syndrome and cognitive disturbances. All these three dimensions are more or less distinct from the positive syndrome, although there are often associations between positive symptoms and e.g. negative symptoms (secondary negative symptoms) These and other aspects of the rich clinical phenomenology of schizophrenia, i lead often clinicians to use co-medications or even polypharmacy. These clinical strategies are often not sufficiently evidence based, however, some have at least a certain empirical support. Antidepressants are applied both in the treat-ment of depressive symptoms as well as also negative symptoms in schizophrenia. Mirtazapine has beside the SSRIs a special place in these indications and might also have in addition a positive effect on cognitive functioning due to its presynaptic alpha 2-receptor antagonistic effect. The new glutamatergic compound Bitopertin, a glycine reuptake inhibitor under clinical development, demonstrated efficacy on negative symptoms, not on positive symptoms in a phase II study, and if further developed, would be a candidate for co-medication strategies. Some data for Modafenil support the co-medicati on use in schizophrenia under different aspects. However, the acetyltylcholinesterase-inhibitors, the typical antidementia medications, did not demonstrate consistent efficacy on cognitive disturbances in schizophrenia.

Policy of full disclosure: Conflict of Interest – Financial Disclosure Statement Prof. Dr. Moeller has received grants or is a consultant for and on the speakership bureaus of AstraZeneca, Bristol-Myers Squibb, Eisai, Eli Lilly, GlaxoSmithKline, Janssen Cilag, Lundbeck, Merck, Novartis, Organon, Pfizer, Sanofi-Aventis, Schering-Plough, Schwabe, Sepracor, Servier and Wyeth.

S-31-002 Concomitant antidepressant and antipsychotic medication in schizophrenia and depression. Mechanisms of action.

T. Svensson. *Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden*

Objective: Clozapine and add-on antidepressant drugs (AD) to other antipsychotic drugs (APD), may improve positive, negative and cognitive symptoms and also reduce suicidality in schizophrenia. Moreover, co-medication with low doses of atypical APD may augment and hasten the onset of clinical response to AD in treatment-resistant major depression (TRD). We have here analyzed in rats the underlying neurobiological mechanisms for these clinical results, focusing on monoaminergic and glutamatergic systems in the medial prefrontal cortex (mPFC).

Methods: We used electrophysiological intracellular recording in pyramidal cells in a prefrontal cortical slice preparation to assess NMDA-R function, microdialysis in freely moving animals to assess regional monoamine efflux in brain, and behavioral methodologies, i.e. the conditioned avoidance response (CAR) test to assess antipsychotic activity, the 8-arm radial maze to study working memory (WM) and a catalepsy test for extrapyramidal side effects (EPS).

Results: Contrasting typical D2 antagonists, both clozapine and a combination of other APD and AD or the selective alpha2-R antagonist idazoxan effectively suppressed CAR at reduced D2 occupancy levels, caused no significant catalepsy, selectively enhanced mPFC DA outflow and, via D1-R activation, facilitated prefrontal NMDA-R mediated transmission., Clozapine also reversed the WM impairment induced by the selective NMDA-R antagonist MK-801. Add-on low nanomolar concentrations of APD to SSRIs also facilitated AMPA- induced responses in pyramidal cells of the mPFC, an effect not attainable by each drug alone and blocked by a selective D1-R antagonist. Analogous effects on both AMPA-and NMDA responses in the mPFC were produced by a systemic antidepressant dose of ketamine 24 h after administration.

Conclusion: We propose that facilitation of prefrontal monoaminergic and NMDA-R mediated glutamatergic transmission may be critically involved in the beneficial effects of combined treatment with AD and APD in schizophrenia, and that activation of AMPA-R may be critical for the APD augmentation of AD in TRD.

Policy of full disclosure: Grants/research support: The Swedish Research Council, The Karolinska Institutet, Stockholm (Sweden), The Brain Foundation (Sweden), AstraZeneca, Organon, Schering-Plough, Merck Sharp and Dome, Lundbeck, Otsuka, Astellas Consultant/advisory board: AstraZeneca, Janssen, Lundbeck, Otsuka, Merck Sharp and Dome, Organon, Pfizer, Carnegie Health Care Funds (Sweden).

S-31-003 The role of atypical antipsychotics as add-on medication in major depression

S. Kasper. *Medical University of Vienna, Department of Psychiatry and Psychotherapy, Vienna, Austria*

Objective: There is a wide-spread use of atypical antipsychotics (AAPs) and low-potency typical neuroleptics as add-on for the treatment of depression in clinical practice, even in a time when controlled studies had not been conducted and health regulatory authorities had not provided treatment indication either.

Methods: We set out to investigate the use of AAPs in a European sample of depressed inpatients and the possible changes in their prescription over the time period from 2000 to 2007. On two reference days in the years 2000 (32 psychiatric institutions, N=1.078) and 2007 (54 psychiatric institutions, N=1.826), the following data were recorded for all depressed inpatients (ICD-10: F32.00, F32.01, F32.1, F32.10, F32.11, F32.2, F33.0, F33.00, F33.01, F33.1, F33.10, F33.11 and F33.2) monitored as part of the AMSP (Arzneimittelsicherheit in der Psychiatrie), a drug surveillance program of participating hospitals in Germany, Switzerland and Austria: age, sex, ICD-10 diagnosis and all medication applied on that day. Depressed inpatients with psychotic symptoms were excluded.

Results: We found a significant increase in the number of AAP-treated inpatients from 37.9% in 2000 to 45.8% in 2007. The number of inpatients who received an AAP rose significantly between 2000 and 2007, from 12.8% to 28.3%. In contrast, the percentage of inpatients receiving typical neuroleptics showed a significant decrease from 30.2% to 24.1% over the same time-period. Examining only the subgroup of severely depressed inpatients we found an increase in the number of AP-treated inpatients, but this was not statistically significant. Our study reveals a significant increase in the usage of AAPs.

Conclusion: The study is insofar of importance since it emphasizes the fact that although controlled studies were scarce and health regulatory authorities did not provide treatment indication, this therapy principle was used among clinicians.

Policy of full disclosure: Prof. Kasper has received grant/research support from Bristol Myers-Squibb, Eli Lilly, GlaxoSmithKline, Lundbeck, Organon, Sepracor and Servier; he has served as a consultant or on advisory boards for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen, Lundbeck, Merck Sharp and Dome (MSD), Novartis, Organon, Pfizer, Schwabe, Sepracor, and Servier; and he has served on speakers' bureaus for Angelini, AstraZeneca, Bristol Myers-Squibb, Eli Lilly, Janssen, Lundbeck, Neuraxpharm, Pfizer, Pierre Fabre, Schwabe, Sepracor, and Servier.

S-31-004 Cognitive dysfunction in depression: Implications for treatment

B. J. Sahakian. *University of Cambridge, School of Clinical Medicine, Cambridge, United Kingdom*

Objective: Depression is a common, debilitating and life threatening disorder, projected to become the second leading cause of disability by 2020 by the World Health Organization. It robs individuals and societies of mental capital and wellbeing, and is extremely expensive to governments due to absenteeism and presenteeism at work. In this talk, we will consider 'hot' and 'cold' cognitive processes and how these are impaired in depression. Implications for treatment of cognitive dysfunction in depression will be discussed.

Methods: Cognitive dysfunction is a core feature of depression and cognitive symptoms are included in the diagnostic criteria of the DSM 5. The criteria for depression include a reduced ability to concentrate and indecisiveness. Objective measurement of cognitive impairments in depression using CANTAB (www.camcog.com; www.cantab.com) and other cognitive tests will be discussed.

Results: Cognitive domains that are altered in patients with depression include executive control, decision making, memory, affective processing and feedback sensitivity.

Conclusion: Depressive disorders account for a substantial proportion of disease burden across the globe and have a devastating impact on quality of life, wellbeing and occupational functioning. Given the cost of depression in terms of distress to the individual and their family as well as cost financially to society and governments, new developments for treatments which preserve or enhance cognition, functionality and return to work should be a priority so that all members of society can flourish.

Policy of full disclosure: Barbara Sahakian consults for Cambridge Cognition, Lundbeck, Servier, Roche and holds a grant from Janssen/J & J. She also receives funding from the Wellcome Trust and is a member of the MRC/Wellcome Trust Behavioural and Clinical Neuroscience Institute.

S-32. New insights into the role of NMDA receptors in cognition and psychosis

S-32-001 NMDA-GluN2B receptors govern corticostriatal learning

A. Holmes. *NIAAA, Rockville, USA*

Objective: Corticostriatal systems are known to mediate choice learning and flexibility, but the molecular mechanisms of these processes are not well understood. I will present data on integrated mouse behavioral, immunocytochemical, in vivo electrophysiological, genetic and pharmacological approaches to study discrimination and reversal learning. The objective of the presentation is to provide a point of comparison and convergence with the other presentations in this session that together aim to provide both preclinical and clinical researchers with a state of the art update on current understanding of how NMDA receptor mediate cognition and the mechanisms by which NMDA receptor dysfunction produces cognitive dysfunction in psychotic illness.

Methods: This presentation will present convergent data from pharmacology, in vivo electrophysiology and optogenetics that reveal a critical role for NMDA receptor subunits, notably GluN2B, in controlling prefrontal-striatal circuits mediating learning and cognitive flexibility.

Results: The dorsal striatum (DS) is increasingly activated with learning, whereas reversal of learned choice engaged prefrontal regions. In vivo, DS neurons show altered activity associated with learning and relearning. Corticostriatal or striatal deletion of Grin2b (encoding the NMDA-type glutamate receptor subunit GluN2B) or DS-restricted GluN2B antagonism impairs choice learning, whereas cortical Grin2b deletion or OFC GluN2B antagonism impairs early relearning.

Conclusion: These convergent data demonstrate how corticostriatal GluN2B circuits govern the ability to learn and relearn in a choice task.

Policy of full disclosure: None.

S-32-002 NMDA receptor-associated proteins, cognition, and neuropsychiatric disorders: Translation between mouse and human

T. Bussey. *Cambridge University, Cambridge, United Kingdom*

Objective: The NMDA receptor complex, comprising glutamate receptor subunits and scaffold and signalling proteins, is organised into a signal transduction complex thought to be essential for synaptic plasticity and behaviour. Furthermore many of these molecules have been implicated in neuropsychiatric disease. The specific functional role of the vast majority of proteins within the NMDA receptor complex is, however, less well understood.

Methods: The experiments I will discuss evaluated the cognitive profiles, on a battery of touchscreen tests, of mice with mutations in genes coding for various NMDA receptor-associated scaffolding proteins in the same gene family – Dlg1 (SAP-97, hDlg), Dlg2 (PSD-93, Chapsyn-110), Dlg3 (SAP-102) and Dlg4 (PSD-95, SAP-90). In addition I will discuss the cognitive profiles, on comparable touchscreen tasks, of human individuals with mutations in dlg2.

Results: The mice show dissociable phenotypes on tests of cognition including learning and memory, behavioural inhibition, and attention. Human subjects were impaired in the same cognitive domains as the corresponding mutant mice.

Conclusion: Our results provide evidence that even closely related proteins within the NMDA receptor complex have different roles in cognition. The findings have implications for understanding cognitive dysfunction in brain disorders, particularly psychiatric conditions such as schizophrenia, where aberrant plasticity associated with the NMDA receptor is thought to underlie the disease.

Policy of full disclosure: None.

S-32-003 NMDA receptors and behavioural flexibility: For when things aren't the way they used 2B

S. Floresco. *UBC, Vancouver, Canada*

Objective: NMDA glutamate receptors are critical for formation of new memories, such as aversive Pavlovian associations and discrimination learning. However, these receptors also play a key role in regulating certain higher-order executive functions governed by the prefrontal cortex. The ability to adjust ongoing behaviour in the face of changing environmental contingencies is one collection of functions mediated by the frontal lobes regions that are perturbed in a variety of psychiatric disorders. How different subtypes of NMDA receptors may make selective contributions to these processes related to behavioural flexibility remains to be clarified.

Methods: Recent psychopharmacological studies in rodents have pointed to GluN2B subunit-containing NMDA receptors in facilitating modifications of existing associations or rules in a manner distinct from other NMDA receptors, which appear to play a more generalized role in learning. These findings will be reviewed, focusing on the contribution of GluN2B NMDA receptors to processes such as extinction, reversal and strategy shifts and probabilistic learning.

Results: As opposed to the effects of non-specific NMDA receptor antagonism, selective blockade of GluN2B-NMDA receptors with the Ro25-6981 does not affect the initial learning of conditioned fear response. However, GluN2B blockade markedly impairs within-session extinction and extinction recall of conditioned fear a context-dependent manner. Similarly, GluN2B antagonism does not affect the initial learning of visuospatial discriminations, but induces marked perseverative deficits during reversal or strategy shifts. Interestingly, GluN2B blockade actually facilitated performance of a probabilistic reversal task, with these effects resembling those induced by inactivation of the medial prefrontal cortex.

Conclusion: Collectively, these studies suggest that activity at GluN2B receptors make a fundamental contribution to multiple forms of behavioral flexibility, potentially via actions within the frontal lobes. Development of compounds that may selectively enhance activity at these receptors may lead to novel treatments for impairments in these executive functions associated with numerous psychiatric disorders.

Policy of full disclosure: None.

S-32-004 The human ketamine model: Translational insights into psychosis

P. R. Corlett. *Yale University, Department of Psychiatry, Connecticut Mental Health Center, New Haven, USA*

Delusions are odd and persistent beliefs. They characterize serious mental illnesses like schizophrenia. Cognitive neuroscience approaches to delusions conceive of them forming via aberrant learning mechanisms. The NMDA glutamate receptor antagonist drug ketamine has been used to test these hypotheses. Ketamine induces a state redolent of the early phases of psychosis, transiently, reversibly and safely, in healthy volunteers. It does so by engaging inappropriate prediction error signals, mismatches between expectation and experience, that drive attention and learning toward irrelevant stimuli, thoughts and percepts. Such signals render the world strange, unpredictable and pregnant with new meaning. Across subjects, aberrant prediction error signals measured with functional magnetic resonance imaging correlate with ketamine induced psychotic symptoms; a relationship that has also been observed in patients with endogenous psychotic illnesses. Learning theories of delusions explain odd belief formation. However, delusions can be fixed, tenacious in the face of contradictory evidence. How can a promiscuous learning mechanism explain delusion fixity? I will suggest that this process involves memory reactivation and reconsolidation such that, even when delusions do not come true they are maintained or even strengthened. Appetitive and aversive memories that are reactivated whilst subjects are on ketamine are strengthened. The magnitude of strengthening correlates with ketamine induced psychosis and aberrant prediction error signaling. Such a mechanism can explain the peculiar elasticity of delusions – they expand and envelop contradictory information rather than yielding. By taking inspiration from preclinical behavioral neuroscience and psychopharmacology, we approach an explanation of delusions in terms of cognitive processes and neural mechanisms.

Policy of full disclosure: I have no financial conflicts of interest.

S-33. Converting biological findings into routine clinical tests – Psychiatry's next big challenge

S-33-001 Converting biological psychiatry into clinical tests – why it has been so hard and what to do about it

A. Mechelli. *Department of Psychosis Studies, Institute of Psychiatry, King's College London, London, United Kingdom*

Despite the publication of thousands of scientific articles on the biological correlates of psychiatric disorders, the findings have not resulted in any significant changes in everyday clinical practice. In my presentation, I will provide a brief overview of the current state-of-the-art regarding the development of diagnostic and prognostic biological markers in psychiatry. As part of this overview I will discuss the main theoretical and practical challenges that need to be overcome in order to be able to translate current research evidence into clinical practice. I will then discuss the use of machine learning methods as a possible way of overcoming some of these challenges. Machine learning methods allow inferences at single-subject level and, therefore, have the potential of informing the diagnostic and prognostic assessment of individual patients. I will show a number of recent applications of machine learning methods in biological psychiatry, and will illustrate how this approach could be used to develop stratified interventions in everyday clinical practice.

Policy of full disclosure: None.

S-33-002 Clinical significance: What does it mean when developing biomarker and clinical tests for treatment response in depression and schizophrenia

R. Uher. *Dalhousie University, Halifax, Canada*

Objective: Clinical and biomarker tests have been suggested to improve personalized indications of treatment for depression and schizophrenia. To be useful in clinical settings, such tests have to fulfill criteria for clinical significance in addition to statistical significance. However, no benchmark is available for what is a clinical significant prediction.

Methods: We reviewed information on what effect size of prediction is clinically significant and we performed simulations, based on large datasets, to translate benchmark into a metric of percentage of variance explained, that is broadly applicable to most biomarker and clinical tests.

Results: For tests predicting treatment outcome in major depressive disorder, a clinical significant prediction should explain at least 6.3% of variance in outcomes (e.g. HAMD or MADRS). For tests predicting treatment outcome in schizophrenia, definite clinical significance requires explaining 15% of variance in outcomes.

Conclusion: We provide benchmarks for clinical significance of a range of biomarker and clinical tests. On-line calculators facilitate evaluation of tests for clinical significance.

Policy of full disclosure: None.

S-33-003 From pharmacogenetics to clinical tests: The role of electronic health records

R. Perlis. *Harvard University, Boston, USA*

Objective: Common genetic variation, in aggregate, has been associated with antidepressant treatment response. Characterizing individual variants which are clinically actionable remains a challenge.

Methods: This presentation will review emerging evidence of association between common or rare genetic variation and antidepressant response. It will emphasize barriers to clinical application, including modest effect sizes and absence of evidence of specificity, and suggest ways in which these barriers may be addressed.

Results: Large-scale application of electronic health records provides a means to identify relevant variants, integrate them with other clinical predictors, and assess their utility. Examples of these applications, including recent examinations of rare variants and development of clinical risk stratification tools, will be discussed.

Conclusion: The identification and application of individual variants associated with antidepressant treatment response will require consideration of novel study designs and approaches; electronic health records represent one such strategy.

Policy of full disclosure: Dr. Perlis serves on scientific advisory boards or provides consultation to Genomind, Perfect Health, Proteus Biomedical, Psybrain, and RID Ventures.

S-33-004 Pharmacogenomic tests for psychotropic medications – A journey from bench to bedside

T. Altar. *AssureRx Health, Inc., Mason, OH, USA*

Objective: Assurex Health has developed a combinatorial pharmacogenomic test for 36 antidepressant and antipsychotic medications, GeneSight® Psychotropic. The test measures individual genotypes for the cytochrome P450 enzymes 1A2, 2D6, 2C9, 2C19, 2B6 and 3A4 and the serotonin receptor HTR2A and transporter protein SLC6A4 (Altar et al., Int. Rev. Psychiatry, 2013, 25: 509) to recommend medication selection and dosing.

Methods: DNA was collected for 96 subjects in a 1 year retrospective healthcare utilization study, and 258 subjects in three 8 week, prospective antidepressant studies. In the later studies, the GeneSight report was either provided to clinicians of guided patients to use at their discretion, or not given to clinicians of patients who were treated as usual (TAU).

Results: The test identified 29 of the TAU subjects who, at baseline, were prescribed one or more "red bin" medications, to "Use with increased caution and more frequent monitoring". They showed only a

13.4% symptom improvement, less than the 32% improvement of 59 TAU subjects on yellow status drugs ("Use with caution"), and 28.6% improvement of 31 on green ("Use as recommended") status drugs ($p=0.023$). Four kinds of greater annual health care utilizations or burdens were predicted retrospectively for patients on red bin medications. When provided to the 128 GeneSight-guided subjects, the test increased the odds of clinical response by 2.3-fold compared to the 126 TAU subjects ($p=0.004$), demonstrating a 1.71-fold relative benefit ($p<0.0003$). Compared with TAU subjects, guided subjects originally prescribed green, yellow, or red bin medications showed 6.5%, 13.8% and 23.3% greater HAMD score decreases at eight weeks.

Conclusion: The GeneSight Psychotropic test predicted the lesser improvement and greater healthcare burdens of depressed patients prescribed genetically inappropriate medications and, when used by clinicians, influences medication selection and dose adjustment, and doubles antidepressant responders.

Policy of full disclosure: Genetic testing and funding for data collection and analysis personnel were provided by AssureRx Health, Inc. Dr. Altar is employed by AssureRx Health, Inc.

S-34. Boosting and blunting neurocognitive function in the laboratory and in life

S-35. Adult ADHD and obesity: Neurotransmitter imaging and pharmacotherapies targeting impulsivity

S-35-001 Preclinical models of impulsivity: Pharmacological and dietary manipulations

C. Winstanley. *University of British Columbia, Department of Psychology, Vancouver, BC, Canada*

Objective: High impulsivity has been associated with obesity, and may lead to an inability to control further food consumption despite negative consequences. However, impulsivity has thus far only been considered as a vulnerability factor for over-eating; whether consumption of palatable dietary constituents influences impulsivity itself is unclear. Given that highly palatable food stimulates activity in some of the same neurotransmitter systems as we know to be involved in the regulation of impulse control, we therefore hypothesized that appetitive foods could precipitate impulsivity directly.

Methods: We examined the effects of a high-fat or high-sugar diet on performance in the 5-Choice Serial Reaction Time task (5CSRT), a rodent analogue of the continuous performance test used clinically to assess impulse control and attention. Molecular mechanisms underlying behavioural effects were subsequently assessed. All rats were fed calorie-equivalent amounts of their respective diets.

Results: Rats on the high-fat diet showed a selective and sustained enhancement of impulsive responding, with no change in other behavioural measures. In contrast, the high-sugar diet had no effect on task performance. Molecular analyses revealed that animals on the high-fat diet had reduced levels of D1 receptor protein and DARPP in the striatum, and reduced D2 receptor protein, CREB and pCREB in the nucleus accumbens, compared to controls.

Conclusion: Prolonged consumption of high-fat, but not high-sugar, food increases motor impulsivity in rats which is associated with marked reductions in dopaminergic markers in the dorsal and ventral striatum similar to those seen in chemical addictions. These data suggest that chronic consumption of foods rich in fat lead to molecular and behavioural alterations in mesolimbic impulse control circuits, which may, in turn, contribute to compulsive over-eating in obesity.

Policy of full disclosure: I do not have any financial conflicts of interest.

S-35-002 Imaging of the dopaminergic system in ADHD, binge eating and obesity

G.-J. Wang[1], N. Volkow[2]. [1]*Brookhaven National Laboratory, Upton, NY, USA;* [2]*NIDA, NIH, Rockville, MD, USA*

Objective: Recent literatures suggest a possible comorbidity between Attention-Deficit/Hyperactivity Disorder (ADHD) and obesity. ADHD is characterized by a persistent and pervasive pattern of inattention and/or impulsivity, which might foster binge eating and obesity. The neurobiology mechanism underlying abnormal eating behaviors in subjects with ADHD is unknown.

Methods: We used positron emission tomography (PET) to assess the involvement of brain dopamine (DA) in adults with ADHD and with obesity.

Results: DA modulates circuits in pathological eating behaviors. Food cues increase striatal DA, indicating the involvement of DA in the motivational properties of food. Food cues also increase metabolism in the orbitofrontal cortex indicating its association with the motivation for food consumption. Striatal DA D2/D3 receptor availability (D2R) is reduced in obese subjects, which predisposes obese subjects to seek food to temporarily compensate for under-stimulated reward circuits. Decreased D2R in the obese subjects is also associated with decreased metabolism in prefrontal regions involved in inhibitory control that may underlie their inability to control food intake. Using food cues and methylphenidate, a drug that blocks the DA reuptake transporter, we found obese binge eaters increased DA in the caudate and putamen but not in obese non-binge eaters. DA increases in the caudate were correlated with the binge eating scores. The greater DA increases occur when exposed to a salient stimulus, i.e. food cues that presumably increases DA cell firing in the binge eaters. In the studies of ADHD, the ADHD subjects had reduced D2R in the nucleus accumbens and midbrain regions. The D2R measures in the nucleus accumbens were correlated with their dimension of attention and motivation.

Conclusion: The results from these studies suggest that the lower D2R in striatum in ADHD subjects would have greater risk for compulsive/binge eating to compensate their DA deficits.

Policy of full disclosure: None.

S-35-003 Imaging of the noradrenergic system in adults with obesity and ADHD

S. Hesse. *University of Leipzig, Department of Nuclear Medicine, Leipzig, Germany*

Objective: Although obesity (OB) has been attributed to failure in impulse control and alterations of brain norepinephrine (NE) system, the role of impulsivity and NE levels has not yet been investigated in vivo in OB. In this study, we tested whether in-vivo NE transporter (NET) availability as measured with PET using the highly selective radiotracer [^{11}C] methylreboxetine (MRB) is associated with trait impulsivity in heavily OB individuals compared with normal-weighted, healthy controls (HC).

Methods: Ten OB (Body-Mass-Index 42.4±3.3 kg/m^2, age 34.4±9 years, 4 females) without co-morbidities and ten HC (BMI 23.9±2.5 kg/m^2, age 33.3±10 years, 4 females) underwent dynamic MRB-PET and MRI. Assessment included behavioral inhibition scale (BIS)/activation Scale (BAS) and Barrett impulsiveness scale (BIS-11).

Results: MRB binding potential BP did not differ between OB and HC; by applying discriminant analysis, groups were correctly identified based on regional NET availability. BP correlated significantly with the BIS-11 (mainly attentional scores) in distinct brain areas in OB but not in HC including the prefrontal cortex (PFC) and limbic system (i.e., the hippocampus), and with BIS in the thalamus ($r=0.81$, $p<0.001$). BAS Reward and BP correlated in the PFC, head of the caudate and hippocampus in OB ($r=0.66$; $p=0.04$, $r=0.61$; $p=0.06$ and $r=0.83$; $p<0.001$) in an opposite manner when compared with BP versus BIS-11.

Conclusion: These correlations suggest NET changes and thus an altered NE tone are related to cognitive control and behavioral performance as an adaptive mechanism that fails in OB. They link attention/arousal to NE and as a possible explanation an altered neuronal responsiveness in reward anticipation as it was found in adult ADHD. Findings integrate in particular the hippocampus and help to frame joint future research on adult ADHD and OB by generating new testable hypotheses.

Policy of full disclosure: None.

S-35-004 Pharmacological treatment of ADHD in adults: Implications for binge eating and obesity

U. Muller. *University of Cambridge, Cambridge, United Kingdom*

Objective: To compare current and emerging pharmacological treatments for ADHD in adults with ADHD and eating disorders.

Methods: This is a review of published clinical trials, reviews, meta-analyses and guidelines.

Results: Stimulants like methylphenidate and D-amphetamine as well as the noradrenaline reuptake inhibitor atomoxetine are recommended as first-line pharmacological treatment for adults with ADHD by evidence-based guidelines. Non-stimulant drugs modulating noradrenaline, acetylcholine, histamine, adenosine, glutamate, GABA and multiple transmitters have been investigated in animal models of ADHD and

clinical trials in adults with ADHD – but none of the newer medications is established or has been approved for the treatment of ADHD. The most recent review of approved medications for obesity is positive about longer-term effects of lorcaserin, orlistat and phentermine/topiramate. A review of clinical trials in binge eating disorder found some evidence for positive effects of topiramate on binge eating frequency and weight reduction; but psychological treatments are generally recommended.

Conclusion: Animal studies and clinical PET studies have demonstrated overlapping noradrenergic and dopaminergic mechanisms in ADHD, binge eating and obesity. So far, no controlled trials have investigated the use of approved ADHD or obesity medications in adults with ADHD and comorbid eating disorder. Single case studies and case series found positive effects of stimulants on ADHD symptoms and binge eating in comorbid patients. Noradrenergic modulation of impulsive behaviour and dopaminergic modulation of reward mechanisms are promising approaches for the treatment of patients with ADHD and comorbid binge eating disorder and obesity. More clinical research is needed.

Policy of full disclosure: Honoraria for consultancy, speaking at and organising conferences and travel expenses for attending and presenting at conferences from Eli Lilly, Heptares, Janssen-Cilag, Lundbeck, Shire and UCB Pharma.

S-36. Synaptic plasticity and neurodegeneration

S-36-001 Synaptic plasticity and AD: Roles of GSK-3beta and the JAK/STAT pathway

G. Collingridge. *University of Bristol, Bristol, United Kingdom*

Objective: To identify the signalling cascades that are involved in N-methyl-D-aspartate (NMDA) receptor-mediated long-term depression (LTD) in the hippocampus. To establish how dysregulation of components of these pathways leads to synaptic injury and cognitive deficits in neurodegenerative diseases, such as Alzheimer's disease.

Methods: Experiments were performed on acute and organotypic hippocampal slices prepared from juvenile rats. Proteins were targeted pharmacologically and using RNAi.

Results: We have identified the following pathways in NMDAR-LTD. GluA2/NSF/hippocalcin Akt1/GSK-3beta/tau PI3 K JAK2/STAT3 GIT1/Arf-1/PICK1/Arp2/3

Conclusion: We propose that synaptic injury, an early event in AD, is caused, at least in part, by dysregulation of NMDA receptor-dependent LTD. This process is normally involved in physiological synaptic pruning but in response to a variety of genetic or environmental influences can prune synapses in an aberrant manner. A fuller understanding of this mechanism should lead to better therapeutic strategies.

Policy of full disclosure: None.

S-36-002 Molecular mechanisms underlying the maintenance of LTP and memory

Y. T. Wang. *University of British Columbia, Vancouver, Canada*

Objective: Hippocampal long-term potentiation, one of the most well characterized forms of synaptic plasticity, can be temporally and mechanistically classified into early phase, decaying LTP (E-LTP) and late phase, non-decaying LTP (L-LTP). While the non-decaying nature of L-LTP is thought to be dependent on protein synthesis and contributes to memory maintenance, little is known about the mechanisms and roles of the decaying E-LTP. Our objective is to test our working hypothesis that the decaying of E-LTP is mediated by an active process involving homeostatic endocytosis of postsynaptic a-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid glutamate receptors (AMPARs) at the potentiated synapses during E-LTP and that during the L-LTP, there is a transcription and translation of a PKMz-like molecule that tonically inhibits this homeostatic AMPAR endocytosis, thereby preventing LTP from decaying.

Methods: The hypothesis was tested using a combination of electrophysiological investigation of hippocampal CA1 E-LTP and L-LTP using extracellular recordings of field potentials and behavioral assessments of memory performance using passive avoidance tasks in freely moving rats and transgenic mice carrying APP23/PS45 double mutations.

Results: In support of our hypothesis, we demonstrate that inhibiting endocytosis of postsynaptic AMPARs prevents the decay of E-LTP, thereby converting it into L-LTP. Conversely, releasing AMPAR endocytosis by inhibiting a PKMz-like molecule with ZIP peptide causes L-LTP to decay, thereby converting it into E-LTP. Similarly, inhibition of AMPAR endocytosis is able to prolong memory retention in normal animals, and reduce memory loss in Alzheimer's transgenic mice.

Conclusion: These results strongly suggest that the decay of E-LTP is mediated by an active process involving facilitated AMPAR endocytosis, and inhibiting this process can prolong the longevity of LTP as well as memory under both physiological and pathological conditions.

Policy of full disclosure: None.

S-36-003 Caspases in synaptic plasticity, neurodegeneration and cognitive function

M. Sheng. *Genentech, San Francisco, USA*

NMDA receptor-dependent synaptic modifications such as long-term potentiation (LTP) and long-term depression (LTD) are essential for brain development and function. LTD and synapse elimination are natural processes that sculpt the developing brain, akin to programmed cell death (also termed apoptosis). NMDA receptor-dependent LTD and synapse elimination share common molecular mechanisms with apoptosis. Stimulation of the mitochondrial (or intrinsic) pathway of apoptosis, which culminates in caspase-3 activation, is required for LTD and AMPA receptor internalization in hippocampal neurons. This pathway is activated transiently, moderately and locally in the vicinity of synapses to effect synapse depression without killing the cell. Local activation of the mitochondrial apoptosis pathway in dendrites of neurons by an optogenetic approach is sufficient to cause local loss of dendritic spines and retraction of dendrite branches, without neuronal death. Thus apoptotic mechanisms can sculpt the morphology of neurons in localized fashion. The ubiquitin proteasome system is important for spatially limiting the activation of the apoptotic mechanisms and preventing cell death. Similar 'synaptic apoptosis' mechanisms are co-opted by amyloid-beta to impair synaptic plasticity, which could contribute to the synapse dysfunction and loss of Alzheimer's disease. Mice lacking caspase-3 have normal LTP but show deficits in LTD and homeostatic synaptic plasticity (synaptic downscaling during heightened activity). Behaviorally, caspase-3 knockout mice show hyperactivity as well as defects in attention, habituation to novel stimuli and cognitive flexibility, which are characteristic of human ADHD.

Policy of full disclosure: Morgan Sheng is a full time employee of Genentech Inc, a member of the Roche Group.

S-36-004 Inflammation and hypoxia trigger synaptic depression via microglia CR3 receptors

B. MacVicar[1], J. Zhang[1], A. Malik[1], H. B. Choi[1], R. W. Y. Ko[1], L. Dissing-Olesen[1]. [1]*University of British Columbia, Vancouver, Canada*

Complement receptor 3 (CR3) activation in microglia is involved in neuroinflammation-related brain disorders and pruning of neuronal synapses. Hypoxia, often observed together with neuroinflammation in brain trauma, stroke, and neurodegenerative diseases, is thought to exacerbate inflammatory responses and synergistically enhance brain damage. Here we show that when hypoxia and an inflammatory stimulus (lipopolysaccharide, LPS) are combined, they act synergistically to trigger long-term synaptic depression (LTD) that requires microglial CR3, activation of nicotinamide adenine dinucleotide phosphate oxidase (NADPH oxidase) and GluA2-mediated A-amino-3-hydroxy-5-methyl -4-isoxazolepropionic acid receptor (AMPAR) internalization. Microglial CR3 triggered LTD is novel in that it is independent of N-methyl-D-aspartate receptors (NMDARs), metabotropic glutamate receptors (mGluRs) or patterned synaptic activity. This type of LTD may contribute to memory impairments and synaptic disruptions in neuroinflammation-related brain disorders. This work was supported by operating grants from the Canadian Institutes of Health Research (CIHR Funding reference numbers 8545 and 115121 (B.A.M.), a Canada Research Chair in Neuroscience (B.A.M.), a Natural Sciences and Engineering Research Council of Canada Studentship Award (A.M.), a CIHR studentship award (R.W.Y.K.) and a Heart and Stroke Studentship Award (L.D.O.).

Policy of full disclosure: None.

Educational Workshops

Monday 23 June 2014

EW-02. The use of psychotropic drugs during pregnancy and breast feeding

EW-02-001 **The use of psychotropic drugs during pregnancy and breast feeding**

M.-J. Poulin. *Institut Universitaire en Sante Mentale de Quebec, Quebec, Canada*

Policy of full disclosure: None.

EW-03. Managing treatment resistance in psychiatry

EW-03-001 **Managing treatment resistance in psychiatry**

R. Murray. *Institute of Psychiatry, King´s College London, London, United Kingdom*

Policy of full disclosure: None.

EW-03-002 **Treatment resistant depression**

C. Nemeroff. *University of Miami, Miami, USA*

It is now well-established that a minority of patients with major depression attain remission after treatment with antidepressant monotherapy. This presentation will focus on the factors associated with treatment-resistance including a history of child abuse and neglect, prominent anxiety and certain comorbid medical and psychiatric conditions. The importance of accurate diagnosis will be highlighted including family history and evaluation for medical disorders associated with poor treatment response such as hypothyroidism and hypogonadism. Once a patient has failed an adequate trial of an antidepressant, a decision to either: 1) increase the dose of the current antidepressant, 2) engage in combination therapy of the current agent and another antidepressant or evidence-based psychotherapy (e.g. CBT), 3) utilize an augmentation strategy by adding an agent (e.g. lithium or T3) that is not an effective antidepressant, but when added to an antidepressant converts non-remitters to remitters, 4) switch to an entirely different antidepressant class, e.g. SSRI → SNRI or SSRI → MAOI or 5) use a somatic non-pharmacological approach such as rTMS, VNS, or ECT. The evidence for these approaches will be summarized. Finally, the status of experimental treatments including ketamine and DBS will be discussed.

Policy of full disclosure: Research/Grants: National Institutes of Health (NIH) Consulting: Xhale, Takeda, SK Pharma, Shire, Roche, Lilly, Allergan, Mitsubishi Tanabe Pharma Development America, Taisho Pharmaceutical Inc., Lundbeck Stockholder: CeNeRx BioPharma, PharmaNeuroBoost, Revaax Pharma, Xhale, Celgene, Seattle Genetics, Abbvie Scientific Advisory Boards: American Foundation for Suicide Prevention (AFSP), CeNeRx BioPharma (2012), National Alliance for Research on Schizophrenia and Depression (NARSAD), Xhale, PharmaNeuroBoost (2012), Anxiety Disorders Association of America (ADAA), Skyland Trail Board of Directors: AFSP, NovaDel (2011), Skyland Trail, Gratitude America, ADAA Income sources or equity of $10,000 or more: PharmaNeuroBoost, CeNeRx BioPharma, NovaDel Pharma, Reevax Pharma, American Psychiatric Publishing, Xhale Patents: Method and devices for transdermal delivery of lithium (US 6,375,990B1) Method of assessing antidepressant drug therapy via transport inhibition of monoamine neurotransmitters by ex vivo assay (US 7,148,027B2) Speakers Bureau: None Honoraria Various Royalties Various Expert Witness Various.

Tuesday 24 June 2014

EW-05. Understanding modern genetics

EW-05-001 **Genetic prediction of antipsychotic response and side effects**

J. Kennedy[1], A. Tiwari[1], D. Taylor[1], C. Zai[1], J. Pouget[1], N. Chowdhury[1], J. Lieberman[2], H. Meltzer[3], D. Mueller[1]. [1]*University of Toronto, Toronto, Canada;* [2]*Columbia University, Department of Psychiatry, New York, USA;* [3]*Northwestern University, Department of Psychiatry, Chicago, USA*

Objective: In terms of antipsychotic response we have begun to examine the glutamate system gene variants for their potential role in predicting changes in negative and/or positive symptoms. For antpsychotic-induced weight gain (AIWG), we have examined genetic markers from the biological systems involved in appetite and satiety in the hypothalamus. Previously, the MC4R gene has shown consistent association with the same genotype across four independent AIWG samples, with an overall p=5×10E-12 (Malhotra et al., 2012). Continued development of predictive genetic models is an important area currently under investigation.

Methods: Our sample of schizophrenia patients was prospectively treated with clozapine. Response (n=252) and weight gain (n=100)were measured at 6 weeks and 3 months, and genetic variants were typed using standard PCR methods.

Results: A combination of markers in the glycine transporter gene (GLYT) predicted improvement in response to clozapine (corrected p=0.017). Weight gain was associated with the MC4R gene and replications have been found in two additional clinical samples. The NPY gene also exhibits significant association with AIWG (corrected p<0.03). An algorithm to combine these and other markers together for AIWG has shown very promising results in our sample with over 60% of the variance accounted for (p<0.0001).

Conclusion: Overall there is increasing support indicating that testing of the GLYT gene, along with previously reported dopamine system genes (DRD2), may be useful to help predict which patients will be good versus poor responders. Also, an algorithmic genetic model incorporating genes expressed in the hypothalamus shows strong potential to help clinicians avoid antipsychotic induced weight gain in a given individual patient.

Policy of full disclosure: Dr Kennedy has received honoraria from Novartis, Roche, and Eli Lilly. He is an unpaid member of the AssureRx Health Inc scientific advisory board.

EW-05-002 **Pharmacogenetics: Using genetic information to enhance treatment**

A. Malhotra. *The Zucker Hillside Hospital, Glen Oaks, USA*

Objective: To review key issues in the design and interpretation of pharmacogenetic studies of psychotropic drug response. To discuss the potential clinical implications of pharmacogenetic studies of psychotropic drug response.

Methods: Pharmacogenetics offers the prospect of the identification of readily accessible biological predictors of psychotropic drug response, may provide information about the molecular substrates of drug efficacy, and guide new drug development strategies for the treatment of psychiatric disorders. In this presentation, we will review basic methodological concerns encountered in pharmacogenetic studies. These include design issues, power considerations, appropriate outcome measures, and issues pertaining to candidate gene and GWAS studies. These issues will be discussed in the context of pharmacogenetic studies of antipsychotic drug response – including data implicating the dopamine D2 receptor gene in antipsychotic drug efficacy, as well as results suggesting that genetic factors may be highly predictive of key adverse events associated with treatment. The implication of these developments for the state of the art treatment of psychiatric disorders will be discussed.

Policy of full disclosure: None.

EW-07. Treatment of ADHD across the lifespan

EW-07-001 Treatment of ADHD across the lifespan: The psychotherapeutic perspective

S. Groß-Lesch. *Germany*

Objective: Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder with profound cognitive, behavioural and psychosocial impairments in multiple domains of personal and professional life frequently persisting across the lifespan. Given a prevalence of 4.4% (NCS-R; Kessler et al., 2005), the persistence of ADHD is associated with a psychiatric comorbidity rate of more than 60% in adults (Jacob et al., 2013). Due to the high prevalence and societal impact of ADHD and the limited effectiveness of existing pharmacologic treatment strategies there is a considerable need for psychotherapeutic treatment options.

Methods: Taking into account the disorder's variable and changing phenotype and also different expectations regarding age-related behaviour the main focus here will be on non-medical options which are propagated in various national and international guidelines. Since for pre-schoolers and school children stimulant medication may – dependent on the severity of symptoms and impairments – not be the first-line treatment, the initial step is to provide information about diagnosis and treatment options to parents or caregivers. Emphasis will be on parental training programs, most often offered as group training. Providing information to teachers should support behavioral interventions at school. With moderate to severe levels of impairment, and for older children individual psychological interventions rather than group training, focus should be put on acquiring social skills with peers, problem solving, self control, listening skills and dealing with and expressing feelings.

Results: For adolescents and adults there are CBT programmes with different therapeutic aims, e.g. comorbidity, disorganisation, or problems with keeping a daily routine. A recent German study used a different therapeutic approach, taking into account some shared symptoms between ADHD and borderline personality disorder. Mindfulness offers a opportunity to improve self-awarness, a typical problem related to the core symptom of inattention, and therefore is the critical step into emotion regulation and improving impulsivity.

Policy of full disclosure: I declare that I received speaker's fees from Medice Company.

EW-07-002 Treatment of ADHD across the lifespan

U. Muller. *University of Cambridge, Cambridge, United Kingdom*

Policy of full disclosure: None.

EW-08. Translating schizophrenia to animal models: What works and what doesn't

Shared presentation of Prof. Weiner, Dr. Howland, Prof. Grace and Dr. Floresco

EW-08-001 Translating schizophrenia to animal models: What works and what doesn't

I. Weiner[1], S. Floresco[2], A. Grace[3], J. Howland[4]. [1]*School of Psychological Sciences, Tel Aviv University, Tel Aviv, Israel;* [2]*UBC, Vancouver, Canada;* [3]*University of Pittsburgh, Pittsburgh, USA;* [4]*University of Saskatchewan, Health Sciences Building, Saskatoon, SK, Canada*

Schizophrenia is a complex disorder with prominent symptoms that are uniquely human and a poorly understood etiology. As a result, the development of animal models of the disorder has proven difficult. Recently, well-validated and standardized testing procedures for animal models of schizophrenia have been established by initiatives such as the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS). These procedures are useful in furthering hypotheses related to the etiology, symptoms, and pathophysiology of the disorder, as well as novel treatment strategies. This educational session will enable a discussion of these testing procedures. The panelists will give brief presentations regarding rodent models that involve manipulations either during adulthood (acute NMDA receptor antagonism, pharmacological reductions in prefrontal GABA transmission) or early development (maternal immune activation, methylazoxymethanol acetate treatment during gestation). Presentations will include a particular focus on rodent behavioural tests that translate to the MATRICS battery, electrophysiological recordings, brain imaging approaches, and drug development. The remainder of the session will be dedicated to an open discussion among the panelists and audience regarding the strengths and weaknesses of the various approaches.

Policy of full disclosure: None.

Wednesday 25 June 2014

EW-10. Optimising clinical trial designs

EW-10-001 Increasing signal detection in clinical trials: Lessons learned

G. Sachs. *Bracket Global, Wayne, USA*

Policy of full disclosure: None.

EW-10-002 From biological psychiatry to stratified medicine clinical trials – lessons for psychiatry from the rest of medicine

S. Kapur. *Institute of Psychiatry, KCL, London, United Kingdom*

Policy of full disclosure: None.

Thursday 26 June 2014

EW-11. The ABCs and CpGs of epigenetics

EW-11-001 The ABCs and CpGs of epigenetics

G. Turecki[1], P. Albert[2]. [1]*McGill University, Douglas Research Institute, Montreal, Canada;* [2]*University of Ottawa, Ottawa, Canada*

This educational workshop will review the rapidly changing landscape of epigenetics and its application to mental health. We will cover basic concepts and review some of the major findings, both in animal models of mental disorders and in humans.

Policy of full disclosure: None.

EW-11-002 The ABCs and CpGs of epigenetics

P. Albert. *University of Ottawa, Ottawa, Canada*

Objective: In this session I will provide an introduction to epigenetic mechanisms of relevance to mental health.

Methods: Basic concepts of DNA and chromatin structure, nucleosome structure, histone structure and regulation and mechanisms by which these are modified to alter gene expression will be presented.

Results: Epigenetic mechanisms including Chromatin modification (histone acetylation, phosphorylation, methylation); DNA methylation; and non-coding RNA's will be presented. The effect of environment, signaling and genome on epigenetic modifications and resulting vulnerability to mental illness will be discussed.

Conclusion: The participants will obtain a comprehensive yet comprehensible overview of which and how epigenetic mechanisms can translate enviromental stress into lifelong predisposition.

Policy of full disclosure: None.

EW-12. The impact of neuroimaging on understanding psychiatric disorder

EW-12-001 Bright future of PET and fMRI?

R. Lanzenberger. *Medical University of Vienna, Psychiatry, Vienna, Austria*

Policy of full disclosure: R. Lanzenberger received travel grants and conference speaker honoraria from AstraZeneca, Roche and Lundbeck A/S.

EW-12-002 The impact of neuroimaging on understanding psychiatric disorders

D. Nutt. *Imperial College, London, United Kingdom*

My talk will explore the nature of anxiety disorders and their treatments from the perspectives of neuro-imaging both PET and fMRI. The role of GABA 5HT and noradrenaline neurotransmitters will be discussed particularly in relation to how current treatments such as benzodiazepines and antidepressants might work.

Policy of full disclosure: None.

Monday 23 June 2014

SW-01. The pitfalls, problems using gene knockout animals in neuropsychopharmacology

SW-01-001 **Should we do away with the knockout mouse?**

C. McOmish. *Florey Institute of Neuroscience and Mental Health, Melbourne, Australia*

Our understanding of psychiatric disorders is accelerating rapidly, revealing extraordinary levels of complexity, heterogeneity and pleiotropy, requiring systematic analysis to experimentally explore the mediators and modulators of each condition. Commonly, we turn to animal models; a reductionist approach by which we may begin to dissect the neurochemical and structural components involved, while still working at a systems level, with the intention of using this knowledge to develop novel and effective neuropsychopharmacological treatments. However, to date, these approaches have failed to deliver effective treatments and we must thus critically assess the strategies that have been employed. In this workshop we will explore the progress that has been made in establishing valid animal models of psychiatric disorders, and the use of these models for the development of novel therapeutics, while beginning to unravel the complex factors that may be contributing to the limitations of current methodological approaches. Emerging approaches for optimizing the validity of animal models and developing effective interventions will be discussed. We will address the key aspects of construct, face, and predictive validity in animal models, incorporating genetic and environmental factors. We will also cover novel transgenic technology and how this may contribute towards improving translational outcomes of preclinical studies.

Policy of full disclosure: no conflicts of interest.

SW-04. GPCRs and psychotherapeutic drug development

SW-04-001 **GPCRs and psychotherapeutic drug development**

H. Manji. *Johnson & Johnson, Titusville, USA*

Policy of full disclosure: None.

SW-04-002 **GPCRs and psychotherapeutic drug development**

G. Gründer. *RWTH Aachen University, Aachen, Germany*

Policy of full disclosure: None.

Wednesday 25 June 2014

SW-09. Pathways to drug discovery in CNS

SW-09-001 **Novel therapeutic approaches constituting multi target neurorstorative drugs, with cell cycle activity and mitochnondria biogenesis for neurodegenerative disorders**

M. Youdim. *Technion-Faculty of Medicine, Haifa, Israel*

Alzheinmer's disease (AD), Parkinson's disease (PD), Huntington disease (HD), amyotrophic lateral sclerosis (ALS) and multiple Sclerosis (MS) are initiated by cascade of neurotoxic events, that includes oxidative stress, brain iron dysregulation, glutamate excitotoxicity, nitric oxide, inflammatory process, neurotxic processes. These also include misfolding and aggregation of Aβ~amyloid peptide and α-synuclein resulting from the demise of ubiquitin-proteasome system (UPS) as demonstrated neurochemically and transcriptomics and proteomic profiling. AD and PD subjects are benefiting from symptomatic effects of cholinesterase inhibitors, memantine, monoamine oxidase B inhibitors, L-dopa, dopamine receptor agonists, COMT inhibitors and amantadine. These drug were developed to act on a single molecular target. For HD and ALS there are no effective drugs. The present drugs have limited symptomatic activities and current pharmacological approaches have sever limitation in their ability to modify the course of the diseases (neuroprotection), offering incomplete and transient benefit to patients. However, the new therapeutic strategies for neurodegenerative and neuropsychiatric diseases are those in which drug candidates are designed expressly to act on multiple neural and biochemical targets involved in the disease process and to possesses neuropotective and neurorestorative activities. Thus we have hypothesized and developed a series of innovative novel multi target neurorestorative drugs from our successful neuroprotective disease modifying anti Parkinson drug, rasagiline (Azilect). These drugs possess anti Parkinson, anti Azlheimer and anti depressant activities in animal models employed by the pharma to develop mono target drugs.

Policy of full disclosure: None.

SW-09-002 **Pathways to drug discovery in CNS**

P. H. Andersen. *Hongaard Consulting, Farum, Denmark*

Understanding of the biology of most CNS diseases has historically in the best case been limited. Consequently, Drug Discovery in the CNS have until recently been guided primarily by a retro pharmacological approach, i.e. trying to either mimic or prevent the effect of various psycho-active drugs. This has led to several generations of me-too drugs with only minor improvements in both the efficacy and side-effect profile. However, in the past decade or so we have seen a number of identified genes conferring increased risk of acquiring a given CNS disease, however, the increased risk mediated by these genes are typically low and cannot alone explain the family linked frequency of these diseases. Thus, a strong influence of social, environmental or other "external" factors can via Epigenetic mechanisms be expected to explain the real life penetrance of these genes. The changes seen in CNS Drug Discovery over the past 30 years will be discussed and potential areas for identification of novel targets for treating CNS diseases will be presented.

Policy of full disclosure: None.

Monday 23 June 2014

CP-01. Biological tests to aid decision making in clinical psychiatry – how long will the clinician have to wait?

CP-01-001 Developing biological tests for clinical psychiatry: How long will the clinician have to wait?

S. Kapur. *Institute of Psychiatry, KCL, London, United Kingdom*

Patients with mental disorders show many biological abnormalities; however, few of these have converted into tests with clinical utility. Why is this the case? The talk will suggest that the lack of a biological 'gold standard' definition of psychiatric illnesses; a profusion of statistically significant, but minimally differentiating, biological findings; 'approximate replications' of these findings; and a focus on comparing prototypical patients to healthy controls has limited clinical applicability. Overcoming these hurdles will require a new approach. Rather than seek biomedical tests that can 'diagnose' DSM-defined disorders, the field should focus on identifying biologically homogenous subtypes within the current psychiatric classifications (thereby side-stepping the issue of a gold standard). Rather than chasing p-values versus normal controls, we must focus on clinically meaningful effect sizes within a diagnosis and in particular identify biomarkers that lead to 'discordant predictions'. And validating these new biomarker-defined subtypes will require longitudinal studies, standardised measures at a scale not previously attempted by biological psychiatry. To achieve this scale will need to consortia that share individual patient-data across studies – thereby overcoming the problem of significance chasing and approximate replications. Such biological psychiatry derived clinical tests, and the subtypes they define, will exist, at least for the foreseeable future, side-by-side of the DSM-like diagnosis. However, they will provide a natural basis for new therapeutics and if this venture is successful, it will give rise to a 'stratified psychiatry' that will improve clinical outcomes across conventional diagnostic boundaries. The talk will make the case for these assertions by reviewing data from within psychiatry and from the rest of medicine – and will point out the early signs of success.

Policy of full disclosure: None.

Wednesday 25 June 2014

CP-02. Strategies to manage treatment resistant depression

CP-02-001 Strategies to manage treatment resistant depression

S. Kasper. *Medical University of Vienna, Department of Psychiatry and Psychotherapy, Vienna, Austria*

The term treatment resistant depression (TRD) was introduced in 1974 and since then it has been a topic of different publications and research strategies. Unfortunately, different definitions of TRD are used. Based on the literature available it is evident that the following four categories need to be distinguished: insufficient response, treatment resistant, treatment refractory and chronic depression. These definitions have practical as well research implications and different results can be expected when these patients are summarized as a group. For pharmacotherapy of TRD it is evident that switching the mechanism of action of antidepressant medication does not benefit the patient and it is apparent that augmentation with another agent, for instance atypical antipsychotics, the combination with another antidepressant or the addition of lithium or T3 might provide a better option. Unfortunately genetic characterization is not there as yet to be of practical value to predict treatment response but a more refined methodology like the new generation exome and full genome-sequencing and genome-wide pathway analysis promises to be helpful for prediction and prevention of depression and to identify molecular targets for new generations of psychotropic medication.

Policy of full disclosure: Prof. Kasper has received grant/research support from Bristol Myers-Squibb, Eli Lilly, GlaxoSmithKline, Lundbeck, Organon, Sepracor and Servier; he has served as a consultant or on advisory boards for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen, Lundbeck, Merck Sharp and Dome (MSD), Novartis, Organon, Pfizer, Schwabe, Sepracor, and Servier; and he has served on speakers' bureaus for Angelini, AstraZeneca, Bristol Myers-Squibb, Eli Lilly, Janssen, Lundbeck, Neuraxpharm, Pfizer, Pierre Fabre, Schwabe, Sepracor, and Servier.

Tuesday 24 June 2014

PP-01. DSM5 will be the death of psychopharmacology

PP-01-001 DSM and psychopharmcology – the New Normal

I. Everall. *Department of Psychiatry, University of Melbourne, Parkville, Australia*

The DSM is a classification system for mental health problems that exists alongside the international classification of diseases that is used globally for all physical and mental illnesses. Originally the DSM was utilized for research purposes. Within the United States it has also become the staple for making clinical diagnoses, however globally just over 20% of psychiatrists rely on the DSM for clinical practice. In the research sphere the use of the DSM has remained dominant globally in terms of deciding whether potential research study subjects exhibit the necessary signs and symptoms to achieve the threshold for a categorical mental health disorder diagnosis. Consequently, changes in disorder classification, as occurs in evolving versions of the DSM, can have major impacts on research efforts that can significantly affect study outcomes. Psychopharmacology is one research discipline that is heavily reliant on DSM criteria for the design of testing the efficacy on new molecules in treating disorders such as major depressive disorder (MDD). Over recent years it has been noted that the observed efficacy of antidepressant such as selective serotonin reuptake inhibitors (SSRI) has diminished in psychopharmacological study to just above the effect of placebo. This lack of efficacy could be real and should lead to a questioning of the validity of the serotonin hypothesis of MDD or it could reflect broadening of the diagnostic criteria for MDD resulting inappropriate subjects being admitted to therapeutic trials. In this presentation I will present some of the difficulties that the DSM poses to fields such as psychopharmacology, the challenge of an increasingly medicalized society and potential ways forward.

Policy of full disclosure: None.

PP-01-002 DSM5 will be the death of psychopharmacology

G. Burrows. *University of Melbourne, Richmond, Australia*

Policy of full disclosure: None.

Monday 23 June 2014 – Wednesday 25 June 2014

RA-01. Rafaelsen Award Posters

RA-01-001 Reduction of hippocampal leptin levels may be involved in anxiety-like behavior observed in balb-c mice fed with carbohydrate-enriched diet

D. Aguiar[1], A. L. Oliveira[1], C. Santos[1], A. Ferreira[2]. [1]*UFMG-ICB, Belo Horizonte, Brazil;* [2]*UFMG-Nursing School, Belo Horizonte, Brazil*

Objective: The obesity is a chronic disease which is frequently associated with other diseases such as, diabetes type II and metabolic syndrome. Moreover, obesity and stress related psychiatric disorders are comorbidity. Epidemiologic data have been shown that obesity constitutes a risk factor for the development of mood disorders, such as anxiety. However, the understanding of the relationship between diet, stressful events and the development of psychiatric disorders is poorly understood. Thus, the aim of this study is verify if animals underwent to a diet normocaloric/high carbohydrate, which does not modify the weight of the animals, but promotes the expansion of abdominal fat are more susceptible to stressful events.

Methods: Balb-c mice with five weeks of age were fed over 12 weeks with standard (C-39.5% carbohydrate, 8% fiber) or high-carbohydrate diet (HC-58% carbohydrate). After this period, the behavioral effects induced by acute stress restriction were observed in animals exposed to the elevated plus maze (EPM) 24 hours after stress. After this, animals were sacrificed immediately after EPM, their hippocampus was dissected and the leptin levels were measured

Results: Animals fed with HC diet displayed reduced the percentage of entries into the open arms of the EPM 24 h after the restraint stress (control stress=69.7±5.5; HC stress=36.8±6.1, $p<0.05$ two-way ANOVA). The number of enclosed arms entries in the E.P.M. was significantly higher in diet stress animals as compared to control stress animals (control stress =6.8±1.8; HC stress=12.±1.2, $p<0.05$ two-way ANOVA). However, this is not due impairment in locomotor activity since no effect was observed in the open field test. These behavioral effects were followed by a reduction of leptin levels in HPC (control stress=1309±70.21; HC stress=759.3±46.6, $p<0.05$ two-way ANOVA).

Conclusion: The animals fed with HC diet displayed anxiogenic-like behavior in the E.P.M 24hours after stress. These data suggest that exposure to an imbalance diet facilitates susceptibility to stressful events. Moreover, the mechanisms responsible for these effects may be related with impairment in hippocampal leptin signaling

Policy of full disclosure: Finnancial Suport: CAPES, CNPq (475899/2010-5).

RA-01-002 Increased MIF and IL-1ß mRNA blood levels and childhood trauma events as accurate predictors of treatment response in depressed patients

A. Cattaneo[1], L. Bocchio Chiavetto[2], R. Uher[3], M. A. Riva[4], C. Pariante[1]. [1]*King´s College London, London, United Kingdom;* [2]*IRCCS San Giovanni di Dio, Brescia, Italy;* [3]*King´s College London, SGDP, London, United Kingdom;* [4]*University of Milan, Milan, Italy*

Objective: A third of patients do not respond to any currently available antidepressants and there is a need to establish predictive biomarkers of treatment response useful for therapy personalization.

Methods: To identify predictive biomarkers of treatment response to be easily replicated in different laboratories we measured by Real Time PCR the absolute blood mRNA expression of MIF and IL-1β, two proinflammatory genes that we previously found associated with treatment response.

Results: The absolute number of molecules for MIF and IL-1β were higher in non responders (83.1±4.8×106 for IL-1β and 102.5±4.2×106 for MIF) as compared with responders (50.4±2.1×106 for IL-1β, and 55.4±1.9×106 for MIF). By using a Linear Discriminant Analysis we combined MIF and IL-1β values with treatment response and we defined a rule able to discriminate responders vs. non-responders. We also calculated MIF and IL-1β cut-off values and the relative probability of being a responder or a non-responder. We then validated these findings in an independent sample of depressed patients and we found that our predictive model had 14% of false positives and 16% of false negatives. The patients which erroneously have been identified as non responders because of high baseline levels of cytokines showed a reduction in the cytokines levels -to levels similar to responders- already at week 4; moreover, the patients which were erroneously classified as responders because of normal baseline cytokine levels reported severe childhood trauma events.

Conclusion: Our data suggest that both high cytokines levels and a history of childhood trauma may provide a clinically-suitable approach to identify patients who are non-responders to classic antidepressants and maybe benefit from immune-targeted therapy.

Policy of full disclosure: None.

RA-01-003 Genetic predictor of antidepressant response for major depressive disorder accounting for clinical subgroups: A genome-wide association study

W. Nakano[1], D. Mehta[2], M. Ising[3], H. Pfister[3], D. Czamara[3], T. Carrillo-Roa[3], F. Holsboer[3], S. Lucae[3], A. Erhardt-Lehmann[3], E. Binder[3]. [1]*UOEH, Kitakyushu, Japan;* [2]*Max Planck Institute of Psychiatry, Munich, Germany;* [3]*Munich, Germany*

Objective: To date, a number of genome-wide association studies, including a meta-analysis have tried to detect genetic associations with antidepressant response for major depressive disorder (MDD) but with limited success. We performed a genome-wide association analysis and tested the hypothesis that accounting for clinical subgroups of depression (anxious depression group: ANX versus non-anxious depression group: NON-ANX) will provide increased sensitivity and higher power to detect subgroup-specific genetic variants associated with antidepressant treatment response.

Methods: A total of 626 inpatients (n=366 ANX, n=260 NON-ANX) with MDD were treated with antidepressants from the Munich Antidepressant Response Signature (MARS) project. The association between genotypes and percentage improvement in Hamilton Depression Rating Scale (HAM-D) scores was tested using PLINK.

Results: No single-nucleotide polymorphism (SNP) reached genome-wide significance in the whole sample but upon stratification into subgroups we identified 2 SNPs (rs4278478 and rs10831500) within the mastermind-like 2 (MAML2) gene on chromosome 11 significantly associated with percent improvement HAM-D score at the genome-wide significance level ($p=3.04\times10–8$ and $p=3.57\times10–8$) in NON-ANX. The direction of the effects for these SNPs was in the opposite direction in non-anxious depression group versus anxious depression group. In NON-ANX, each SNP explained >11% variance of percentage improvement in HAM-D scores.

Conclusion: In the current study, we reported SNPs within the MAML2 gene significantly associated with response to antidepressant treatment in MDD at the genome-wide level but this association was observed only after stratification into subgroups and not when assessing the whole sample. A replication in an independent sample is currently underway. This study highlights that it is essential to identify and interrogate specific clinical subgroups of depression, to allow identification of robust and reliable genetic predictors of antidepressant treatment. We are confirming our findings in independent samples.

Policy of full disclosure: None.

RA-01-004 Cognitive function, serum IL-10 level, and IL-10 -592 A/C polymorphism in first-episode drug naive patients with schizophrenia versus healthy controls

M. Xiu[1], D. Chen[1], X. Zhang[1]. [1]*Beijing Hui-Long-Guan Hospital, Beijing, China*

Objective: Numerous studies have shown that activation of the peripheral innate immune system induces production of cytokines within the brain that can have deleterious effects on cognition. Recent study has shown that IL-10, a potential anti-inflammatory cytokine, can exert neuroprotection and may play a role in pathogenic processes leading to cognitive dysfunction. Cognitive impairment is a core feature in the pathology of schizophrenia, and recent studies showed altered IL-10 in schizophrenia.

However, no study has explored the role of IL-10 in cognitive deficits of schizophrenia.

Methods: In the present study, we recruited 241 first episode and drug-naïve patients with schizophrenia and 240 healthy controls and compared them on the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), serum IL-10 levels and the IL-10 -592A/C polymorphism. We assessed patient psychopathology using the Positive and Negative Syndrome Scale.

Results: Our result showed a significant difference in the allelic frequency ($p<0.05$) and a trend toward to significant difference in the genotypic frequency ($p<0.1$) between patients and healthy controls. Further analysis showed significant differences in the genotype and allele distributions between patients and controls only in males. The A variant was associated with worse attention performance among schizophrenia patients but not among normal controls. Serum IL-10 levels were significantly decreased in patients compared with that in normal controls. Moreover, IL-10 levels among the schizophrenia A allele carriers were correlated with the degree of cognitive impairments, especially attention performance.

Conclusion: Our results suggest that the IL-10 -592A/C polymorphism may play a role in susceptibility to male schizophrenia. Further, we demonstrated an association between the IL-10-592A/C polymorphism and poor attention in schizophrenia. The association between lower IL-10 levels and cognitive impairment in schizophrenia is dependent on the IL-10-592A/C polymorphism.

Policy of full disclosure: None.

RA-01-005 Genetic variations across remote regulatory regions of 14 obsessive-compulsive disorder candidate genes in antidepressant response

G. Zai[1], C. Zai[1], V. Goncalves[1], K. Wigg[2], J. Kennedy[1], M. Richter[3]. *[1]CAMH, University of Toronto, Toronto, Canada; [2]Toronto Western Hospital, UHN, Toronto, Canada; [3]Sunnybrook Health Sciences, Centre, Toronto, Canada*

Objective: Obsessive-compulsive disorder (OCD) is a chronic and debilitating disorder with a strong genetic etiology. Genetic associations between OCD and several candidate genes including the glutamate transporter (SLC1A1), monoamine oxidase (MAOA), glutamate NMDA receptor 2B (GRIN2B), serotonin 2A receptor (5HTR2A), serotonin transporter (SLC6A4), brain-derived neurotrophic factor (BDNF), and catecholamine-O-methyl transferase (COMT) genes have previously been reported. Pharmacogenetics represents a valuable alternative strategy to define subtypes of OCD and to define clinically useful inter-individual genetic variation in drug response. We investigated 14 genes including those mentioned above as well as top hit genes from a recent OCD genome-wide association study: Disks Large (drosophila) homolog-associated protein 1 (DLGAP1), BTB (POZ) domain containing 3 (BTBD3), serotonin 1B receptor (5HT1B), SLIT and NTRK-like family (SLITRK5), Fas apoptotic inhibitory molecule 2 (FAIM2), glutamate receptor, ionotropic, kainite 2 (GRIK2), and fucosyl-transferase 2 (FUT2).

Methods: examined a total of 32 single nucleotide polymorphisms across these candidate genes and their regulatory regions using a custom-made 32-SNP OpenArray chip and genotyping was performed using the QuantStudioTM 12 K Flex Real-Time PCR System in 222 OCD patients with retrospective response data on multiple serotonin reuptake inhibitor (SRI) trials. Individuals were grouped into those who improved following an adequate trial of one or more SRI(s) as compared with those who reported "minimal", "no change", or "worsening". Genotypes and response data were examined on a combined SSRI/SRI basis.

Results: Interesting associations ($P<0.05$) were detected for DLGAP1, SLITRK5, BTBD3, 5HT1B, and SLC1A1 in SSRI/SRI response. These results suggest that genetic variants may play a role in SRI response to OCD.

Conclusion: Combination of these variants may be clinically useful in predicting treatment resistance versus response in OCD.

Policy of full disclosure: – Gwyneth Zai = no financial disclosure – Clement Zai = Eli Lilly (fellowship research salary support) and Gerson Lehrman Group (consultant fees) – Vanessa Goncalves = no financial disclosure – Karen Wigg = no financial disclosure – James Kennedy = AssureRx (scientific advisory board member), Eli Lilly (speaker honorarium and expenses), Novartis (speaker honorarium), and Roche (consultant honorarium and expenses) – Margaret Richter = Lundbeck (speaker honorarium and speaker fees) and Roche (research support/grant).

RA-01-006 Toxoplasma gondii seropositivity is positively associated with anxiety and burnout-syndrome

C. Bay-Richter[1], H. Buttenschøn[1], L. Foldager[1], H. Kolstad[2], L. Kærlev[3], J. Thomsen[4], N.P. Ole Mors[2], G. Wegener[1]. *[1]TNU, Aarhus University, Risskov, Denmark; [2]Aarhus University, Aarhus, Denmark; [3]Odense University Hospital, Odense, Denmark; [4]Bispebjerg Hospital, Copenhagen, Denmark*

Objective: Toxoplasma gondii (TOX) is a common parasite affecting approximately one-third of the human population, primarily targeting neurons. An increasing number of studies are now providing evidence that the disease is associated with behavioural changes and psychiatric disease. It has for example been demonstrated that TOX seropositivity was higher in schizophrenia, depression, anxiety, and bipolar patients compared to healthy controls. The objective of this study is to examine TOX seropositivity in a large human population in relation to psychiatric symptoms.

Methods: A population of 548 participants was initially included and the participants went through a semi-structured diagnostic interview (SCAN interview) followed by blood sampling. From this population, a control group (n = 158) with no diagnosis of psychiatric disorders was extracted as well as a group consisting of subjects showing symptoms of anxiety (SCAN interview, n = 106) and burnout syndrome (Copenhagen Burnout Inventory, n = 51). Blood serum was examined for IgG antibodies to TOX using ELISA assays.

Results: Data were analysed using logistic regression models with gender, age and BMI as confounding factor and show that seropositivity of TOX is positively associated with anxiety (adjusted odds ratio [OR] = 2.05; 95% CI, 1.14-3.70; $p=0.016$). In addition, we find an association between seropositivity and burnout syndrome (OR = 3.43; 95% CI, 1.67–7.05; $p<0.001$).

Conclusion: These data supports the notion that TOX is associated with psychiatric disorders. Our results are consistent with previous reports on an association between TOX and anxiety. Furthermore, we show a positive association between TOX seropositivity and the stress related syndrome, burnout syndrome.

Policy of full disclosure: None.

RA-01-007 Antidepressant-like activity of 1-(7-methoxy-2-methyl-1,2,3,4-tetrahydro-isoquinolin -4-YL)-cyclohexanol, a beta-substituted phenylethylamine in animal models of behavioral despair

A. Dhir[1], S. K. Kulkarni[2]. *[1]Gujarat Forensic Sciences University, Institute of Research and Development, Gandhinagar, India; [2]University Institute of Pharmaceutical Sciences, Panjab University, Chandigarh, India*

Objective: The β-phenylethylamines are known to act as ligands for the trace amine receptors, a novel family of G-protein-coupled receptors that is known to play an important role in the pathophysiology of major depression. The present study is an attempt to evaluate one of such molecules, 1-(7-methoxy-2-methyl-1,2,3,4-tetrahydro-isoquinolin-4-yl)-cyclohexanol, in animal models of depression.

Methods: Various behavioral paradigms of despair such as forced swim and tail-suspension tests were used to assess the antidepressant-like activity. Further, an alteration in the levels of various neurotransmitters (norepinephrine, serotonin, and dopamine) in the mouse brain was evaluated.

Results: The molecule (4–16 mg/kg., i.p.) dose-dependently inhibited the immobility period in mouse forced swim test and tail-suspension tests, the effect comparable to venlafaxine. Additionally, the molecule at 8 mg/kg., i.p. reversed reserpine-induced behavioral despair in mouse forced swim test. When administered simultaneously, it enhanced the antidepressant activity of sub-effective doses of imipramine or fluoxetine in the mouse forced swim test. The molecule at 8 mg/kg., i.p. enhanced the levels of norepinephrine without affecting serotonin in the mouse brain. However, at higher dose (16 mg/kg., i.p.), it increased the levels of norepinephrine, serotonin, and dopamine. The molecule enhanced the locomotor activity in mice only at higher doses. The molecule, unlike venlafaxine, which potentiated barbiturate-induced hypnosis, was devoid of any sedative activity. Finally, there is an involvement of L-arginine-nitric oxide-cyclic guanosine monophosphate signaling pathway in its antidepressant action.

Conclusion: In conclusion, 1-(7-methoxy-2-methyl-1,2,3,4-tetrahydro-isoquinolin-4-yl)-cyclohexanol, possess antidepressant-like activity in animal models of depression by modulating the neurotransmitter levels in the brain. Such an activity might be due to the modulating action of this novel molecule on trace amine receptors.

Policy of full disclosure: None.

RA-01-008 Review of trait impulsivity in suicide: A pharmacological target

S. Sahoo[1], C. Schuetz[2]. [1]*Essendon, Australia;* [2]*University of British Columbia, Vancouver, Canada*

Objective: This paper aimed to review trait impulsivity in suicidal attempts, which can serve as unique pharmacological target.

Methods: Using keywords "impulsivity and suicide" to search on Medline, EMBASE, Psychinfo & including those studies that had reported trait impulsivity scores using validated and reliable assessment measures, we searched all English language studies from 1990 to December 2012 with 33 studies meeting inclusion criteria, which were then reviewed by the two reviewers independently. We generated standardized mean differences (SMDs) for impulsivity using RevManager 5.1 from Cochrane analysis.

Results: The Barratt Impulsivity Scale (BIS) 11 was the instrument commonly used in attempted suicides. 33 studies met criteria for inclusion in suicide, yielding a SMD of 0.71 on all assessment measures combined.

Conclusion: Impulsivity is significantly higher in patients attempting suicide than normal controls, which indicates that trait impulsivity can drive suicidal attempts, and can serve as an unique pharmacological target for intervention.

Policy of full disclosure: None.

RA-01-009 Parahippocampal and insular gray matter volume correlates with empathic concern

C. Kraus[1], G. S. Kranz[2], D. Pfabigan[3], A. Hoffmann[4], A. Hahn[2], S. Eva-Maria[3], M. Küblböck[4], S. Kasper[2], C. Windischberger[4], C. Lamm[3], R. Lanzenberger[2]. [1]*Medical University of Vienna, Vienna, Austria;* [2]*Medical University of Vienna, Department of Psychiatry, and Psychotherapy, Vienna, Austria;* [3]*Faculty of Psychology, University of Vienna, Vienna, Austria;* [4]*Medical University of Vienna, Center for Medical Physics and Biomedical Engineering, Vienna, Austria*

Objective: While functional magnetic resonance imaging (MRI) studies have identified brain regions, which are tightly linked to empathy, evidence of structural variance due to the ability to empathize is scarce. Therefore, we aimed to investigate cortical gray matter associated with the ability to empathize.

Methods: Gray matter volume (GMV) was measured with structural MRI at 3 T and voxel-based morphometry (VBM) in 25 sex and age-matched healthy young volunteers (13 female, age: 25.4±5.2years). High-resolution anatomical images were acquired using a MPRAGE sequence (240×256×160 voxels, 1mm3 isotropic; TR=2.3 s, TE=4.2 ms). Data were preprocessed with an optimized VBM protocol applying Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) as implemented in SPM8. Empathic concern was quantified with a German version of the interpersonal reactivity index (IRI). A voxel-wise multiple linear regression analysis was performed in SPM8 between GMV maps and empathy scores with total brain GMV as covariate in a-priori selected brain regions (insula, amygdalae, hippocampus, parahippocampus, anterior cingulate). All analyses were performed in standardized Montreal Neurological Institute (MNI)-space at statistical threshold of $p<0.001$ uncorrected, the family-wise-error (FWE) rate at $p<0.05$ was applied to correct for multiple comparisons where appropriate.

Results: Significant positive correlations of regional GMV with empathy scores were observed in the left anterior parahippocampal gyrus ($p=0.024$, FWE-corrected, x,y,z=−27, −9, −30, $r=0.615$) and in the right anterior insula ($p<0.001$, x, y, z=24, 22, −9, $r=0.618$).

Conclusion: We have detected significant gray matter increases according to empathic ability. Both, the parahippocampal gyrus and the anterior insula are involved in emotional processing, which is a prerequisite for empathy. Furthermore, this study confirms previous work showing the central role of the anterior insula in empathizing.

Policy of full disclosure: Without any relevance to this work, S. Kasper declares that he has received grant/research support from Eli Lilly, Lundbeck A/S, Bristol-Myers Squibb, Servier, Sepracor, GlaxoSmithKline, Organon, and has served as a consultant or on advisory boards for AstraZeneca, Austrian Sick Found, Bristol-Myers Squibb, GlaxoSmithKline, Eli Lily, Lundbeck A/S, Pfizer, Organon, Sepracor, Janssen, and Novartis, and has served on speakers' bureaus for AstraZeneca, Eli Lilly, Lundbeck A/S, Servier, Sepracor and Janssen. R. Lanzenberger has received travel grants and conference speaker honoraria from AstraZeneca, Lundbeck A/S and Roche Austria GmbH. C. Kraus received travel grants and conference speaker honoraria from Roche. G.S. Kranz received travel grants from Roche and AOP Orphan.

RA-01-010 In vivo phenotyping of a mouse model of the human 22q11.2 deletion syndrome

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Objective: Recent findings have provided strong evidence that specific copy number variants (CNVs) pose a considerably increased risk of neuropsychiatric disorders. Up to 30% of adolescents and adults with the 22q11.2 deletion syndrome develop schizophrenia-like psychosis and related cognitive problems. Therefore, this rare and highly penetrant CNV represents an important model for understanding the pathophysiology of schizophrenia. Several mouse models for the human 22q11.2 deletion have been engineered, however, their phenotype remains to be fully characterized.

Methods: The present study was designed to further investigate phenotypic manifestations in a novel mouse model for the human 22q11.2 deletion syndrome (Df(h22q11)/+) recently generated within the NEWMEDS consortium. A broad range of neurophysiological and behavioural functions was assessed at baseline as well as under acute psychological stressor or pharmacological challenge. These include sleep architecture, locomotor activity, prepulse inhibition, reaction time, impulsive responding, sustained attention, spatial learning and memory, and spatial working memory.

Results: Df(h22q11)/+ mice showed no or minor changes in baseline and/or stress-induced sleep architecture, locomotor activity, operant reaction time, sustained attention, impulsive responding, spatial learning and memory and spatial working memory. However, they had a robust deficit in prepulse inhibition and an increased sensitivity to psychostimulant-induced hyperactivity.

Conclusion: These results suggest that the deletion in mice of an orthologous region of the human 22q11.2 locus recapitulates some of the phenotypic manifestations observed in the 22q11.2 deletion syndrome and schizophrenia. Detailed electrophysiological and molecular characterization of the mechanisms underlying these alterations is currently ongoing.

Policy of full disclosure: NEWMEDS – The research leading to these results has received support from the Innovative Medicine Initiative Joint Undertaking under grant agreement n° 115008 of which resources are composed of EFPIA in-kind contribution and financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013).

Monday 23 June 2014

P-01. Addictive disorders A

P-01-001 Problems with the prescription of benzodiazepines in Japan. Evaluation of suicide attempts by overdosing

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Objective: In Japan, larger doses of benzodiazepines are known to be prescribed than in Western countries. This raises doubts about whether Japanese physicians have sufficient knowledge and understanding about the risk of benzodiazepines. Recently, suicide attempts by overdosing on psychotropic drugs prescribed by physicians are increasing, and benzodiazepines are used in many of such suicide attempts. We investigated the contents of prescriptions by previous physicians for patients who attempted suicide by overdosing on psychotropic drugs and were admitted to our emergency medical center to clarify the actual situation concerning the prescription of benzodiazepines and evaluate the relationship between benzodiazepines and repeated suicide attempts by drug overdosing.

Methods: The 116 patients were investigated. On the basis of the clinical data obtained on admission from the previous physicians, the doses of benzodiazepines were calculated. The doses are expressed as diazepam equivalents. The doses of benzodiazepines were compared between patients with and without a history of suicide attempts.

Results: Benzodiazepines were prescribed to all 116 patients, their diazepam-equivalent dose was 27.78±21.92 mg. The dose of benzodiazepines was compared between the patients with and without a history of suicide attempts by overdosing on psychotropic drugs, but no significant difference was observed. However, in those who attempted or repeatedly attempted suicide using psychotropic drugs, the dose of benzodiazepines markedly exceeded 15 mg/day, which is the maximum dose of diazepam, and it was 31.88±24.81 mg, more than twice the maximum dose, in the 47 patients who had repeatedly attempted suicide.

Conclusion: Benzodiazepines are known to infrequently cause impulsive actions, i.e., violence, self-injury behavior, and suicide attempts, due to their pharmacological effect of disinhibition. The results of this study did not rule out the possibility that the prescription of large doses of benzodiazepines is a factor affecting suicide attempts by overdosing. Therefore, the appropriate use of benzodiazepines may contribute to the prevention of repeated suicide attempts by overdosing.

Policy of full disclosure: None.

P-01-002 Pathway-specific modulation of nucleus accumbens in reward and aversive learning behaviors and drug addiction via selective transmitter receptors

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Objective: The basal ganglia-thalamocortical circuitry plays a central role in reward and aversive learning and drug addiction. Inputs of the nucleus accumbens in this circuitry are transmitted through two parallel striatonigral direct and striatopallidal indirect pathways and controlled by dopamine transmitter. We explored how dopaminergic modulation of nucleus accumbens in the basal ganglia circuitry regulates the associative learning behavior and drug addiction.

Methods: We developed an asymmetric reversible neurotransmission-blocking technique in which transmission of each pathway was unilaterally blocked by transmission-blocking tetanus toxin and the transmission on the intact side was pharmacologically manipulated by local infusion of a receptor-specific agonist or antagonist. Reward learning and addictive behaviors was measured by chocolate-associated and cocaine-induced conditioned place preference. Aversive learning was tested by performing one-trial inhibitory avoidance task.

Results: The activation of D1 receptors and the inactivation of D2 receptors postsynaptically control reward learning/cocaine addiction and aversive learning in a direct pathway-specific and indirect pathway-specific manner, respectively. Furthermore, this study demonstrated that aversive learning is elicited by elaborate actions of NMDA receptors, adenosine A2a receptors, and endocannabinoid CB1 receptors, which serve as key neurotransmitter receptors in inducing long-term potentiation in the indirect pathway.

Conclusion: Reward and aversive learning and cocaine addiction is regulated by pathway-specific neural plasticity via selective transmitter receptors in the nucleus accumbens circuit.

Policy of full disclosure: None.

P-01-003 Associations of an orexin (hypocretin) receptor 2 gene polymorphism with nicotine dependence found in genome-wide and following association studies

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Objective: Many genetic and environmental factors can be involved in the etiology of nicotine dependence. To date, several candidate genetic variations have been identified to be associated with smoking behaviors and vulnerability to nicotine dependence by candidate gene or genome-wide association studies (GWAS), which is mostly conducted for subjects with European ancestry. However, genetic factors have not been reportedly investigated for Japanese population utilizing whole-genome genotyping arrays. To elucidate genetic factors involved in nicotine dependence in Japanese, the present study comprehensively explored genetic contributors to nicotine dependence by using whole-genome genotyping arrays with more than 200,000 markers in Japanese subjects.

Methods: Subjects for GWAS and replication study were 300 and 700 patients, respectively. A two-stage GWAS was conducted using 150 samples for each stage using the Fagerström Test for Nicotine Dependence (FTND), the Tobacco Dependence Screener (TDS), and the numbers of cigarettes smoked per day (CPD), as indices of nicotine dependence. For additional association analyses, patients undergoing major abdominal surgery, patients with methamphetamine dependence/psychosis, healthy subjects with schizotypal personality trait data, and subjects of autopsy specimens with various diseases, were recruited.

Results: After association study between over 200,000 marker single nucleotide polymorphisms (SNPs) and FTND, TDS, and CPD, the nonsynonymous rs2653349 SNP (1237G>A; Val308Ile) located on the gene encoding orexin (hypocretin) receptor 2, was selected as the most promising SNP associated with FTND, and the association was replicated for remaining 700 samples. This SNP was also associated with postoperative pain, initiation of methamphetamine use, schizotypal personality traits, and susceptibility to goiter.

Conclusion: The nonsynonymous rs2653349 SNP located on the orexin (hypocretin) receptor 2 gene was suggested to be a genetic factor for nicotine dependence and possibly pain, schizotypal personality traits, and goiter in Japanese population.

Policy of full disclosure: This work was supported by grants from the MEXT KAKENHI (Grant Number 20602020, 20390162, 23390377, 22240072, 25242062, and S-001), the Ministry of Health, Labour and Welfare (MHLW) of Japan (no. H21-3jigan-ippan-011 and H22-Iyaku-015, H23-016, H23-119, H24-Nanchi-Ippan-005 and H25-Iyaku-020), Grants-in-Aid for the U.S.-Japan Cooperative Medical Science Program, National Cancer Center Research and Development Fund, Smoking Research Foundation, Astellas Foundation for Research on Metabolic Disorders, and a Grant-in-Aid for Scientific Research on Innovative Areas (Comprehensive Brain Science Network) from the Ministry of Education, Science, Sports and Culture of Japan. This work was partly supported by the Smoking Research Foundation. The funders including the Smoking Research Foundation had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. Dr. Ikeda reports having received support from Eisai for a project unrelated to this research and speaker#s fees from Taisho Pharmaceutical Co., Ltd. and Japan Tobacco Inc. The authors report no other biomedical financial interest or potential conflicts of interest.

P-01-004 Study of anxiety and depression in alcoholic patients during therapy

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Objective: Anxiety is among the most frequent affective disorder in alcohol dependence – from 11 up to 100%. In the remission period alcoholic anxiety becomes protracted, pharmacoresistence over and often contribute to relapse. The link between alcohol and depressive disorder indicates that the alcohol is used as a 'modifier' of mood, to alleviate the condition of stress, anxiety and depression. Thus, alcohol, used to improve mood affects subsequent (probable) formation of alcoholic illness.

Methods: 45 patients were examined in order to study the dynamics of anxiety and depressive disorders in alcoholic patients admitted to the Republican Narcological Dispensary. It was included in the study 5 patients female and 40 male patients. The median age was 38.8±9.8 years. All patients were evaluated using the Hospital Anxiety and Depression Scale. This technique allows the dynamic monitoring of alcoholic anxiety and depression during treatment. Amitriptyline at a daily dose of 150 mg 3 weeks was used to treat clinically expressed depression accompanied by anxiety disorders. In the forefront of depressive disorders with subclinical anxiety patients appointed Venlafaxine dose 75–150 mg, depending on severity of depression.

Results: High level of depression (18 +/- 4 points) and anxiety (13 +/- 3 points) were founded in all 45 examined patients. There was only a slight improvement in the level of anxiety (1 +/- 2 points) and depression (2 +/- 2 points) in 8 patients during the treatment. The remaining 33 patients has showed clinically meaningful improvement: the level of anxiety has decreased on average by 6 +/- 4 points, while the depression decreased by 5 +/- 3 points.

Conclusion: The data indicate a high level of both depression and anxiety in patients that allows to treat alcoholic affective disorders. Thus reducing the clinical manifestations of alcoholic anxiety may prevent development of relapse.

Policy of full disclosure: None.

P-01-005 Win-related cues drive risky decision-making on a rodent gambling task

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Objective: Animal models of gambling behavior allow insight into the neurobiology of gambling that is otherwise lacking because of technical, practical and ethical limitations of human research. Our laboratory has developed a model of gambling behavior for use with rodents called the rodent Gambling Task (rGT).

Methods: The rGT allows animals to choose between four options that are associated with varying levels of risk and reward; the optimal strategy on the task is to choose the option with a relatively small reward but also infrequent punishment, allowing the animal to collect the maximum amount of reward over the course of the 30 minute session. A new version of the rGT incorporates flashing lights and tones to signal wins. These win cues are not proportional to the win size; as in a human gambling paradigm, the win-related cues are exponentially larger for large wins, making these options more attractive despite the fact that they are ultimately disadvantageous. Current work is aimed at delineating the specific contributions of catecholamines to this behavior, with a focus on dopaminergic D2-like receptors.

Results: Animals quickly learn the task, and their behavior has been well characterized; most animals adopt an optimal strategy and perform well on the task, while some behave in a riskier manner, preferring a high-risk, high-reward strategy, much like a high-stakes human gambler. It appears that the addition of cues drives a detrimental, risk-seeking pattern of behavior, as rats trained on this task show a higher preference for the risky options than rats trained on the uncued version of the task.

Conclusion: The use of the rGT provides greater insight into the neurobiology of gambling, especially risky decision-making in the face of uncertain or probabilistic outcomes, and use of the cued version enables exploration of the neuropsychopharmacology of the influence of cues on the decision-making process.

Policy of full disclosure: None.

P-01-006 Efficacy of energotropic modulators of cellular metabolism in therapy of withdrawal syndrome in associated forms of alcoholism

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Objective: For overcoming polypharmacy during treatment of alcoholism (A) in patients with remote consequences of comorbid brain injury and associated dismetabolic effects, search for new energotropic modulators of cellular metabolism is relevant. Composite medication "Reamberin" for intravenous injections is a metabolic corrector with antioxidant activity and represents by itself a balanced poly-ionic solution with addition of succinic acid.

Methods: In parallel groups, simple comparative study of efficacy of 7-day application of medication "Reamberin" in therapy of alcohol withdrawal syndrome (AWS) in 32 alcoholic patients with comorbid brain injury (group 1; F10.2; S06.00; mean age 41,2+/-6,3 years) as compared with group (2) of 46 patients without the above medication. All patients gave informed consent. Scales were used: CIWA-Ar, HDRS, and HARS in 3 points. The sign of endogenous intoxication (EI) was increase of content of molecules with low mean molecular weight (MMW) and oligopetides in serum of blood.

Results: In patients of groups 1 and 2 in AWS, EI with reliable increase of toxic fraction (TF), recorded during wavelength A254 and nuclear fraction of MMW230 has been revealed. Increase of nuclear fraction of MMW230 is likely associated with accumulation in blood of nucleic acid residues as a result of reinforcement of apoptosis of cells and heightened protein breakdown. At the end of the therapy in group 1, reliable decrease of content of TF has been recorded, concerning nuclear fraction, trend to decrease was observed. In group 2, reliable dynamics in alteration of spectrum of MMW have not been revealed. In group 1, accelerated reduction of somatovegetative manifestations of AWS with normalization of its affective components has been shown.

Conclusion: Use of medication "Reamberin" in therapy of AWS positively influences decrease of level of endogenous intoxication, improves dynamics of basic somatovegetative and psychopathological disorders, reduces polypharmacy, normalizes the metabolic background for stabilization of remission.

Policy of full disclosure: None.

P-01-007 The prevalence and patterns of continuous use of benzodiazepines following a psychiatric admission as a risk factor for benzodiazepine use disorder. Preliminary report

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Objective: Benzodiazepines (BDZ) are addictive drugs widely prescribed in psychiatric units as PRN (pro re nata) – "as needed" basis. More than 50% of the psychiatric inpatients have a history of substance use disorders (SUD) therefore they are more vulnerable to the harms associated with the exposure to addictive drugs. Objective: To determine the prevalence and patterns of the use of BDZ following the prescription during a psychiatric admission after one and three months from discharge.

Methods: Twenty-three adult inpatients non-regular users of BDZs admitted to the psychiatric unit at Sunnybrook Health Sciences Centre were recruited. We collected demographic and clinical data; and data about prescription and administration of PRN BDZ, including dosage, route, frequency, indication, reasons for administration and prescription at discharge. Patients were contacted by phone at one (n=19) and three months (n=11) after discharge and were asked about the use of BDZ since the discharge.

Results: The mean age of the participants was 40.4 years old. Most of them were female (65.2%), single (65.2%), unemployed (56.2%) and had a history of SUD (52.1%). Sixteen patients (60%) had at least one benzodiazepine prescribed and fourteen (48%) received at least one administration of benzodiazepine. Lorazepam was the most frequently prescribed (87.5%) and administered (87.3%). At one month follow-up, five patients (26%) were using benzodiazepines and at three months follow-up, two patients (18%) were still using the medication.

Conclusion: Considering that (1) the indications for long term use of benzodiazepines are quite scarce; (2) these patients were not chronic users at admission; and (3) chronic use of BDZs is associated with addiction and its complications; the proportion of patients still using BDZ one and three months after discharge is of concern.

Policy of full disclosure: Pamela Sabioni is supported by the Conselho Nacional de Desenvolvimento Cientifico e Tecnologico – Brazil.

P-01-008 The effects of behavioral drug and risk counseling on methadone patients in Taiwan

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Objective: Few methadone maintenance treatment (MMT) programs in Taiwan offer drug counseling to injecting drug users (IDUs). Behavior and drug risk behavior reduction counseling (BDRC) provides a cognition behavior therapy (CBT)-based approach to patents in MMT. We conducted a study to evaluate the BDRC add-on treatment in MMT patients in Taiwan.

Methods: Patients were invited to attend the research program while they first time visit methadone clinic. They signed consent forms and voluntarily randomly assigned to either 12 sessions BDRC or treatment as usual (TAU) programs. BDRC was performed weekly in the first month, and every two weeks in the following two months, and once a month in the following period. Two training nurses provided the counseling. Both the two groups were assessed by individual interviewing with Addiction Severity Index, Risk Assessment Battery and Quality of life every three months. Urine morphine tests were done with counseling in BDRC and with outpatient visits in TAU.

Results: From May 2012 to Aug 2013, there are 51 patients recruited (BDRC n=27 and TAU n=24). Patients received average 6.3 sections of counseling in the first three months. From preliminary analysis, there are better treatment retention rates (BDRC 77.78% vs. TAU 66.67%) and attendance rates of methadone treatment (BDRC 90.45% vs. 79.15%) in BDRC groups after three months follow up. Both of the groups had improved quality of life and lower drug-related risk behaviors after receiving methadone treatment. The positive morphine urine test rate was obvious reduced in BDRC group (BDRC 28.60% vs. TAU 72.10%).

Conclusion: BDRC might reduce heroin use behaviors of patients in the initial months of methadone treatment program and improve their retention rates. The effects need further confirmation with long-term follow up.

Policy of full disclosure: None.

P-01-009 Neurocognitive and individual drug use characteristics for predicting in-treatment performance and relapse in methamphetamine users

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Objective: This study aims to examine the utility of neurocognitive and individual drug use characteristics for predicting in-treatment performance and relapse in methamphetamine (METH) users.

Methods: METH abusers among individuals who were preparing to participate in a 12-week weekly out-patient treatment program using a psychosocial and behavioral model received neurocognitive measurements including Conners' Continuous Performance Tests, Wisconsin Card Sorting Test, Iowa Gambling Task, and The Barratt impulsiveness scale. After baseline assessments, the subjects started a12-week weekly out-patient treatment program. The in-treatment performance variables used in analyses include abstinence and completion.

Results: Thirty-four METH users were categorized into METH users without psychosis (N=16) and METH users with past experience of brief psychosis or perceptual disturbance (N=18). METH users with past experience of psychosis had poorer performances in perseverative responses, perseverative errors than those without psychosis experience. Younger age of first METH use was associated with more omission error, more perseverative errors, and high novelty-seeking. Higher doses of METH use were associated with poor self-control. High CPT confidence index and not-married status were significantly associated with earlier relapse of METH use.

Conclusion: High impulsivity was significantly associated with earlier onset of METH use, larger dose of METH use and earlier relapse of METH use during socio-behavioral treatment. METH users with past experience of psychosis or perceptual disturbance after use of METH have poorer executive function than those without psychosis experience.

Policy of full disclosure: None.

P-01-010 Dopamine D4 receptors in the anterior cingulate cortex appear to modulate reward expectancy on a rodent slot machine task

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Objective: Pathological gambling is a growing public health concern, yet treatment options remain limited and of questionable efficacy. Slot machines represent a particularly potent form of gambling, purportedly due to the reinforcing effects of 'near-misses' (unsuccessful outcomes that are proximal to a win). We have previously demonstrated that D4 receptors may underlie susceptibility to the reinforcing effects of putative winning signals within non-winning trials. D4 receptors are predominantly located within frontal-cortical regions, and thus present an intriguing target for modulating higher-order cognitive processes. One area that has a relatively high proportion of D4 receptors is the anterior cingulate cortex (ACC); human imaging studies have shown robust activation of the ACC during slot machine play and evidence suggests a role for the ACC in biasing choice towards a prepotent but sub-optimal response. Taken together, this suggests that ACC activation may underlie the ability of 'near-misses' to evoke reward expectancy in human gamblers.

Methods: We have developed a rodent slot machine task wherein animals respond to three flashing lights that could be set to on or off. A win was signaled if all three lights were set to on, whereas any other light pattern indicated a loss. Rats then chose between responding on the collect lever, which delivered 10 sugar pellets on win trials but a 10-second time penalty on loss trials, or to start a new trial instead

Results: Inactivations of the ACC increase animals' erroneous expectations of reward on non-winning trials. Additionally we have preliminary evidence to suggest this effect may be driven by D4 receptors as local infusions of a D4 agonist into the ACC produced similar impairments in performance.

Conclusion: This data suggests that the D4 receptors within the ACC may be critically involved in generating reward expectancy in response to winning signals within non-winning outcomes on slot machines.

Policy of full disclosure: None.

P-01-011 Motor activity, anxiety, and learning in adolescent and adult rats undergoing tobacco smoke withdrawal

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Objective: Tobacco addiction is one of the most prevalent addictions worldwide. It is a chronic, relapsing, and in most cases lifelong problem. Individuals addicted to tobacco (cigarette) smoking experience withdrawal symptoms upon smoking cessation. In the present study we seek to evaluate the motor activity, anxiety, and learning of adolescent and adult animals undergoing tobacco smoke withdrawal.

Methods: Adolescent (4–6 weeks) and adult (8 weeks onward), male, Sprauge-Dawley rats were exposed to tobacco smoke through a standard smoking machine (whole body exposure machine) for 7 or 14 days. After tobacco smoke exposure, changes in motor activity (open-field test), anxiety (elevated plus-maze test), and learning (passive-avoidance test) were evaluated. Nicotine withdrawal-related behaviors were also assessed (e.g. rearing, burrowing, grooming, scratching, etc.). These behavioral evaluations were conducted during the first, third, and seventh day after last tobacco smoke exposure.

Results: The results showed that adolescent and adult rats repeatedly exposed to tobacco smoke significantly exhibited nicotine withdrawal-related behaviors, as compared to the control (no exposure) group. Furthermore, these rats displayed increased locomotor activity in the open-field test and anxiety-like behavior in the elevated-plus maze test. However, no alterations in learning and memory were observed in the passive-avoidance test.

Conclusion: These results suggest that individuals undergoing tobacco/nicotine withdrawal may be hyperactive and anxious.

Policy of full disclosure: None.

P-01-012 The addictive potential of nicotine in tobacco smoke-naïve or pre-exposed adolescent and adult rats

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Objective: Chronic tobacco (cigarette) smoking starts young. Most adult smokers started when they were teenagers. The main psychoactive and

addictive component in tobacco is nicotine. Here, we investigated the addictive potential of nicotine in tobacco smoke-naive or pre-exposed adolescent and adult rats.

Methods: The rewarding and reinforcing effects of nicotine were evaluated in tobacco smoke-naive or pre-exposed adolescent (4–6 weeks) and adult (8–10 weeks), male, Sprauge-Dawley rats. Two of the most widely used and accepted animal models of addiction were employed; the conditioned place preference (CPP) and self-administration (SA) tests.

Results: Consistent with previous reports, tobacco smoke-naïve adolescent rats demonstrated enhanced nicotine CPP (0.2 mg/kg) and SA (0.03 mg/kg/infusion) as compared to the naïve adult group. Rats pre-exposed to tobacco smoke exhibited greater CPP for the initially unrewarding high dose (0.06 mg/kg) of nicotine, especially appreciable in adolescent rats. However, in the SA test, smoke pre-exposed adolescent and adult rats demonstrated reduced/diminished nicotine (0.03 mg/kg) SA.

Conclusion: These results suggest that (1) adolescents are more vulnerable to the addictive effects of nicotine or tobacco smoke, and (2) repeated tobacco smoke exposure affects subsequent response to nicotine.

Policy of full disclosure: None.

P-01-013 Acute cocaine administration decreases advantageous decision-making but does not affect impulsive action as measured by a rodent gambling task

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Objective: Drug addiction is a behavioural disorder that poses a worldwide health concern. Higher levels of impulsivity and maladaptive decision-making are common traits found amongst substance abusers and may play an integral role in commencement of drug use. Studies using the Iowa Gambling Task (IGT), a validated measure of decision-making, have found that substance-dependent individuals tend to choose the least advantageous option (associated with less reward over the course of the task) and are less likely to change their strategy following losses compared to controls. However, the majority of studies in humans and in related animal models have explored the effects of chronic cocaine exposure. We therefore examined the effects of acute cocaine administration on decision-making behaviour, in efforts to gain insight into behavioural changes that follow initial drug use.

Methods: We trained 16 male Long-Evans rats on the Rodent Gambling Task, a rodent analogue of the IGT designed to assay decision-making and impulsive action. Following training, the animals were administered saline, 5, 10, or 20 mg/kg of cocaine via i.p. injection prior to engaging in the task.

Results: We found that, compared to saline, the medium dose of cocaine decreased choice of the most advantageous option and increased choice of the least advantageous option. Similarly administration of the high dose of cocaine decreased choice of the advantageous option but also increased the number of omissions, a common effect of high doses of psychostimulants in operant tasks. Interestingly, impulsive action as measured by premature responses, or the inability to withhold responding in the task, was not affected by acute cocaine treatment.

Conclusion: These data indicate that singular administration of cocaine may be enough to initiate changes in decision-making behaviour, providing a foundation to understand how these behaviours involved in addiction begin and change following chronic cocaine exposure.

Policy of full disclosure: None.

P-01-014 Changes in [3 h]mpep binding to brain mglu5 receptors in rats trained to self-administer cocaine and assigned to live in different living conditions during abstinence

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Objective: Several evidence suggests that the glutaminergic transmission and mGlu5 receptors (mGluR5) play critical role in cocaine seeking and relapse behaviors. As found in animals models, self-administration of cocaine is reduced by mGluR5 antagonists while neither conditioned or passive cocaine injections altered density of mGluR5 in rat brain regions.

Methods: The aim of study was to further uncover the role of mGluR5 in craving-related brain neuroadaptations in the cocaine addicted rats. With using the titrated receptor antagonist [3H]MPEP, binding assays were performed to evaluate mGluR5 densities in the neural circuitry of rats trained to self-administer cocaine (0.5 mg/kg/inf., FR5) that were subsequently assigned to live in either isolation conditions (HC), exposed to experimental cage (EC), or to enriched environment (EE) during an abstinence, and a #yoked# procedure was used.

Results: EC resulted in a significant decrease (29%) in density of mGluR5 in the prefrontal cortex (PFC) and an increase (26%) in the nucleus accumbens (NAc) in rats previously self-administered cocaine. A trend to decrease in mGluR5 density was detected in PFC (20%) in cocaine #yoked# rats. Abstinence in EE in rats self-administered cocaine evoked a significant decreased in the PFC (11%) and increase in the NAc (20%) with no changes in cocaine #yoked# animals. In the brains of rats withdrawn in HC we observed a significant reduction in density of mGluR5 in the hippocampus of rats actively (24%) and passively (19%) administered cocaine. Moreover, cocaine self-administration and subsequent HC isolation produced decreases in mGluR5 density level in the PFC (25%).

Conclusion: To conclude, differences in density of mGluR5 in several brain structures depend on living condition during abstinence from cocaine. mGluR5 may be a target to reduce drug craving, and presumably incentive motivation. Supported by the grant no. 2011/03/D/NZ7/06295 by the NCN (Poland) and by the statutory activity of Institute of Pharmacology PAS.

Policy of full disclosure: None.

P-01-015 Gaining insights from patients seeking treatment in drug de addiction centre: A retrospective study of 2 years

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Objective: To study the socio-demographic and clinical profile of substance users attending the out-patient services of a de-addiction centre attached to a tertiary level health set-up in north India on a yearly basis for 2 consecutive years and thereby to understand the pattern as well as trend of substance use in this part of the country.

Methods: This is a retrospective record analysis and the data pertains to the period from 1st Jan 2012 to 31st December 2013.These years have been chosen because these were the first 2 calendar years when full records were maintained according to the semi-structured standardized proforma as recommended by National Drug Dependence Treatment Centre. The data was analysed using the SPSS.

Results: A total of 1598 patients (703 in 2012 and 895 in 2013) utilised the services of the centre in the given period. The mean age was 36.18± 11.8 years (2012) and 36.24±11.3 years (2013). Majority were self-employed males (98.7% in 2012 and 98.3% in 2013) and were married. The most common substance used was alcohol showing an increasing trend (59.7% to 63%) along with tobacco (41.4% to 45.4%), cannabis (13.8% to 17.1%), sedative-hypnotics (1.7% to 4.8%), multiple substances use (5.8% to 6.5%) and injection drug use (2.3% to 4.1%). There was also a rise in adolescent substance users (3.6% to 4.8%).

Conclusion: Our observations point towards the rising trend of substance use disorder both in terms of prevalence and early age of onset. This may be attributed to major socio- economic changes and towards the ineffective regulatory control mechanisms. It is recommended that analysis of case records in different types of set ups should be carried out to understand the changing trend of the substance use problems and gain insights to plan better and effective services.

Policy of full disclosure: None.

P-01-016 DRD4 and SLC6a4 are not associated with sustained binge drinking in young adults

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Objective: Binge drinking often persists from adolescence into adulthood and is associated with numerous poor health outcomes. Twin studies have shown that alcohol use disorder is highly heritable, although the genes that contribute to binge drinking are not fully known. Several but not all studies implicate DRD4 (dopamine receptor 4) and SLC6A4 (a serotonin transporter gene). Our objective was to examine whether these genes were associated with sustained binge drinking in a cohort of young adults.

Methods: Data were drawn from the Nicotine Dependence in Teens Study, a longitudinal study of a school-based cohort in Montreal. The analytic sample comprised 458 Caucasians who had given blood or saliva samples for genotyping and had completed self-report questionnaires at age 20 and 24 years that collected data on the frequency of binge drinking. Participants who reported binge drinking at both ages were categorized as

"sustainers" while those who reported binge drinking at age 20 but not at age 24 were considered "stoppers". Ordinal logistic regression was used to study the associations between frequency of sustained binge drinking (less than monthly, monthly, and weekly) and 4 and 7 tag SNPs in DRD4 and SLC64A, respectively.

Results: One single nucleotide polymorphisms (SNP) in DRD4, rs3758653, was associated with frequency of sustained binge drinking (OR (95% CI)=0.65 (0.45–0.94)), but the association was no longer statistically significant after adjusting for multiple comparisons. None of the SNPs in SLC6A4 were associated with frequency of sustained binge drinking.

Conclusion: Our study differed from previous studies by examining sustained binge drinking, which may be a more useful indicator of severity of alcohol misuse than binge drinking at a single time-point. However, neither DRD4 nor SLC6A4 was associated with this outcome after correcting for multiple testing. The use of genetic risk scores which examine cumulative risk of multiple genetic variants rather than single candidate genes may be more successful at predicting frequency of sustained binge drinking.

Policy of full disclosure: None.

P-01-017 The genetics of binge drinking: A systematic review

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Objective: Binge drinking continues to be a problem in American youth with a prevalence that is highest amongst adult males age 21–25 years old. Binge drinking is associated with a number of negative outcomes including cardiac disease, pancreatic cancer, and mortality. Although alcohol dependence has been shown to be highly heritable, studies examining the genetic determinants of binge drinking have yet to be reviewed systematically. Our objective was to perform as systematic review to determine which genes have been linked to binge drinking.

Methods: An extensive keyword literature search was developed for each database with the help of a librarian. MEDLINE, Embase, and PsycINFO were searched from their inception until September 2013. This search yielded 525 citations. Abstracts were assessed independently and in duplicate. Genome-wide association studies, candidate gene studies, and linkage studies conducted in humans were included in the review.

Results: Genetic studies have found that polymorphisms in ALDH1B, ALDH2, DRD4, SLC6A4, CRHR1, and PER1 are associated with increased binge drinking. These studies were generally limited by small sample sizes and other methodological weaknesses.

Conclusion: Polymorphisms in genes associated with alcohol metabolism, novelty seeking, mood regulation, stress response, and circadian rhythm regulation are associated with binge drinking. A consensus regarding the definition of binge drinking would improve the quality and comparability across studies. Future studies should look for additional genetic determinants and seek to further elucidate the molecular and psychological mechanisms by which known polymorphisms confer increased risk.

Policy of full disclosure: None.

P-02. Anxiety disorders A

P-02-001 Effectiveness of long-term benzodiazepine use in the treatment of anxiety disorders; a systematic review

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Objective: Although current experts consensus and clinical guidelines do not endorse long-term use of benzodiazepines in the treatment of anxiety disorders for fear of adverse consequences, many patients are routinely receiving those medications in the real world. The objective of this study was to synthesize the evidence of effectiveness on long-term use of benzodiazepines in anxiety disorders.

Methods: A literature search was performed to identify randomized controlled trials (RCT) that examined effectiveness of benzodiazepines in patients with anxiety disorders for 13 or more weeks, using PubMed. The search terms included "benzodiazepine" and "long-term", "maintenance", or "prevention". Cross-referencing was also performed.

Results: The literature search identified six studies. Two of them were ordinary RCTs lasting 16 and 24 weeks, while the other four were follow-up studies subsequent to RCTs lasting 6, 8, 8, and 36 months, respectively. Comparators to benzodiazepines were placebo for 1 trial, paroxetine for 1 trial, buspirone for 1 trial, and imipramine and placebo for 2 trials, and 1 trial was a head-to-head comparison of katazolam and diazepam. In all studies, benzodiazepines were found to be effective, which was maintained during the follow-up periods without any significant increase in the dosage. In each study, adverse events were not generally so problematic but inadequately recorded, and attrition rates in patients receiving benzodiazepines (4–59%) were in general lower than those on placebo (74–92%), paroxetine (11%), buspirone (28%), and imipramine (65–74%).

Conclusion: The literature search clearly underscores the inadequacy of data, which warrants further investigations on this controversial but common and highly relevant clinical practice. As evidence to date is rather scarce, careful and thorough risk assessment with benzodiazepine usage is critically needed in light of a number of well-known side effects.

Policy of full disclosure: None.

P-02-003 Measurement of anxiety in young obese adult

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Objective: Anxiety is easily assessed by Zung Self Rating Anxiety Scale questionnaires as they are easy to understand by the participants. This study was planned to assess anxiety using in young obese adults. Zung Self Rating Anxiety Scale (SAS) of I year MBBS students & to correlate Body Mass Index (BMI) with anxiety levels

Methods: 138 medical students were involved in the study (56 males and 82 females). Without knowing the interpretation of the scoring system, subjects were asked to fill the anxiety inventories in speculated time using Zung Self Rating Anxiety Scale (SAS), a 20-item self-report assessment device which included measures of state and trait anxiety.

Results: There was no statistical significance in the anxiety score of overweight and normal weight group even though the mean levels were higher in overweight group.

Conclusion: This study demonstrated no statistically significant difference in anxiety scores of overweight & normal weight young adults. Also there is no statistically significant association between anxiety & BMI. This type of study will help in detection of high anxiety students at an early stage which will be helpful in implementation of preventive measures at an early age. This will prevent harmful effects of stress on body functions

Policy of full disclosure: None.

P-02-004 Ssri and antipsychotic usage in rehabilitation setting

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Objective: Rehabilitation setting includes patients with comorbid psychiatric disorders. Varieties of psychiatric symptoms are substantial during the rehabilitation course. We aimed to examine the usage of SSRI and antipsychotic drug usage at liaison psychiatry department referrals in one year.

Methods: Referrals to Consultation Liaison Department between November 2011 and November 2012 were examined retrospectively. Age, sex, marital status, referring clinic, major complaint, primary and comorbid psychiatric diagnoses and given treatment data were collected from the patient records.

Results: A total of 544 patients were admitted to the Consultation Liaison Psychiatry Department. Seventy point eight percent (n=385) of them were male, and 29.2% of them (n=159) were female. Patients were 42.5±20.9 years old (mean±SD). Anxiety (47.6%, n=246) was the most often complaint among the patients. The three most common psychiatric diagnoses were anxiety disorder (46.4%, n=246), depression (20.6%, n=109), and post-traumatic stress disorder (12.1%, n=64). SSRI and antipsychotic drugs were prescribed for 59.6% (n=324), and 15.2% (n=83) patients respectively.

Conclusion: High prevalence of comorbid psychiatric disorders among rehabilitation setting inpatients leading extensive usage of psychopharmacologic treatment agents such as SSRI, and antipsychotic drugs. Potential positive or negative effects of the psychopharmacologic treatments on rehabilitation course need to be addressed.

Policy of full disclosure: None.

P-02-005 Role of astrocytic network on hippocampal-dependent functions

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Objective: Astrocytes, classically considered as supportive cells for neurons without a direct role in brain information processing, are emerging as relevant elements in brain physiology through their ability to regulate neuronal activity, synaptic transmission and plasticity. Recent evidence demonstrates that astrocytes may regulate high brain functions including emotional states. One of the main characteristics of astrocytes is their high network connectivity underlied by connexin 30 and 43 proteins. The aim of this study was to investigate the link between stress and hippocampal connexins expression.

Methods: Mice were administered with corticosterone given either alone for 8 weeks or in combination with the antidepressant fluoxetine or an overexpression of BDNF in the hippocampus using a lentiviral approach. Consequences of these treatments on anxiety along with the hippocampal expression of connexins were determined.

Results: CORT-administered mice displayed an anxious like-phenotype compared to controls as reflected in the elevated plus maze by an attenuated time spent in the open arms (3.7±1.6 vs. 11.6±5.3; $p<0.05$) and in the novelty suppressed feeding paradigm (NSF) by an increased latency to feed (305.8±50.8 vs. 41.7±9.8; $p<0.001$). These behavioral anomalies were accompanied by an attenuation of the unphosphorylated Cx43/Total Cx43 ratio (0.403±0.06 vs. 0.505±0.02; $p<0.05$). Fluoxetine but not hippocampal BDNF overexpression, produced anxiolytic-like activity in the NSF (102.8±18.8; $p<0.01$). However, both fluoxetine and BDNF overexpression restored a normal ratio of unphosphorylated Cx43/Total Cx43 compared to CORT-mice administered with the vehicle alone (0.523±0.02, $p<0.05$; 0.550±0.03, $p<0.01$; respectively).

Conclusion: These data raise the possibility that modifications of astrocytic network by acting directly on Cx43 may reverberate on hippocampal dependent-functions. Experiments are in progress in order to determine whether adult hippocampal neurogenesis is affected by pharmacological or genetic manipulation of Cx43.

Policy of full disclosure: None.

P-02-006 Evidence for association between Brain-Derived Neurotrophic Factor (BDNF) gene and panic disorder: Novel haplotype analysis study

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Objective: Panic disorder(PD) is a common psychiatric disorders with a complex etiology and several studies have suggested a genetic component to PD. Brain-derived neurotrophic factor (BDNF) is the most abundant of the neurotrophins in the brain, and is recognized as playing an important role in the survival, differentiation and growth of neurons. Several lines of research have suggested possible associations between the BDNF gene and PD. In this study, we investigated the BDNF 196G/A (rs6265), 11757G/C (rs16917204), and 270C/T (rs56164415) SNPs for association with PD. We also identified the genetic sequence associations with PD via haplotype analysis.

Methods: The participants in this study were 136 PD patients and 263 healthy controls. Male and female subjects were analyzed separately. The genotype and allele frequencies of the PD patients and controls were analyzed using #2 statistics. Frequencies and haplotype reconstructions were calculated using the SNP analyzer 2.0.

Results: We found no significant statistical differences in the genotype distributions or allele frequencies of the three tested polymorphisms between the PD and control groups. In addition, no differences were found between PD patients and controls in either the male or female subgroups. However, we found that, the frequency of the GC haplotype was significantly higher in PD patients than in the controls.

Conclusion: Our result is the first study to identify associations between two BDNF SNPs and PD in the Korean population by investigating the related haplotypes. Further studies are needed to replicate the associations that we observed.

Policy of full disclosure: None.

P-02-007 Non-verbal memory abnormality of checking symptoms with obsessive-compulsive disorder

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Objective: The purpose of this study is to examine the role of memory dysfunction in obsessive-compulsive disorder (OCD). Especially we tested the memory function of checking type of obsessive-compulsive disorder compare to that of cleaning type and that of normal controls.

Methods: Subjects were 16 patients aged 18–45 years who met the diagnostic criteria of obsessive compulsive disorder and 8 normal controls. Informed consent was done. 16 OCD patients was divided into two groups, 8 #checking# type and 8 #cleaning# type patients by evaluation of Yale-Brown Obsessive compulsive scale and Maudsley Obsessive compulsive inventory. All patients were tested memory functions by Rey-Osterrich comlex figure test (RCFT) for non-verbal memory function, Hopkins verbal learning test (HVLT) for verbal memory function, Wisconsin card sorting test (WCST) and evaluated depression and anxiety by Beck Depression Inventory (BDI) and Taylor Anxiety scale.

Results: The Reyimmediate and Reydelayed memory test scores were significantly lower ($P<0.05$) in checking types than in cleaning types and normal controls(student t-test). There were no significant differences of Reycopy test scores, and verbal memory test(HVLT) scores, BDI and Taylor Anxiety scale scores in checking, cleaning type groups and normal controls.

Conclusion: The non-verbal memory function of checking type OCD patients were significantly decreased than other OCD patients and normal controls. This non-verbal memory dysfunction is not related to depression and anxiety. This results suggest that checking symptoms development of OCD is related to non-verbal memory dysfunctions.

Policy of full disclosure: None.

P-02-008 Clinical characteristics of obsessive compulsive disorder with schizophrenia

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Objective: We investigated the prevalence of obsessive compulsive disorder (OCD) among patients with schizophrenia. We also investigated the differences in the psychotic symptoms and suicidality between patients with schizophrenia who did or did not have OC symptoms.

Methods: Seventy-one subjects with the DSM-IV diagnosis of schizophrenia were evaluated by the Structured Clinical Interview for DSM-IV Axis I disorders, the Yale-Brown Obsessive-compulsive Scale and the Positive and Negative Syndrome Scale.

Results: The OCD patients with schizophrenia were 20 (28.2%) among 71 subjects. The 20 subjects with OCD had significantly more severe negative and total psychotic symptoms evaluated with PANSS than subjects without OCD. The schizophrenia with OCD had significant higher recent suicidal attempt rate than the subjects without OCD.

Conclusion: The results of this study suggest the possibility that OCD symptoms in schizophrenia may be related to negative symptoms and the OC symptoms may be related to the impulsivity expressed as suicidal attempts.

Policy of full disclosure: None.

P-03. Bipolar disorders A

P-03-001 Retrospective prediction of behavioral state by hippocampal transcriptome of the mice showing infradian rhythm

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Objective: Our mood changes over time, regardless of the amplitude and the period; however, biological mechanism underlying such mood changes remain unknown. We previously reported that αCaMKII heterozygous knockout mice show periodic mood-change-like behavior. In the mutants, locomotor activity level in their home cage gradually and greatly changes over time with an approximate cycle length of 10–20 days, suggesting that they may serve as an animal model showing mood cyclicity.

Methods: In the present study, to elucidate molecular basis of the periodic mood-change-like behavior, we conducted a genome-wide gene expression analysis of the dentate gyrus (DG) in the hippocampus of 37

mutant mice after longitudinal monitoring of their locomotor activity over 70 days.

Results: We revealed that locomotor activity of a mouse can be accurately estimated by the gene expression levels. The retrospective prediction was successful for the past 4 days, suggesting that gene expression patterns in the DG may contain information about locomotor activity of the past several days. The periodic change in locomotor activity was concomitant with changes in expression level of circadian clock genes and of genes related to maturational status of certain types of cells in the DG.

Conclusion: These results demonstrate that the gene expression patterns in the DG can be predictors of behavioral state of a mouse, and that the expression of circadian clock genes and the reversible maturation of cells in the DG might be involved in an infradian rhythm in the mutant mice.

Policy of full disclosure: None.

P-03-002 Efficacy of olanzapine monotherapy in the treatment of bipolar mania with mixed features as defined by DSM-5

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Objective: The objective of this analysis was to compare the efficacy of olanzapine monotherapy in bipolar I patients having manic episodes with or without mixed features, as newly defined in DSM-5.

Methods: Pooled data from 3 double-blind placebo-controlled olanzapine studies in patients with bipolar I disorder with manic episode were analyzed (Total 447 patients; 228 olanzapine monotherapy, 219 placebo). Patients were categorized for mixed features by the number of concurrent depressive symptoms at baseline (0, 1, 2 [category A] and $\geqslant$3[category B]) as determined by HAMD item score $\geqslant$1. Depressive symptoms corresponded to the 6 HAMD items used in the DSM-5 definition of a manic episode with mixed features: Depressed mood, work and activities, retardation, somatic symptoms general, feelings of guilt, suicide. Efficacy was evaluated by changes in YMRS total score from baseline to 3 weeks.

Results: Of the 447 patients, 322 patients (72.0%) were categorized in mixed feature category A and 125 patients (28.0%) in mixed feature category B. The mean baseline YMRS total scores were 28.1 in category A and 27.8 in category B. Least-squares mean change of YMRS total scores after 3 weeks (LOCF) in categories A and B (olanzapine vs. placebo [LS Mean difference]) were −11.78 vs. −6.86 [−4.93] and −13.21 vs. −4.72 [−8.48], respectively. Patients in the olanzapine-group experienced a statistically significantly greater mean decrease in YMRS total score compared with those in the placebo group for both categories ($p<0.001$). An interaction between mixed features and treatment was seen in the YMRS change at the significance level of 0.3 ($p=0.175$).

Conclusion: Olanzapine monotherapy was efficacious in the treatment of bipolar I mania, in both mixed feature categories A & B. Greater efficacy was seen in the mixed feature category B (patients with $\geqslant$3 depressive symptoms at baseline).

Policy of full disclosure: The studies were funded by Eli Lilly and Company and/or Eli Lilly Japan. Dr. Katagiri and Mr. Fujikoshi are employees of Eli Lilly Japan. Dr. Tohen was an employee of Eli Lilly and Company (1997–2008). He has served as consultant for Eli Lilly and Company and has received honoraria from Eli Lilly and Company. His spouse is a former employee of Eli Lilly (1998–2013). Dr. McIntyre has received speaker/consultant fees from Eli Lilly. He sits on the advisory board and receives research funding from Eli Lilly. Dr. Kanba has received grant/research support from Eli Lilly Japan. He was a consultant for Eli Lilly Japan and has also received honoraria from Eli Lilly Japan.

P-03-003 One-year rehospitalization rates in patients with first-episode bipolar mania on lithium and valproate with adjunctive atypical antipsychotics

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Objective: We compared the 1-year rehospitalization rates of first-episode bipolar manic patients who were discharged while being treated with lithium or valproate in combination with an atypical antipsychotic.

Methods: We investigated the rehospitalization status of first-episode bipolar manic patients who were discharged between January 1, 2003, and December 31, 2010, while they were taking lithium or valproate in combination with aripiprazole, olanzapine, quetiapine, or risperidone. Rehospitalization rates during a 1-year period after discharge were compared between the group receiving lithium plus an atypical antipsychotic and the group receiving valproate plus an atypical antipsychotic using the Kaplan#Meier method. A Cox regression model was used to analyze covariates hypothesized to affect time to rehospitalization.

Results: The rehospitalization rate was 17.3% during the 1-year follow-up period. We found significant differences in the rehospitalization rates of patients in the lithium (23.1%) and the valproate (13.3%) groups using the Kaplan#Meier formula. According to Cox proportional hazards regression analysis, higher Clinical Global Impression-Bipolar Version Severity (CGI-BP-S) score at discharge ($p=0.005$) and lithium treatment ($p=0.055$) contributed to the risk of rehospitalization.

Conclusion: Treatment with valproate and an atypical antipsychotic can be more effective than treatment with lithium and an atypical antipsychotic in preventing rehospitalization during the 1 year after hospitalization due to a first manic episode in patients with bipolar I disorder. Higher CGI-BP-S scores at discharge also negatively affected rehospitalization rates.

Policy of full disclosure: None.

P-03-004 The current state of maintenance treatments for bipolar patients: A focus on the transition from acute treatments

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Objective: We examined prescription patterns in maintenance treatment for recovered bipolar patients and compared these with acute treatments.

Methods: This study entailed a nationwide review of medical records of 14 Korean hospitals. From among adult patients with a diagnosis of bipolar disorder, including types I, II, NOS, who had been treated for acute episodes, the patients who met the criteria of clinical recovery (Clinical Global Impression Bipolar Version [CGI-BP] score #2 for 6 months) were selected. We reviewed the demographic data, present condition, and differences between prescription patterns at remission and after a maintenance period of at least 6 months.

Results: A total of 340 patients were selected. During the maintenance period, more than half of patients (192, 56.5%) took a MS+AP combination. Among MSs, valproate (149, 43.8%) was most prescribed, and lithium (98, 28.8%) was second, but as patients moved into maintenance treatment, lithium use decreased, and the use of lamotrigine (86, 25.3%) increased. Preferred APs were quetiapine (125, 36.8%), aripiprazole (67, 19.7%), risperidone (48, 14.1%), and olanzapine (39, 11.5%). The use of olanzapine in maintenance was greatly decreased compared with that during acute treatment (67, 19.7%). Most patients did not take an AD, but the proportion using an AD was increased during maintenance (18.0 to 30.3%), and bupropion (28, 8.2%) was the preferred AD. Doses were decreased in all drugs, but lamotrigine was maintained at a dose of 133.2±68.5 mg/day.

Conclusion: This study shows that the most common prescription combination for bipolar maintenance treatment was MS+AP, but the type of MS and AP changed. Olanzapine and lithium were decreased, whereas lamotrigine was increased. Finally, the doses of MSs and APs were generally decreased during the maintenance periods, with the exception of lamotrigine.

Policy of full disclosure: None.

P-03-005 Changes of cortical excitability as markers of antidepressant response in bipolar depression

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Objective: It is still unclear which biological changes are needed to recover from a major depressive episode. Current perspectives focus on cortical synaptic neuroplasticity. Measures of cortical responses evoked by transcranial magnetic stimulation (TMS) have been correlated with synaptic strenght in rodents, and change with sleep homeostasic pressure in humans. Using repeated total sleep deprivation (SD) as a model antidepressant treatment, we aimed at correlating recovery from depression with these measures of synaptic potentiation.

Methods: We recorded electroencephalographic responses to TMS in the prefrontal cortex of 21 bipolar depressed inpatients (BPD) treated

with repeated SD combined with light therapy. We performed 7 TMS/EEG sessions during one week, in the morning and in the evening, before and after the first SD, after the first sleep recovery night, and at the end of treatment. We calculated three measures of cortical excitability (slope of the first evoked component, local and global mean field power.

Results: Twelve patients responded to treatment. Cortical excitability progressively increased during the antidepressant treatment and as a function of time awake. Higher values differentiated responders from non responders both at baseline, during, and after treatment on all measures.

Conclusion: Changes in measures of cortical excitability, which reflect the build-up of synaptic strength during wake, parallel and predict antidepressant response to combined SD and light therapy. Data suggest that promoting cortical plasticity in bipolar depression could be a major effect of successful antidepressant treatments, and that patients not responding could suffer a persistent impairment in their neuroplasticity mechanisms.

Policy of full disclosure: None.

P-03-006 Is the association between mood disorders and alcohol use disorders modified by social support? Results from a large nationally, representative study (CCHS 1.2)

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Objective: There is a strong association between alcohol use disorders and mood disorders (i.e., mania and depression), and the co-occurrence of these disorders is associated with worse outcomes for both disorders. This study aims to examine the twelve month prevalence of mood disorders, co-occurrence with alcohol use disorders, and the role of social supports in the association between alcohol use disorders and mood disorders

Methods: The 2002 Canadian Community Health Survey, Mental Health and Well-Being Cycle 1.2 (CCHS 1.2) used the World Mental Health Composite International Diagnostic Interview (WMH#CIDI), and included mood and alcohol use disorders. Social support was measured using the Medical Outcomes Social Support Survey which assesses tangible, affective, emotional/informational and social interaction dimensions of support. Chi-square and ANOVA tests were conducted to compare the social support variables between the mood disorders. Logistic regression models were conducted adjusting for the 4 different types of social supports to examine their role as potential moderators of the association between mood and alcohol use disorders.

Results: Subjects with mania have an earlier age of onset and co-occurrence with alcohol use disorders. Mood disorders are strongly associated with alcohol dependence, but not alcohol abuse. Only positive social interaction support was statistically different among the mood disorders, and it diminished the association between mood disorders and co-occurrence with alcohol dependence.

Conclusion: Availability of positive social interactions could be a target of intervention which diminishes the association between mood disorders and alcohol dependence, and has the potential to reduce negative outcomes of both disorders.

Policy of full disclosure: None.

P-03-007 Cognitive styles in bipolar disorder and unipolar depression

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Objective: Specific cognitive styles could trigger a mood episode, or result in worsening of existing mood symptoms, in the presence of stressful events. Bipolar disorder is related to high levels of Behavioral Activation System (BAS) sensitivity in situations with the potential for high-reward and immediate gratification. However, both unipolar and bipolar depression are characterized by high levels of Behavioral Inhibition System (BIS) sensitivity in response to potentially threatening events. To date, this is the first study to compare the cognitive styles between patients with bipolar disorder and unipolar depression.

Methods: 22 subjects with unipolar depression and 34 subjects with bipolar disorder were recruited from a tertiary-care level specialty outpatient mood disorders clinic. Two self-report questionnaires the CSQ-SF, and the BIS/BAS Scales were employed. Diagnostic interviews were administered to yield mood diagnoses, comorbid psychiatric diagnoses and sociodemographic characteristics. Association between mood diagnosis and specific cognitive styles was studied with multiple regression models.

Results: Compared to bipolar subjects, unipolar subjects (1) tended to respond and react with more negative affect and 'inhibited' behavior in anticipation of potentially threatening events, in addition to (2) exhibiting lower levels of self-worth. In contrast, bipolar subjects (3) showed more 'fun-seeking' behaviors compared to unipolar subjects, implying that they have a stronger tendency to pursue pleasurable things ($p<0.05$).

Conclusion: Mood disorder subjects exhibit specific differences on cognitive styles, specifically in the way they interpret and approach negative and/or threatening events. Cognitive style abnormalities indicate specific targets of therapy and their assessment may be helpful in individualizing treatment.

Policy of full disclosure: None.

P-03-008 Efficacy and safety of treatment with lurasidone adjunctive with lithium or valproate in bipolar I depression: Results of two 6-week studies

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Objective: To evaluate the efficacy and safety of lurasidone adjunctive with lithium (Li) or valproate (VPA) in bipolar I depression.

Methods: Data were pooled from 2 studies in which patients meeting DSM-IV-TR criteria for bipolar I depression received 6 weeks of double-blind treatment with lurasidone 20–120 mg/day (N=355) or placebo (N=327), adjunctive with Li or VPA. The primary and key secondary efficacy measure were, respectively, the Montgomery Asberg Depression Rating Scale (MADRS) and the Clinical Global Impression Bipolar Severity of Illness (CGI-BP-S), analyzed by MMRM. Secondary efficacy outcomes included the Quick Inventory of Depressive Symptomology – Self Report (QIDS-SR16), Hamilton Anxiety Rating Scale (HAM-A), and Quality of Life, Enjoyment and Satisfaction Questionnaire (Q-LES-Q).

Results: At week 6 endpoint, treatment with lurasidone (vs. placebo) was associated with improvement vs. placebo in the mean MADRS (−14.4 vs. −11.9; p=0.003), CGI-BP-S (−1.7 vs. −1.3; p=0.001), QIDS-SR16 (−7.4 vs. −5.7; $p \leqslant 0.001$), HAM-A score (−7.0 vs. −5.0; $p \leqslant 0.001$ [LOCF]), and Q-LES-Q (+18.5 vs. +13.2; $P<0.001$). Responder rates (MADRS reduction $\geqslant$50%) were significantly higher with lurasidone vs. placebo (48% vs. 37%; p=0.002; LOCF-endpoint). Minimal LOCF-endpoint changes were observed for adjunctive lurasidone vs. placebo in mean weight (+0.1 vs. +0.2 kg), median total cholesterol (−4.0 vs. −1.0 mg/dL), LDL (−3.0 vs. −1.0 mg/dL), triglycerides (+4.0 vs. −2.0 mg/dL), and glucose (0.0 vs. 0.0 mg/dL). Discontinuation rates due to adverse events were similar for lurasidone vs. placebo (5.8% vs. 4.8%); adverse events ($\geqslant$5% incidence) were nausea (13.9% vs. 10.2%), Parkinsonism (12.8% vs. 8.1%), somnolence (11.4% vs. 5.1%), and akathisia (10.8% vs. 4.8%).

Conclusion: Results of this pooled analysis demonstrated that adjunctive therapy with lurasidone and Li or VPA was effective in treatment of patients with bipolar depression, with a low rate of discontinuation due to adverse events and minimal effect on weight or metabolic parameters.

Policy of full disclosure: Dr. Calabrese has provided consultant services and/or received grant support and/or received payment for lectures from AstraZeneca, Benecke, Biomedical Development Corp., Cephalon, Convergent Health Solutions, Cortex Congress, Elan, Eisai, Forest Labs, GSK, Health & Wellness, Hoffman LaRoche, Lundbeck, Medwiz Healthcare, Merck, Otsuka, Pfizer, Promedica Scientia, Spirant Communications Private Limitrex, Sunovion, Takeda, and Teva. Dr. Suppes has received funding, medications for clinical grants, consulting fees and/or travel expenses from: Sunovion, Elan Pharma International, H. Lundbeck A/S, NIMH, VA Cooperative Studies Program, and Jones and Bartlett (formerly Compact Clinicals). Drs. Sarma, Silva, Kroger, Cucchiaro, Pikalov, and Loebel are full-time employees of Sunovion Pharmaceuticals Inc.

P-03-009 Insulin resistance: An occult, modifiable risk factor for refractory bipolar disorder?

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Objective: Rates of type II diabetes (T2D) are increased among patients with bipolar disorder (BD). Insulin resistance (IR) typically precedes T2D, but no previous study has explored the relationship between laboratory-established IR and outcomes in BD. Studying IR is relevant as it may be an occult, modifiable risk factor for treatment refractory BD, yet there are no recommendations for testing for IR. This study examines the relationships between IR, T2D, and clinical course and treatment response in BD. We hypothesize that patients with IR or T2D have a more severe and treatment-refractory form of BD.

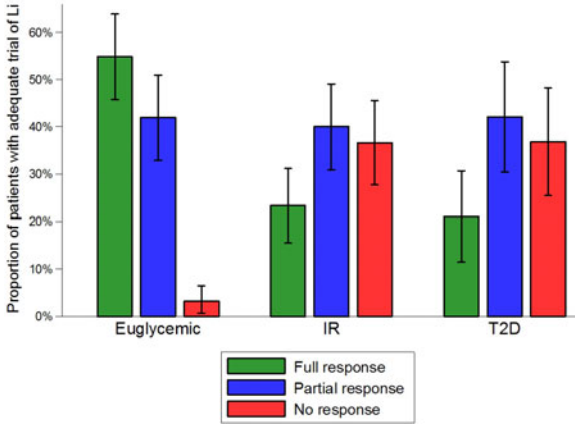
Methods: We measured fasting plasma glucose and fasting serum insulin in 121 adult patients with BD. We established the diagnosis of T2D and determined IR according to the Homeostatic Model Assessment-IR equation. The National Institute of Mental Health-Life Chart Method was used to record clinical course of BD. The Retrospective Criteria of Long-Term Treatment Response in BD scale was used to establish response to prophylactic lithium treatment.

Results: Of 121 patients with BD, 21.5% had T2D and an additional 32.2% had IR. Bipolar patients with T2D or IR had three times higher odds of a chronic course of BD compared to glucose tolerant bipolar patients (50% vs. 27%; OR=3.07, p=0.007). Bipolar patients with T2D or IR were more likely to be refractory to lithium treatment compared to glucose tolerant bipolar patients (37% versus 3.2%, OR=8.40, p<0.0001). All associations remained significant after controlling for antipsychotic exposure in sensitivity analyses.

Conclusion: Insulin resistance and T2D are associated with chronic course and poor response to prophylactic lithium treatment. Notably, patients with IR had comparably poor outcomes to those with T2D. Further studies are needed to explain the mechanism of this relationship and establish whether management of IR and T2D may improve the course of bipolar disorder and treatment response.

Policy of full disclosure: This study was funded by grants to Dr. Calkin from the Brain and Behaviour Research Foundation (formerly the National Alliance for Research on Schizophrenia and Depression, grant number 1003065-NARSAD-CALKIN) and the Capital Health Research Fund (grant number CDHA/RS-2002-061) and to Dr. Alda from the Canadian Institute of Health Research (CIHR grant number 64410). None of the authors have competing interests to declare.

Glucose metabolism and response to lithium:



P-03-010 Differential changes in metabolic profile of bipolar patients following switching to aripiprazole

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Objective: High rate of metabolic derangement necessitate various attempts to enhance the safety of the maintenance treatment of bipolar disorders. This study aimed to investigate the changes in metabolic profile in bipolar patients with antipsychotic-induced weight gain following switching to aripiprazole.

Methods: Patients with DSM-IV bipolar I or II disorder who experienced antipsychotic-induced weight gain were recruited. A total of 31 patients with 7% or more increase in weight due to prior antipsychotic use were randomly assigned to continuation (n=15) or switching to aripiprazole (n=16) for 26 weeks.

Results: In terms of the change from baseline, significant differences in both body weight and body mass index between the two groups were detected at week 12 onward. A significant decrease in fasting glucose was observed in the aripiprazole group at week 18 onward. While no significant change in HDL cholesterol was found, a significant improvement of LDL cholesterol was detected at week 12. In addition, a reduction in triglyceride level was observed in the aripiprazole group at week 8 onward.

Conclusion: Switching aripiprazole from other antipsychotics may reverse weight gain associated with antipsychotic treatment in bipolar patients. Long-term aripiprazole use did not appear to worsen abnormalities in glucose metabolism in patients previously treated with antipsychotics.

Policy of full disclosure: This study was supported by Grant A101915 from the Korea Healthcare Technology R&D Project, Ministry of Health & Welfare, Republic of Korea and a research grant from Korea Otsuka Pharmaceutical. The authors report no additional financial or other relationship relevant to this study.

P-03-011 Mental disorders in offspring of parents with bipolar disorders in Korea

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Objective: There is limited information on the specificity of associations between parental bipolar disorder and the risk of psychopathology in their offspring. The chief aim of this study was to investigate the association between bipolar disorders in the parents and mental disorders in the offspring in Korea.

Methods: The sample consisted of 100 child and adolescent offspring (aged 6.0–18.9 years; mean±S.D.=13.6±3.9 years) from 65 nuclear families with at least one parent with BPD. Parents with BPD were recruited through inpatient/outpatient clinics at department of Psychiatry, Soonchunhyang University Hospital between January, 2012, and December, 2013. Probands, offspring were interviewed by psychologists, and the offsprings were diagnostically evaluated using the K-SADS-PL.

Results: 59 of the 100 participants met the DSM-IV criteria for at least one psychiatric disorder, most commonly a mood disorder. Of these 59 children, 22 were diagnosed with BPD. 16 children received a diagnosis of any depressive disorder. The remaining 21 received other Axis 1 diagnoses, as follows: Four were diagnosed with ADHD, mostly combined type; four with any anxiety disorder and two with DBD alone; one with Tic disorder; one with an autistic disorder; and one with schizophrenia plus anxiety disorder. 41 of the children and adolescents did not receive any psychiatric diagnosis. Comorbidity with ADHD was present in 12 of the 38 children with mood disorders, including those with BPD; In all 12 of these subjects, ADHD onset occurred at least one year before the onset of mood disorders. The mean age at onset of mood symptoms among the subjects with bipolar and major depressive disorder was 11.8±2.3 years.

Conclusion: Offspring of parents with BPD are at high risk for psychiatric disorders and specifically for early onset BP spectrum disorders. These findings further support the familiality and validity of BPD in youth and indicate the need for early identification and treatment.

Policy of full disclosure: None.

P-03-012 Effects of cytokines on brain serotonin transporter in bipolar I disorder

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Objective: A growing body of studies has demonstrated the reciprocal relationships between serotonin metabolism and immune-inflammatory pathways in depression but lack of data in bipolar disorder (BD). The aim of this study was to investigate the interaction of cytokines and brain serotonin transporter (SERT) in BD.

Methods: Twenty-eight patients with euthymic BD and 28 age- and sex-matched healthy controls (HCs) were recruited. Single photon emission computed tomography with the radiotracer 123I-ADAM was used for the SERT image. Specific uptake ratio, which represents the SERT availability, was the primary measured outcome. Regions of interest included the midbrain, thalamus, putamien and caudate. Seven cytokines included the pro-inflammatory cytokine, tumor necrosis factor-alpha (TNF-alpha), interferon-gamma (IFN-gamma), interleukin-1-alpha (IL-1-alpha), IL-1-beta, IL-4, IL-6 and the anti-inflammatory cytokine, IL-10 were measured using an enzyme linked immune-sorbent assay.

Results: The SERT availability in the midbrain and caudate was significant lower in BD than HCs. IL-1-beta was significant higher, whereas IL-10 was significant lower in BD than those in HCs. Pearson's correlation showed that IL-1-alpha was significantly correlated with the SERT availability in the midbrain and caudate, TNF-alpha was significantly correlated with the SERT availability in the thalamus in HCs. However, these correlations cannot be found in BD. A stepwise regression model that considered these cytokines showed similar results.

Conclusion: This study firstly demonstrates the effects of cytokines on the SERT availability in different brain regions. Apparently, IL-1-alpha plays an important role in regulating the SERT availability in HCs but this relationship was disrupted in BD.

Policy of full disclosure: None.

P-03-013 Clinical assessment of lurasidone benefit and risk in the treatment of bipolar I depression using number needed to treat, number needed to harm, and likelihood to be helped or harmed

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Objective: To assess the clinical utility of lurasidone for bipolar depression, using number needed to treat (NNT, for benefits), number needed to harm (NNH, for harms), and likelihood of being helped or harmed (LHH, ratio of NNH to NNT, for trade-offs between benefits vs. harms).

Methods: Data are from two 6-week placebo-controlled registration studies, one using lurasidone monotherapy at 20–60 or 80–120 mg/d, and the other using 20–120 mg/d adjunctive to lithium or valproate.

Results: NNT vs. placebo for response (>=50% reduction on the Montgomery Asberg Depression Rating Scale (MADRS) total score) was 5 for lurasidone monotherapy (both dose ranges) and 7 for adjunctive therapy. NNT vs. placebo for remission (MADRS total score <=12) for lurasidone monotherapy was 6 for 20–60 mg/d and 7 for 80–120 mg/d and 7 for adjunctive lurasidone. NNH vs. placebo for discontinuation due to an adverse event (AE) for lurasidone monotherapy was 642 for 20–60 mg/d and -181 for 80–120 mg/d, and for adjunctive lurasidone was −54. Lurasidone was not associated with any clinically meaningful weight/metabolic changes vs. placebo. The three most frequently occurring AEs with the largest difference in incidence for lurasidone vs. placebo were nausea, akathisia, and somnolence, with NNH values for lurasidone vs. placebo ranging from 11 (nausea with lurasidone monotherapy 80–120 mg/d) to 130 (somnolence with lurasidone monotherapy 20–60 mg/d). LHH was consistently >1 (indicating benefit being more likely than harm) when contrasting response or remission versus AEs or weight gain.

Conclusion: Lurasidone, compared to other treatments approved for bipolar depression, yielded comparable benefits (all had single-digit NNT vs. placebo for response or remission), and less risk of harm (double-digit or greater NNHs with lurasidone compared to single-digit NNHs for sedation with quetiapine and for weight gain with olanzapine-fluoxetine combination).

Policy of full disclosure: This study was supported by Sunovion Pharmaceuticals Inc., Marlborough, MA and Fort Lee, NJ. In the past 36 months L. Citrome has engaged in collaborative research with, or received consulting or speaking fees, from: Alexza, Alkermes, AstraZeneca, Avanir, Bristol-Myers Squibb, Eli Lilly, Envivo, Forest, Genentech, Janssen, Lundbeck, Merck, Mylan, Novartis, Noven, Otsuka, Pfizer, Reckitt Benckiser, Reviva, Shire, Sunovion, Takeda, and Valeant. In the past 36 months T. Ketter has engaged in collaborative research with, or received consulting or speaking fees, from Abbott, Allergan, AstraZeneca, Avanir, Bristol-Myers Squibb, Cephalon, Eli Lilly, Forest, GlaxoSmithKline, Janssen, Otsuka, Pfizer, Sunovion, and Teva; T. Ketter's spouse is an employee of and holds stock in Janssen Pharmaceuticals. J. Cucchiaro and A. Loebel are full-time employees of Sunovion Pharmaceuticals.

P-03-014 Categorical improvements in severity of mania and schizophrenia symptoms: Pooled analyses of cariprazine phase II/III trials

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Objective: Cariprazine, a dopamine D3 and D2 receptor partial agonist with preferential binding to D3 receptors, has demonstrated efficacy in the treatment of both schizophrenia and bipolar I disorder in Phase II/III clinical trials. In this analysis, the effect of cariprazine on overall disease severity in both patient populations was evaluated by measuring clinically relevant shifts in CGI-S scores.

Methods: Data from 6 phase II/III, double-blind, placebo-controlled trials in patients with schizophrenia or bipolar mania (6-week schizophrenia trials: NCT00694707, NCT01104766, NCT01104779; 3-week bipolar mania trials: NCT00488618, NCT01058096, NCT01058668) were analyzed; data were pooled separately for each disease and cariprazine dose groups were combined (schizophrenia, 1.5–9 mg/day; bipolar mania, 3–12 mg/day). The secondary efficacy parameter in all studies was change from baseline in CGI-S. This analysis evaluated the proportion of patients who improved from more severe CGI-S categories at baseline to less severe categories at endpoint.

Results: In schizophrenia studies, a significantly greater proportion of severely ill patients at baseline (CGI-S $\geqslant$ 6, n=161) improved to mildly ill or better (CGI-S $\leqslant$ 3) in the cariprazine group vs. placebo (42% vs. 18%; odds ratio [OR]=3.43; P=0.004). In patients who were markedly ill or worse at baseline (CGI-S $\geqslant$ 5, n=1033), 7% of cariprazine vs. 3% of placebo patients improved to borderline ill/normal (CGI-S $\leqslant$ 2) at Week 6 (OR=2.33; P=0.022). In bipolar mania studies, a greater percentage of cariprazine vs. placebo patients shifted from markedly ill or worse (n=1033) to borderline ill/normal (32% vs. 18%; OR=2.10; P<0.001). In severely or extremely ill patients (n=97), 55% and 36% of cariprazine and placebo patients, respectively, improved to mildly ill or better (OR =2.12; P=0.09).

Conclusion: Cariprazine treatment compared with placebo resulted in a significantly greater proportion of patients achieving clinically relevant improvements in global disease severity as measured by CGI-S category shifts in both patients with schizophrenia and patients with bipolar mania.

Policy of full disclosure: Supported by funding from Forest Laboratories, Inc. and Gedeon Richter Plc. Suresh Durgam is an employee of Forest Research Institute.

P-03-015 Naturalistic study of efficacy of acute treatment with lithium and valproate in the treatment of manic inpatients

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Objective: The aim of this study was to evaluate the efficacy of acute treatment with lithium compared with valproate in manic inpatients.

Methods: This study included all patients with DSM-IV- diagnosed bipolar I disorder, current episode pure mania (N=234), who were admitted to our Psychiatric inpatient Unit during the years 2009–2013 period. Patients treated with lithium and valproate concomitantly (N=21) and patients no treated with lithium or valproate (N=36) were excluded. Patients were separated into 2 groups according to the medications used: A- Lithium group: All treated with lithium and oral antipsychotics (N=85) B- Valproate group: All treated with valproate and oral antipsychotic (N=92). Outcome was measured using the scores in YMRS and CGI-S scales and the length of stay (LOS).

Results: Baseline characteristics of patients were similar between groups except that lithium -treated patients were significantly (P<0.001) younger (mean of 37,8 years vs. 45), had significantly (P<0.05) more psychotic symptom (86% vs. 36%), had significantly (P<0.02) more percentage of smokers (67% vs. 51%) and had significantly (P<0,003) higher baseline score in CGI-s scale (Mean 0f 5,83 vs. 5.58). In the two groups, all patients were also treated with oral antipsychotics (mainly with olanzapine or risperidone). No significant differences in the initial score in YMRS and in the mean change in YMRS were found (YMRS of 29,8, −25,3 in lithium group vs. 29,7 and −23,9 in valproate group). Mean change in CGI from baseline to the day of discharge were significantly (P<0.05) higher in lithium group (−2,84 vs. −2,6). The LOS was lower in lithium group (Mean of 26,9 days vs. mean of 29,8) but the differences were not significant (P<0.19).

Conclusion: Although it is used in more severe cases, treatment of manic inpatients with lithium associated with antipsychotics is more effective than treatment with valproate associated with antipsychotics.

Policy of full disclosure: None.

Manic Inpatients treated with lithium vs. valproate:

Group Statistics

	Lithium	N	Mean	Std. Deviation	Std. Error Mean
CGIBaseline	Non	90	5,58	,540	,057
	Yes	83	5,83	,559	,061
CGIDischarge	Non	90	2,98	,834	,088
	Yes	83	2,99	,741	,081
CGIChange	Non	90	2,6000	,85853	,09050
	Yes	83	2,8434	,81871	,08987
YMRSBaseline	Non	82	29,72	7,846	,866
	Yes	75	29,85	7,222	,834
YMRSDischarge	Non	82	5,76	5,543	,612
	Yes	75	4,48	3,269	,377
YMRSChange	Non	82	23,9634	7,79276	,86057
	Yes	75	25,3733	7,59405	,87689
LenghtofStay	Non	92	29,76	15,945	1,662
	Yes	85	26,94	12,336	1,338
Age	Non	92	45,02	15,488	1,615
	Yes	85	37,84	10,717	1,162

P-03-016 Naturalistic study of efficacy of acute treatment with paliperidone palmitate as add-on therapy in the treatment of manic inpatients

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Objective: The aim of this study was to evaluate the efficacy of two deltoid injections of Paliperidone Palmitate (PP) (the first injection of 150 mg and, one week after, the second injection of 100 mg) as add-on treatment of manic inpatients.

Methods: This study included all patients with DSM-IV- diagnosed bipolar I disorder, current episode pure mania (N=55), who were admitted to our Psychiatric inpatient Unit during the year 2013. Patients were separated into 2 groups according to the medications used: A- PP Group: Mood stabilizer and oral antipsychotic more two deltoid injections of PP (N=12) B-Standard treatment (ST Group) : mood stabilizer and oral antipsychotic (N=43). Outcome was measured using the scores in YMRS and CGI-S scales and the length of stay (LOS).

Results: Baseline characteristics of patients were similar between groups except that PP-treated patients were significantly (P<0.03) younger (mean of 32,17 years vs. 42,79). In the group treated with PP, all patients were also treated with oral antipsychotics (50% with paliperidone). No significant differences in the initial score in scales between both groups were found (YMRS of 30,8 and CGI of 5,67 in PP group vs. YMRS of 28,9 and CGI of 5,7 in ST group). Mean change in YMRS and CGI from baseline to the day of discharge were similar in both groups (−24,75 and −2,83 in PP group vs. −23 and −2,7 in ST Group). The LOS was significantly lower (P<0.05) in PP group (Mean of 21,33 days vs. mean of 27,35 days in ST group).

Conclusion: Add-on treatment with two deltoid injections of paliperidone palmitate (150 mg and 100 mg one week after) in manic inpatients significantly reduces the length of stay. Multicenter studies with larger samples are needed to verify our data.

Policy of full disclosure: None.

CGI,YMRS scores and LOS in PP and ST groups:

	PPGroup	N	Mean	Std. Deviation	Std. Error Mean
CGIBaseline	Non	43	5,70	,558	,085
	Yes	12	5,67	,492	,142
CGIDischarge	Non	43	3,00	,900	,137
	Yes	12	2,83	,718	,207
YMRSBaseline	Non	40	28,90	6,763	1,069
	Yes	12	30,08	7,255	2,094
YMRSDischarge	Non	40	5,83	6,812	1,077
	Yes	12	5,33	2,229	,644
CGIChange	Non	43	-2,6977	,98886	,15080
	Yes	12	-2,8333	,71774	,20719
YMRSChange	Non	40	-23,0750	6,66174	1,05331
	Yes	12	-24,7500	7,43609	2,14661
LengthOfStay	Non	43	27,35	10,170	1,551
	Yes	12	21,33	7,215	2,083

P-03-017 Inflammation associated with elevation of triglyceride in subsequent remission of bipolar mania

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Objective: Racial difference in lipid metabolism is known. Low density lipid levels have been reported in bipolar mania of Western population. The alteration of circulating lipids throughout the bipolar manic episode remains unclear in Asian patients.

Methods: The physically healthy patients with bipolar I, manic under 45 years of age along with their age-and gender- matched normal subjects were enrolled. We measured the fasting blood levels of glucose, cholesterol, triglyceride (TG), low density lipid (LDL), high density lipid (HDL), and inflammatory parameters including soluble tumor necrosis factor receptor (sTNF-R1) and soluble interleukin-2 receptor (sIL-2R) in acute mania, subsequently partial and full remission.

Results: Twelve female and 21 male patients with mean 31.6 years old and 33 matched normal subjects were recruited .The mean level of LDL in acute mania (85.6±37.1 mg/dl) of bipolar patients was significantly lower than that (105.2±23.2 mg/dl) of normal controls. The levels of TG in partial (126.6±82.0 mg/dl) and full (121.6±88.2 mg/dl) remission were significantly higher than that of normal controls (74.0±42.8 mg/dl). The elevated TG in full remission had positive relationship with levels of sTNF-R1 and sIL-2R.

Conclusion: Metabolism of lipid may vary across manic episode in bipolar disorder and differ from that in Western patients. Activation of inflammatory response system may be associated with higher TG in euthymic bipolar patients.

Policy of full disclosure: None.

P-04. Depression A

P-04-001 COMT gene polymorphism, plasma MHPG, and response to duloxetine in Japanese MDD patients

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Objective: We recently reported that responders to duloxetine increased plasma 3-methoxy-4- hydroxyphenylglycol (MHPG) in patients with MDD (Atake et al., in press). The result suggests that duloxetine improves depressive symptoms via enhancing noradrenergic neurons. In a multicenter European study, an association was found between the COMT gene Val158Met (G324A) functional polymorphism and major depressive disorder (MDD). Therefore it is speculated that the amount of noradrenalin in the patients with Val/Val in less than those with Met-carriers. From these findings into account, we hypothesized that the MDD patients with Val/Val response better to duloxetine than those with Met-carriers. To examine the hypothesis we investigated effects of duloxetine on plasma concentration of catecholamine metabolites for each type of the COMT gene polymorphism and response to duloxetine.

Methods: Sixty-four patients were enrolled in the study. Major depressive episode was diagnosed by using the Structured Clinical Interview for DSM-IV according to the DSM-IV-TR criteria. The severity of depression was evaluated using the 17-item Hamilton Rating Scale for Depression (HAMD-17). All patients were administered duloxetine for 8 weeks. lasma MHPG was analyzed by HPLC-ECD. The genotyping of the COMT gene polymorphism (rs4680) was conducted in the direct sequence in the related region.

Results: 45 of 64 patients have completed the study. The distribution of Val/Val, Val/Met, Met/Met were 19, 25, and 1, respectively. This was fit with the Hardy-Weinberg Equilibrium. Treatment with duloxetine for 8 weeks significantly increased plasma MHPG levels (p=0.049) in Val/Val group but did not change in Met-carrier group, however, the COMT gene polymorphism (rs4680) and duloxetine response was not associated.

Conclusion: The relationship among the COMT gene Val158Met, plasma MHPG levels, and duloxetine response in patients with MDD was complicated. In short, the response to duloxetine and plasma MHPG might not be determined by only COMT activity.

Policy of full disclosure: None.

P-04-002 A novel anesthetical method of ECT using remifentanil, rocuronium and sugammadex, in a patient with depression and Brugada syndrome

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Objective: Brugada syndrome (BS) is one of the most common causes of sudden death in young people and many anesthetic and psychotrophic drugs need to be avoided. Electroconvulsive therapy (ECT) induces significant autonomic change, which could occur malignant arrhythmias. Although propofol and suxamethonium were usually used with anesthesia of ECT, these drugs are discouraged to avoid the vagotonic effects that can precipitate ventricular fibrillation during anesthesia in patients with BS.

Methods: We report the successful anesthetic management of a patient with BS who underwent ECT to treat treatment-resistant depression.

Results: A patient was 49 years-old Japanese man. He received intravenous low dose of thiamylal sodium (effect-site concentration (Ce) was 10#g/ml) and high dose of remifentanil (Ce: 20 ng/ml). Thereafter, The combination of rocuronium (0.8 mg/kg) and sugammadex (4 mg/kg) were used to induce and antagonize neuromuscular block. Total 10 sessions of ECT were safely and effectively underwent through this anesthetical method. Therefore, the depressive symptoms were improved and 17 items of Hamilton Depression Rating Score (HAM-D17) was decreased from 27 to 8.

Conclusion: The ECT anesthetical method of adjuvant use of high-dose remifentanil and the combination of rocuronium and sugammadex may be useful in patients with BS, which could avoid vagotonic effects and malignant arrhythmias.

Policy of full disclosure: None.

P-04-003 Early treatment improvement in predicting later remission in Asian patients with major depressive disorder treated with mirtazapine

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Objective: The objective of this analysis was to examine the usefulness of an early treatment improvement (at weeks one and two) in predicting later remission in Asian patients with major depressive disorder (MDD).

Methods: Data of 261 patients with MDD from a six-week double-blind placebo-controlled randomized trial of mirtazapine in subjects with major depression were used for this post-hoc analysis. We compared trajectories of individual depressive symptoms over six weeks between remitters and non-remitters. Early improvement and remission were defined with a #20% and a #50% decrease in the Hamilton Rating Scale for Depression (HAM-D) total scores, respectively, and reliability parameters were obtained for an early improvement to predict later remission. Moreover, which symptom improvement in the HAM-D at week 2 predicted remission was identified, using binary logistic regression analysis.

Results: Early improvement was a highly sensitive predictor of remission; an improvement at week one was associated with sensitivity of 0.742–0.897, specificity of 0.441–0.639, a positive predictable value of 0.548–0.648 and a negative predictable value of 0.652–0.857 in predicting remission status at week six. The corresponding figures, defined by an early improvement at week two, were 0.968–1.000, 0.364–0.471, 0.588–0.617 and 0.923–1.000, respectively.

Conclusion: While the data pertain to nonpsychotic MDD Asian patients who received mirtazapine, early improvements in depressive symptoms may serve as a predictor of subsequent remission.

Policy of full disclosure: None.

P-04-004 Effect of mirtazapine for benzodiazepines use compared with selective serotonin reuptake inhibitors in patients with major depressive disorder: A multicenter, open-label, randomized, controlled trial

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Objective: We investigated the effect of mirtazapine for continuous use of benzodiazepines, compared with selective serotonin reuptake inhibitors (SSRIs), in treatment with major depressive disorder (MDD). In addition, we identified serum brain-derived neurotrophic factor (BDNF), as biomarker for the treatment response and differential diagnosis for bipolar disorder.

Methods: We examined an open-label, randomized, and controlled trial in out-patients with both MDD and current depressive episode from 10 sites in Japan. Subjects were randomly assigned to a 24-week administration of mirtazapine or SSRIs (sertraline or paroxetine). A total of 76 patients with MDD were enrolled up to the date of 30th Aug 2013. We defined the way of using benzodiazepines was on patient's own judgment, after our drug administration instruction during follow-up. We performed at baseline and 1, 2, 6, 12, and 24 weeks to evaluate clinical assessments, and measured serum BDNF at baseline and 6, 12, 24 weeks. The primary outcome was the rates of patients who used benzodiazepines.

Results: 17 (68%) of 25 people in the mirtazapine group, 20 (65%) of 31 in the sertraline group, 10 (67%) of 15 in the paroxetine group had never received any psychiatric care and any psychotropic medications before this study enrollment. The rates of continuous using of benzodiazepines in the mirtazapine group were significantly lower than other two groups at 6, 12, 24 weeks (#2 test, $p<0001$).

Conclusion: Pharmacological treatment with mirtazapine for major depression could reduce continuous use of benzodiazepines compared with SSRI.

Policy of full disclosure: None.

P-04-005 Differentiated uses of antidepressant agents

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This study attempts to map different uses of new antidepressant agents such as Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitor (SNRIs). Based on cases where antidepressants worked effectively and that were published in casebooks in Japan, the following distinguishing characteristics may be suggested: Fluvoxamine (an SSRI) may be indicated for masked depression with mainly physical complications and for treatment-resistant (refractory) depression with mainly anxiety and physical symptoms, and paroxetine (an SSRI) may be indicated for anxiety, irritation, palpitation, loss of motivation, sense of guilt caused by cerebrovascular disorders, and pain, all of which may be comorbid. In addition, milnacipran (an SNRI) works for inhibition (loss of motivation) and depressed mood (sadness and despair). Furthermore, by adding other SSRIs, such as sertraline and mirtazapine, this study attempts to map differentiated uses of new antidepressant agents.

Policy of full disclosure: None.

P-04-006 Risk for bipolar disorder and physical comorbidity in patients initially hospitalized with severe depression: Results of a retrospective chart review

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Objective: Many cases of bipolar disorder (BD) present with depressive episodes at onset. ICD-10 severe depressive episode (severe depression) may be a risk factor for diagnostic conversion into BD and psychotic depression (PD) has been consistently associated with BD. The aim of the present study was to check the stability of the diagnosis of severe depression within an inpatient setting, as well as to assess the differences between PD and non-psychotic severe depression (non-PD).

Methods: Patients who were hospitalized for severe depression both with and without psychotic symptoms (N=89; mean age=55.6 years, SD=13.9) from 2001 to 2010 were retrospectively assessed. Clinical variables were determined by using clinical records.

Results: By 75 months of follow-up, 11 patients (12.4% of the sample) had developed one or more distinct period(s) of mania or hypomania and their diagnosis was changed to BD. Of these 11 converters, 9 (81.8%) had developed BD within one year after admission. Only the presence of sub-threshold hypomanic symptoms during hospitalization was significantly related to developing BD. 37.1% (33/89) of the patients with severe depression were PD. Number of depressive episodes and history of physical diseases were significantly increased in non-PD compared to PD, while electroconvulsive therapy (ECT) during hospitalization was significantly increased in PD compared to non-PD.

Conclusion: Patients with severe depression were at a higher risk for developing BD, especially within one year after admission. Sub-threshold hypomanic symptoms during severe depressive episode may represent a prodrome of formal BD, which suggests a close follow-up and cautious use of antidepressants. In severe depression, non-PD may often occur secondary to physical diseases and experience more reccurrences than PD, which, on the other hand, may be a more 'primary' disorder and often need ECT for the treatment.

Policy of full disclosure: None.

P-04-007 Ketamine and non-ketamine NMDA receptor antagonists for unipolar and bipolar depression: A meta-analysis

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Objective: Recent studies demonstrated antidepressant efficacy of ketamine and non-ketamine N-methyl-D-aspartate receptor (NMDAR) antagonists, but the effect size trajectory and possible class effects are unclear.

Methods: We conducted a systematic review and meta-analysis of NMDAR-antagonists for depression searching PubMed, PsycINFO, ISI Web of Science, and clinicaltrials.gov from database inception until November 2013 for parallel group or cross-over randomized trials comparing single intravenous infusion ketamine or NMDAR-antagonist versus placebo for major depressive disorder (MDD) and/or bipolar depression (BD). Primary outcome was symptom improvement measured by Hamilton Depression Rating Scale (HAM-D) or Montgomery-Asberg Depression Rating Scale. Secondary outcomes included response, remission, all cause discontinuation, and side effects, such as mania, psychotic symptoms, dissociation and others.

Results: Nine trials (ketamine=6 studies, non-ketamine NMDAR-antagonists=3 studies) with 331 participants (MDD=297, BD=34) were meta-analyzed. Regarding symptom improvement, ketamine (n=163) showed significant superiority over placebo 40 minutes after the infusion of ketamine until day 4, peaking at day 2 (Hedge's g on day 2: 1.015, 95% CI: 0.610-1.419, $p<0.001$), loosing superiority by day 5–8. Conversely, non-ketamine NMDA antagonists (n=168) showed superiority over placebo only on days 5–8 (Hedge's g: 0.422, 95%CI: 0.109-0.735, $p=0.008$).

Response and remission were significant for ketamine from 40 minutes to day 7 and 80 minutes to day 3–5; while for non-ketamine NMDAR-antagonists only response was significant and only at day 3–5. Although some adverse effects were more common with NMDAR-antagonists than placebo, these were transient and clinically insignificant.

Conclusion: Single infusion of ketamine, but less so of other, non-ketamine NMDA antagonists, has ultra-rapid efficacy for MDD and BD, but the effect does not last longer than a week. Development of rapidly acting NMDAR-antagonists that can be given orally and repeatedly without inducing brain toxicity is of key importance.

Policy of full disclosure: Dr. Kishimoto has received consultant fees from Dainippon Sumitomo, Novartis, Otsuka and speaker's honoraria from Banyu, Eli Lilly, Dainippon Sumitomo, Janssen, Mochida, Novartis, Otsuka Pfizer and Shionogi. He has received grant support from the Byoutaitaisyakenkyukai Fellowship (Fellowship of Astellas Foundation of Research on Metabolic Disorders), Eli Lilly Fellowship for Clinical Psychopharmacology, Research Group for Schizophrenia Japan, Dainippon-Sumitomo, Mochida and Otsuka. Dr. Chawla has nothing to disclose. Dr. Kane has been a consultant to Alkermes, Amgen, Astra-Zeneca, Janssen, Pfizer, Eli Lilly, Bristol-Myers Squibb, Dainippon Sumitomo/Sepracor/Sunovion, Johnson & Johnson, Otsuka, Pierre Fabre. Vanda, Proteus, Takeda, Targacept, IntraCellular Therapies, Merck, Lundbeck, Novartis, Roche, Rules Based Medicine, Sunovion and has received honoraria for lectures from Otsuka, Eli Lilly, Esai, Boehringer-Ingelheim, Bristol-Myers Squibb, Merck and Janssen. He is a shareholder of MedAvante. He has received grant support from The National Institute of Mental Health. Dr. Correll has been a consultant and/or advisor to or has received honoraria from: Actelion, Alexza; American Academy of Child and Adolescent Psychiatry, Bristol-Myers Squibb, Cephalon, Eli Lilly, Genentech, Gerson Lehrman Group, IntraCellular Therapies, Lundbeck, Medavante, Medscape, Merck, National Institute of Mental Health, Janssen/J&J, Otsuka, Pfizer, ProPhase, Roche, Sunovion, Takeda, Teva, and Vanda. He has received grant support from BMS, Feinstein Institute for Medical Research, Janssen/J&J, National Institute of Mental Health.

P-04-008 Gray matter volume in the thalamus is correlated with rumination in patients with treatment-resistant depression: A structural magnetic resonance imaging study

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Objective: Magnetic resonance imaging (MRI) studies have previously identified brain regions with gray matter (GM) abnormalities in patients with treatment-resistant depression (TRD). However, it remains to be assessed whether there are brain regions where GM volume is related to rumination, a risk factor for TRD, in such patients.

Methods: We performed structural MRI scans and voxel-based morphometry (VBM) to identify GM volume related to rumination in 29 TRD patients. Response Style Questionnaire was used to assess the degrees of rumination in TRD patients.

Results: Whole brain analysis revealed that rumination correlated to GM volume in the right thalamus in TRD patients. Limitations: Healthy control was not included in this study.

Conclusion: We identified, for the first time, brain regions where GM volume correlated to rumination in TRD patients. These results improve our understanding for the anatomical characteristics of TRD.

Policy of full disclosure: None.

P-04-009 Depression-like behaviors were induced by overexpression of Shati/Nat8l, an N-acetyltransferase, in the striatum of mice

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Objective: We previously identified an N-acetyltransferase Shati/Nat8l from the brain of psychosis animal model. Shati/Nat8l synthesizes N-acetylaspartate (NAA) from aspartate and acetyl-CoA, and then its NAA is converted into N-acetylaspartylglutamate (NAAG) by condensing with glutamate. Several postmortem brain studies are suggested that NAA and NAAG in human brain related to psychiatric disorders including major depressive disorder. In the present study, to clarify the functional roles of Shati/Nat8l, we carried out various behavioral and biochemical analyses in Shati/Nat8l gene-manipulated mice.

Methods: C57BL/6J mice were bilaterally injected adeno-associated virus (AAV)-Shati/Nat8l or AAV-Mock vector in the dorsal striatum.

Results: In general Shati/Nat8l transgenic mice, the expression levels of Shati/Nat8l mRNA were significantly increased in the striatum, but not in the prefrontal cortex and hippocampus. Shati/Nat8l transgenic mice exhibited decreased approach time to the stranger mouse in the three chamber social interaction test. Alternatively, the expression levels of Shati/Nat8l mRNA in AAV-Shati/Nat8l mice were assessed at about seven times in the dorsal striatum compared with that in AAV-Mock mice. As the same to Shati/Nat8l transgenic mice, AAV-Shati/Nat8l mice exhibited decreased sociability in the three chamber social interaction test. In addition, AAV-Shati/Nat8l mice revealed increased immobility time in both the tail suspension and forced swimming tests. These three behavioral impairments in AAV-Shati/Nat8l mice were recovered by treatment with a selective serotonin reuptake inhibitor fluvoxamine (10 mg/kg, i.p.), which has no effect in AAV-Mock mice. Furthermore, in vivo brain microdialysis, the basal levels of extracellular serotonin in the dorsal striatum of AAV-Shati/Nat8l mice were significantly lower than that of AAV-Mock mice.

Conclusion: These findings suggest that overexpression of Shati/Nat8l in the striatum induces depression-like behaviors including diminished sociability and motivation via malfunction of the serotonergic neuronal system.

Policy of full disclosure: None.

P-04-010 The mRNA expressions of the nicotinic acetylcholine receptor genes in rat brains after a 21-day sertraline treatment

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Objective: Most antidepressants, including serotonin selective reuptake inhibitors (SSRIs), work as modulators of monoamines. Nicotinic acetylcholine receptor (nAChR) modulation is also reported to be involved in the effects of antidepressants. For example, cytisine, an a4b2 nAChR partial agonist, and varenicline, an a7 nAChR agonist, are reported to have a potential antidepressive effects. However, it has not been sufficiently examined whether antidepressants work via nAChRs. In the present study, we investigated the effects of sertraline, an SSRI, on nAChRs in rat brains.

Methods: Eight male Wistar rats (5 weeks old) were treated for 21 days with sertraline (15 mg/kg/day), using osmotic pumps. Controls (n=8, 5 weeks old) were not given sertraline, but otherwise were treated the same as the sertraline group After 21 days, rats were sacrificed by decapitation and the brain tissues of nine regions (olfactory bulb, frontal cortex, temporal cortex, striatum, thalamus, hippocampus, midbrain, pons, and cerebellum) were dissected. RNA was extracted from each brain tissue and reversely transcribed. The mRNA expressions of the nAchR genes were examined by real-time quantitative PCR with TaqMan primer-probe sets: a3 (Chrna3), a4 (Chrna4), a7 (Chrna7), and b2 (Chrnb2) with glyceraldehyde-3-phosphate dehydrogenase (Gapdh) as an endogenous control.

Results: The mRNA expression of Chrna3 in the midbrain and that of Chrnb2 in the frontal cortex, the thalamus, and the cerebellum were significantly increased in the sertraline group. The expression of Chrna4 and Chrna7 were not different between groups.

Conclusion: In conclusion, sertraline may modulate some nicotinic acetylcholinergic systems directly or indirectly. Further studies should be conducted to clarify that mechanism.

Policy of full disclosure: None.

P-04-011 Chronic mild stress and antidepressant treatment alter 5-ht1a receptor DNA methylation of a conserved sp4 site

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Objective: The serotonin 1A receptor (5-HT1A), a critical regulator of the brain serotonergic tone, is implicated in major depressive disorder (MDD) and has been found to be dys-regulated in depressive individuals. However, the extent to which stress and antidepressant treatment can affect 5-HT1A methylation remains unclear. In the present study, we addressed the effects of unpredictable chronic mild stress (UCMS), a mouse model of adult depression responsive to chronic antidepressants, on 5-HT1A promoter methylation.

Methods: BALB/c mice were subjected to the UCMS paradigm for 2 weeks, followed by treatment or not with 10 mg/kg imipramine for 7 weeks. Genomic DNA was isolated from prefrontal cortex (PFC) or raphe-midbrain, digested and analyzed for methylation of the 5-HT1A promoter using bisulfite modification procedure.

Results: In PFC and midbrain tissue, UCMS increased DNA methylation of a conserved promoter CpG site, Site 1 located within an Sp1-like element. Chronic imipramine treatment reversed UCMS-induced increase in methylation of Site 1 in the PFC but not significantly in raphe of stressed animals. We show that site 1 is repressed by Sp4, the predominant neuronal Sp1-like factor, and that Sp4-induced repression is attenuated by DNA methylation of Site 1, providing evidence of a novel Sp4-dependent mechanism to link DNA methylation to enhanced gene expression.

Conclusion: These results indicate that adult life stress may induce 5-HT1A receptor expression by antagonizing Sp4 repression at the conserved promoter site. Chronic imipramine treatment is only partially able to reverse the stress-induced molecular changes in 5-HT1A methylation, suggesting that the efficient reversal of the behavioural impairment recruits alternative pathways, which fail to normalize the behavioral vulnerability.

Policy of full disclosure: None.

P-04-012 Vortioxetine: Exploratory analysis of the relation between target engagement and integrated clinical database analysis of MADRS single items

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Objective: Vortioxetine is a multimodal antidepressant with 5-HT3, 5-HT7 and 5-HT1D receptor antagonism, 5-HT1B receptor partial agonism, 5-HT1A receptor agonism and inhibition of the 5-HT transporter (SERT). Lack of clinically validated binding ligands for targets (except SERT) led us to develop preclinical assays relating # dose with target engagement # clinically and pre-clinically determined target occupancies with antidepressant response measured by analysis of single Montgomery-Asberg Depression Rating Scale (MADRS) items.

Methods: Occupancies for all targets were measured in rat brain by ex vivo autoradiography. SERT binding in the human brain was measured using the PET-ligands [11C]-MADAM and [11C]-DASB (1). Clinical efficacy data for single MADRS items for multiple doses of vortioxetine 5, 10 and 20 mg were obtained from an integrated clinical database of 9 short-term major depression studies.

Results: The human PET studies demonstrated increased SERT occupancy with increasing dose. At the clinically efficacious dose of 5 mg, SERT inhibition was about 50%, indicating involvement of 5-HT receptors, since SSRI efficacy requires approximately 80% SERT inhibition (2). For 5 mg, preclinical data predicted that SERT and 5-HT3 receptors were primarily occupied, while at 20 mg all targets were predicted to be occupied at functionally relevant levels. Data from the integrated clinical database illustrated a clear dose-response relationship for 9 of the 10 MADRS items.

Conclusion: The present study suggests not only a quantitative but also a qualitative increase in target engagement over the clinical dose range, i.e., mainly 5-HT3 receptors and SERT are occupied at 5 mg, with functionally relevant occupancy at all targets at 20 mg vortioxetine. We hypothesize that the relation between clinical efficacy and dose can be ascribed to this gradually increasing target engagement. 1. Areberg et al. Basic Clin Pharmacol Toxicol 2012; 110:401–404 2. Meyer. J Psychiatry Neurosci 2007; 32:86–102

Policy of full disclosure: All authors are employed by Lundbeck or Takeda, the sponsors of the studies included.

P-04-013 Clinical experience treating depressive disorders among cancer patients using Fluoxetine 20 mg

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Objective: Cancer patients may request the assistance of the psychiatrists and psychotherapists, but they do it very seldom, because that is their suffering at the forefront and to have an "on mood". A study was designed to assess the effectiveness of 20 mg fluoxetine monotherapy and in combination with psychotherapy.

Methods: 27 patients with cancer of the urinary system in the conservative rehabilitation outpatient clinic of Oncology Institute, Moldova were treated. Of 27 cancer patients, 10 patients were randomized to a fluoxetine-monotherapy treatment group (FT), 10 patients to a fluoxetine prescibing combined with psychotherapeutic intervention treatment group (FPT) and 7 patients to a psychotherapeutic treatment group (PT). The Montgomery and Asberg Depression Scale (MADRS), the Hamilton Anxiety Scale (HAS), the Hamilton Depression Scale (HDS), the Hospital Anxiety and Depression Scale (HADS), were used to assess the efficacy of fluoxetine.

Results: The response rate, defined by a HADS score lower than 8 after 4 weeks of treatment, was not significantly higher in the FT group (10%) compared to the PT group (8%), but lower than in the FPT group (13%). Compared to the PT group, patients in the FT and FTP groups showed a significantly greater decrease in HADS mean score after 4 weeks. No difference between the three groups was found in observer-reported assessments (MADRS, HAS and HDS). Although the frequencies of side-effects of prescribed Fluoxetine 20 mg were not significantly different.

Conclusion: Use monotherapy Fluoxetine20 mg justified out the most acute affective reactions as a maintenance therapy. The most effective use of combination therapy (Fluoxetine+psychotherapy session). Obtained results provoking another aspect, namely, with each of the patients was conducted long solo work more professionals (psychiatrist, psychotherapist, nurses).

Policy of full disclosure: None.

P-04-014 Deficient suppression of the default mode network during working memory engagement in remitted major depression

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Objective: Proper working memory (WM) processing requires activation of the WM network (WMN) going along with suppression of the default mode network (DMN) activation that occurs physiologically during rest. While lacking suppression of the DMN has been recently observed in symptomatic Major Depressive Disorder (MDD), studies dedicated to remitted MDD (rMDD), a condition associated with increased relapse rates specifically in adolescent-onset, are sparse and largely inconclusive.

Methods: We conducted a cross-sectional functional magnetic resonance imaging (fMRI) study in a large sample of long-term remitted, drug-free MDD patients with adolescent- (n=42) and adult (n=36) onset as well as healthy subjects (n=42) without any previous psychiatric life-time diagnosis. The classical digit variant of the n-back task was employed in order to investigate the WM function and its neurobiological correlates on a regional and a brain systems level.

Results: Relative to healthy subjects, significantly reduced suppression of the DMN with punctum maximum in the anterior cingulate cortex (ACC) was found in rMDD patients ($p_{corrected}<0.01$). Insufficient DMN suppression in rMDD patients was further reflected on a brain systems level by a significantly increased coupling between the ACC and the dorsolateral prefrontal cortex ($p_{corrected}<0.01$). Importantly, these regional as well as brain systems measures revealed significant differences between adolescent-onset rMDD patients and healthy subjects. Adult-onset rMDD patients exhibited less pronounced and non-significant effects, which were, however, located between the remaining subgroups.

Conclusion: Incomplete DMN suppression seems to be present in MDD patients even after full recovery and discontinuation of antidepressant maintenance treatment. Furthermore, the present study is in line with clinical evidence that clearly links adolescent-onset with a more severe disease course, and encourages the investigation of DMN suppression as a putative predictor of relapse, which may further support implications for antidepressant maintenance therapy.

Policy of full disclosure: None.

P-04-015 Does coping moderate the association between mood disorders and alcohol dependence? Results from the CCHS study

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Objective: Individuals with mood disorders and alcohol use disorders have a high prevalence of maladaptive coping behaviours compared to individuals without these disorders. This study aims to compare coping behaviours between individuals with mania and depression, and examine their role in modifying the association between mood disorders and alcohol dependence and abuse disorders.

Methods: This study is based on the 2002 Canadian Community Health Survey, Mental Health and Well-Being Cycle 1.2 (CCHS 1.2). The CCHS used the World Mental Health Composite International Diagnostic Interview (WMH-CIDI), and included mood and alcohol use disorders. The coping behaviours were based on validated questionnaires and grouped into three factors. Chi-square and ANOVA tests were used to compare coping behaviours between depression and mania. Logistic regression models were used with alcohol use disorders as outcomes, and mood disorders as main effects. The model was then adjusted for the coping behaviours to examine their role as moderators of the association. Statistical significance was at $p<0.05$ or Odds ratios with 95% CIs.

Results: Mood disorders were strongly associated with alcohol dependence, but not alcohol abuse. The coping behaviours of 'eating often', 'blaming self often', 'rarely talking to others', and 'smoking often' were significantly more common in individuals with mania as compared to depression, and these variables significantly increase the association between mania and co-occurrence with alcohol dependence.

Conclusion: Coping may be a target of behavioural intervention in subjects with mania, and promotion of positive coping behaviours may diminish negative outcomes of both mania and alcohol dependence.

Policy of full disclosure: None.

P-04-016 Attachment styles in bipolar disorder and unipolar depression

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Objective: Maladaptive attachment styles have been previously associated with several well-established depression vulnerability factors. The attachment patterns can be categorized into four types: secure, anxious, preoccupied and dismissive. This study aimed to compare attachment styles between mood disorders by examining differences between patients with unipolar depression versus bipolar disorder on measures of attachment style.

Methods: Data on attachment patterns were collected by administrating two self-report questionnaires (RQ-CV and ECRQ-R) to individuals diagnosed with unipolar depression and bipolar disorder from the Mood Disorders Program of the McGill University Health Centre. Structured diagnostic interviews were conducted by a trained interviewer to obtain participants' psychiatric status and their sociodemographic information. Responses to the close-relationship questionnaires were examined using linear regression models.

Results: The study included 101 subjects 39 of whom had unipolar depression, 62 had bipolar disorder and there were no demographic differences between the two groups. In comparison to patients with bipolar disorder, individuals with unipolar depression reported an attachment pattern associated with significantly higher level of fear in relationships ($p=0.03$) and avoidance in adult romantic relationships ($p=0.01$).

Conclusion: The study included 101 subjects 39 of whom had unipolar depression, 62 had bipolar disorder and there were no demographic differences between the two groups. In comparison to patients with bipolar disorder, individuals with unipolar depression reported an attachment pattern associated with significantly higher level of fear in relationships ($p=0.03$) and avoidance in adult romantic relationships ($p=0.01$).

Policy of full disclosure: None.

P-04-017 Role of central and peripheral monoamine metabolism in obesity induced neuropsychiatric behavioural changes

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Objective: Obesity and increased visceral fat mass is major risk factor for neuropsychiatric illnesses like depression, anxiety and cognitive losses. The present study was designed to investigate the role of central and peripheral monoamines metabolism in neuropsychiatric changes in high fat diet (HFD) fed rats.

Methods: Animals were fed on HFD (58% energy from fat) for 12 weeks. Periodically, blood was collected to estimate serum metanephrine (MN) levels. After 11 weeks behavioural paradigms to assess depression, locomotion and cognitive activity were performed. Central (brain) and peripheral i.e. visceral white adipose tissue (vWAT) and brown adipose tissue (BAT) MN levels, monoamine oxidase A and B (MAO-A & B) and acetylcholine esterase (AChE) enzyme activity was estimated.

Results: HFD significantly increased the body weight which was negatively correlated with the serum MN concentration. However, MN concentration in brain was significantly decreased whereas in vWAT it was significantly increased with no change in BAT. In obese animals immobility time in forced swim test and transfer latency in elevated plus maze was significantly increased while locomotor activity significantly decreased. Central MAO-A and MAO-B activity was increased while it was decreased in vWAT with no change in BAT. Brain AChE levels were also increased significantly in obese rats.

Conclusion: Metabolism of biogenic monoamines can play a critical role in obesity related neuropsychiatric changes.

Policy of full disclosure: None.

P-04-018 Differential effects of pharmacological and restraint stress on effort-based decision-making

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Objective: Decision-making involves choosing between several alternative possibilities after evaluation of the relative costs and benefits. Increasing the amount of effort required to obtain a reward is one type of cost that can diminish the subjective value of objectively larger rewards. Repeated episodes of stress can result in depressive symptoms including anergia, which in turn may reduce the tendency to exert effort to obtain rewards. The goal of the present study was to examine the effects of different types of acute stress on effort-based decision-making.

Methods: Using an operant chamber assay, rats were required to choose between a low effort/low reward lever (LR; 2 pellets), and a high effort/high reward lever (HR; 4 pellets), with the effort requirement increasing over trial blocks (2, 5, 10 and 20 presses). Normally rats will choose the HR lever more often when the effort cost is low, reducing their preference for this option as the amount of effort increases. Acute restraint stress, but not increases in corticosterone, causes rats to choose the HR option less compared to baseline performance.

Results: In a subsequent study, we assessed the effects of the alpha 2 adrenoreceptor antagonist yohimbine (1–3 mg/kg, IP), which mimics increased noradrenaline transmission induced by acute stress, on effort-based decision-making. Our expectation was that yohimbine would decrease choice of the HR option, in a manner comparable to restraint stress. In stark contrast to our expectations, we found that yohimbine increased preference for the HR option compared to vehicle treatment.

Conclusion: This suggests that yohimbine and restraint stress produce divergent effects on some decision-making tasks, highlighting the fact that different types of stressors can induce opposing effects on behavior. Whether other neurochemical changes associated with acute stress, such as increases in corticotropin-releasing factor (CRF), mediates an increase in effort discounting is a topic for future research.

Policy of full disclosure: None.

P-04-020 Investigating the role of picolinic acid in depression

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Objective: Picolinic acid (PIC) and quinolinic acid (QUIN) are metabolites of the kynurenine pathway (KP) of tryptophan metabolism, which breaks down greater than 95% of available tryptophan into NAD+ instead of serotonin under physiological conditions. Proinflammatory cytokines further stimulate KP activity. PIC and QUIN are produced from 2-amino-3-carboxymuconate-semialdehyde (ACMS), an intermediate of the KP. The enzyme 2-amino-3-carboxymuconate-semialdehyde decarboxylase (ACMSD) synthesizes PIC from ACMS while QUIN is produced spontaneously. Additionally, QUIN causes neurotoxicity via NMDA-receptor agonism, whereas PIC prevents this neurotoxicity without affecting excitation through a currently unknown mechanism. The objective of this experiment is to investigate the influence of PIC on central nervous system inflammation and depressive behavior.

Methods: In vitro experiments: Mouse microglia were stimulated with lipopolysaccharide (LPS) to activate cytokine production, and were co-treated with PIC. Supernatants were collected after 24 hours and used to measure cytokine production. Interleukin-6 (IL6) and macrophage inflammatory protein-1b levels were measured by ELISA. Tumor necrosis factor-a (TNFa), IL6, IL8, and IL10 were measured by Mesoscale Discovery (MSD) technology. In vivo experiments: Rats were given PIC in the drinking water at different doses for 12 days. On day 10 animals received intraperitoneal LPS (1 mg/kg) or saline injections. Rats underwent open field tests (OFT) and forced swim tests (FST) before being sacrificed. Cytokine analysis was performed on blood and cerebrospinal fluid using MSD assays.

Results: We found that PIC increases production of IL6 and decreases TNFa production in vitro. PIC had no significant effect on exploratory

behavior in the OFT beyond two hours post-LPS injection. In the FST, PIC decreased floating behavior and increased swimming behavior.

Conclusion: These pilot data show that PIC affects microglia production of inflammatory cytokines and mediates behavioral effects in vivo. ACMSD and PIC could constitute future drug targets for depression, which should be explored in future studies.

Policy of full disclosure: None.

P-04-021 Augmentation with aerobic exercise to pharmacological treatment for Chinese inpatients with moderate to severe depression: A single-blinded randomised controlled study

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Objective: Physical exercise has been found to be an effective treatment and prevention for depression. However, there is a lack of such kind of studies in Chinese population. This study investigates the effect of supervised aerobic exercise training on depressive symptoms and physical performance among Chinese patients in Hong Kong with moderate to severe depression, in their early in-patient treatment phase.

Methods: A randomised controlled study design was used. Subjects in supervised aerobic exercise group received 30 minutes of aerobic training, five days a week for 3 weeks. Depressive symptoms (MADRS and C-BDI) and domains in physical performance were assessed respectively by psychiatrists and physiotherapist, who were blinded to intervention, at baseline and the end of 3 weeks as outcome measures.

Results: 40 out of 52 recruited subjects (exercise group=19, control group=21) completed the program for analysis. After 3 weeks of training, subjects in aerobic exercise group showed a more significant reduction in depressive scores (MADRS) as compared with the control (between-group mean difference in reduction=13.79±8.30; 95% CI 9.79 to 17.79; p=0.003). The exercise group also demonstrated a significant improvement in the sit-and-rearch flexibility test (within-group mean difference=5.19±6.36; 95% CI −8.26 to −2.13; p=0.01).

Conclusion: Aerobic exercise in addition to pharmacological intervention can have a synergistic effect in reducing depressive symptoms and increasing motor flexibility in Chinese patients with moderate to severe depression. Introduction of exercise training in the early phase of illness may also hasten the response to antidepressants, and subsequently reduce the impact on our healthcare service. Limitations: This study did not follow up subjects long enough to examine the long-term effect of aerobic exercise, in terms of its effect size and sustainability.

Policy of full disclosure: None.

P-04-022 The efficacy of vilazodone in achieving remission in patients with major depressive disorder: Post hoc analyses of a phase iv trial

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Objective: In major depression disorder (MDD), symptom remission is the goal of treatment. We evaluated the efficacy of vilazodone, a serotonin reuptake inhibitor and 5-HT1A receptor partial agonist, in achieving disease remission using various criteria.

Methods: A post hoc analysis of a Phase IV, multicenter, randomized, 8-week double-blind, fixed-dose study (NCT01473394) comparing vilazodone 40 mg/day with placebo. The study comprised outpatients aged 18 to 70 years with MDD and a baseline total score ⩾26 on the Montgomery-Asberg Depression Rating Scale (MADRS). The primary efficacy measure was the MADRS; secondary and additional efficacy measure included the Clinical Global Impressions-Severity (CGI-S) and Hamilton Anxiety Rating Scale (HAMA). Post hoc analyses evaluated the percent of patients achieving depression symptom remission (MADRS ⩽10), complete remission (MADRS ⩽5), anxiety symptom remission (HAMA ⩽7), and combined depression/anxiety symptom remission (MADRS ⩽10+HAMA ⩽7). Overall disease remission was also assessed (CGI-S=1). Additional analyses evaluated outcomes in patients with greater depression severity (baseline MADRS ⩾30). Odds ratios (OR) and number needed to treat (NNT) were determined.

Results: The ITT population comprised 252 placebo and 253 vilazodone patients. More vilazodone patients compared with placebo achieved MADRS remission (34% vs. 22%; OR=1.82; P<0.01; NNT=9) and complete remission (18% vs. 8%; OR=2.42; P<0.01; NNT=10). More vilazodone patients compared with placebo met criteria for HAMA remission (49% vs. 35%; OR=1.82; P<0.01) and combined MADRS/HAMA remission (32% vs. 20%; OR=1.84; P<0.01). Additionally, rates of CGI-S remission were higher in vilazodone vs. placebo patients (24% vs. 12%; OR=2.41; P<0.001). In patients with greater depression severity (MADRS ⩾30), statistically significant results were seen on all remission outcome assessments for vilazodone vs. placebo (P<0.01, all outcomes), with larger ORs relative to the overall population (OR range: 1.92–3.46).

Conclusion: These post hoc analyses suggest that vilazodone 40 mg/day is effective in achieving depression and anxiety symptom remission in adult patients with MDD.

Policy of full disclosure: Supported by Forest Laboratories, Inc. The presenting author is Giovanna Forero, an employee of Forest Research Institute.

P-04-023 Clinical relevance of levomilnacipran er treatment in patients with major depressive disorder: Improvements in functional impairment categories

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Objective: To evaluate the categorical improvement in patients with major depressive disorder (MDD) treated with levomilnacipran extended-release (ER) vs. placebo. Patients were analyzed for shifts from greater severity of functional impairment at baseline to lesser severity at end of treatment (EOT).

Methods: Data were pooled from 2 fixed- and 3 flexible-dose randomized, double-blind trials of levomilnacipran ER 40–120 mg/day vs. placebo in adult patients with MDD. Proportions of patients shifting from moderate-to-high baseline impairment (score ⩾4) to mild-to-no impairment (score ⩽3) at EOT were assessed for all SDS items (representing impairment in the domains of work, social life, and family/home). Proportions of shifts from marked-to-high (score ⩾7) at baseline to moderate-to-no (score ⩽6) impairment at EOT also were assessed.

Results: More levomilnacipran ER vs. placebo patients achieved categorical SDS improvement. On the Work Item, a greater percentage of levomilnacipran ER vs. placebo patients improved from moderate-to-high baseline impairment (⩾4) to mild-to-no impairment (⩽3) at EOT (55% vs. 40%, odds ratio [OR]=1.96, P<0.0001); more levomilnacipran ER vs. placebo patients with marked-to-high baseline impairment (⩾7) had moderate-to-no (⩽6) impairment at EOT (73% vs. 64%, OR=1.81, P<0.0001). On the Social Item more levomilnacipran ER vs. placebo patients improved from moderate-to-high impairment at baseline to mild-to-no impairment at EOT (48% vs. 37%, OR=1.73, P<0.0001), and from marked-to-high impairment at baseline to moderate-to-no impairment at EOT (68% vs. 59%, OR=1.61, P<0.0001). On the Family/Home Item, more levomilnacipran ER patients relative to placebo shifted from moderate-to-high impairment at baseline to mild-to-no impairment at EOT (51% vs. 39%, OR=1.72, P<0.0001), and from marked-to-high impairment at baseline to moderate-to-no impairment at EOT (73% vs. 65%, OR =1.47, P=0.0027).

Conclusion: These results suggest that in adult patients with MDD, levomilnacipran ER treatment is associated with greater improvements than placebo in all SDS-measured functional domains of work, social, and family/home life.

Policy of full disclosure: This study was funded by Forest Laboratories, Inc.

P-04-024 Cellular adhesion molecules and cognitive functions in depression

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Objective: Determine the state of cognitive functions and rate of depression in population of diabetic patients and control group as well as to determine the rate of the serum concentration of soluble cellular adhesion molecules (E-selectin, ICAM-1, VCAM-1).

Methods: In a prospective study, sample consisted of 108 patients, 66 of the patients were diagnosed with diabetes mellitus type 2, and 42 were control group. All of them were interwied by psychiatrist and tested with Mini Mental State Examination, Hamilton depression rating scale and questionnaire about sociodemografic data. Also all of the patients gave the blood for complete labaratory analysis and concentration of the soluble cellular adhesion molecules (E-selectin, ICAM-1, VCAM-1). SPSS Statistics version 20 statistical program has been used for the statistical analysis.

Results: In a total sample females (N=48) had more cognitive dysfunctions compared with males (N=60), it was statistically significant

(Pearsons Chi-square value 4,320; df 1; p=0,038). Results showed that depressive symptoms manifested with statistical significance in the group of patients with diabetes mellitus type 2 compared to the control study group (Pearsons Chi-square value 8,577; d.f. 3; p=0,035). Patients with diabetes mellitus type 2 showed statistically significant cognitive dysfunctions compared with control group (Pearsons Chi-square value 10,099; d. f. 1; p=0,001). There were no statistically significant difference between the group of diabetic depressed patients compared with the control group in the expression of the cellular adhesion molecules, ICAM -1 (t=1,980; p=0,055), VCAM-1 (t=0,843; p=0,200), E-selectin (t=-, 285; p=0,778).

Conclusion: In this study we didn't get statistically significant higher levels of cellular adhesion molecules in these group of patients, in other words there were no higher inflammatory response, so future studies are needed to clear this diabetes-depression-cognitive dysfunction link and possible innate inflammatory response.

Policy of full disclosure: None.

P-04-025 Potential antidepressant-like effect of the brain penetrant neuropeptide Y Y2 receptor antagonist SF-11 in the rat model of depression induced by astrocyte ablation.

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Objective: Neuropeptide Y (NPY), a widely distributed peptide in mammalian brain, seems to play a significant role in depression and anxiety by acting via Y1, Y2 and Y5 receptors. Some data showed that the Y2 receptor (Y2R) antagonists BIIE0246 and JNJ-31020028 induced antidepressant-like behavior in olfactory bulbectomized rats.

Methods: The present study investigated the possible antidepressant-like activity of a new Y2R antagonist SF-11 in the rat model of depression induced by medial prefrontal cortex (PFC) astrocyte ablation by the astrocytic toxin L-alpha-aminoadipic acid (L-AAA). That toxin induced depressive-like behavior in rats, reversed by the classic antidepressant imipramine. L-AAA (100 μg/2 μl) was bilaterally microinjected into rat PFC twice, on days 1 and 2. Afterwards, the depressive-like behavior was assessed on day 5 by a forced swim test (FST). SF-11 was administered intraperitoneally (3 or 10 mg/kg) 1 h before the FST. On day 8, brains were dissected and the GFAP protein level was analyzed in the PFC using a western blot method.

Results: Our results showed that L-AAA increased immobility time in the FST, which indicated a depressive-like effect. The Y2R antagonist SF-11 (10, but not 3 mg/kg) significantly decreased immobility time in both control and gliotoxin-treated rats. Western blot analyses showed that L-AAA administration significantly reduced (by 52%) the GFAP protein level in rat PFC, which was reversed by SF-11 administration.

Conclusion: The obtained results indicate that the degeneration of astrocytes in the PFC may be a useful animal model of depression; furthermore, they demonstrate a therapeutic potential of NPY Y2 receptor antagonists in the treatment of depression. This study was supported by Grant POIG.01.01.02-12-004/09.

Policy of full disclosure: None.

P-04-026 Effects of vortioxetine on cognitive symptoms of major depressive disorder (MDD)

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Objective: Cognitive dysfunction is an important feature during the acute phase of MDD and may persist as a residual symptom even after remission of depression. This analysis of a short-term MDD study (NCT01163266) investigated the effects of vortioxetine on self-rating of cognitive symptoms by depressed patients with clinically significant cognitive dysfunction at baseline.

Methods: In this double-blind study, 462 patients randomly assigned (1:1:1) to 10 or 20 mg vortioxetine or placebo for 8 weeks were administered the self-reported cognitive and physical functioning questionnaire (CPFQ) [1]. To evaluate the effect in patients with significant cognitive symptoms, a post-hoc baseline CPFQ total score >25 was introduced as a cut-off. The CPFQ data were analyzed by ANCOVA using observed cases for patients who had completed treatment. Path analysis assessed to what extent improvement in cognition scores was a direct treatment effect.

Results: In the total population, no significant differences were detected between vortioxetine and placebo in CPFQ total score. In a post-hoc analysis of patients with clinically relevant cognitive symptoms (81% [371/457]), separation from placebo on the CPFQ in favor of vortioxetine was found at Week 8, with significant reductions in the CPFQ total score (10 mg/day), the cognitive dimension score (10 and 20 mg/day), and the four single-item scores motivation/interest/enthusiasm, ability to remember/recall information, ability to find words (10 and 20 mg/day), and sharpness/mental acuity (10 mg/day). Path analysis showed that up to two-thirds of the effect of vortioxetine was a direct treatment effect on cognitive symptoms, rather than an indirect effect mediated through improvement of general depressive symptoms.

Conclusion: In this post-hoc study of MDD patients with clinically relevant self-reported cognitive symptoms at baseline, vortioxetine demonstrated a significant alleviation of the cognitive symptoms compared to placebo that could not be accounted for solely by alleviation of depressive symptoms.

Policy of full disclosure: An employee of H. Lundbeck A/S. This study was funded by H. Lundbeck A/S and Takeda Pharmaceutical Company, Ltd.

P-04-027 The efficacy of levomilnacipran er in the treatment of patients with depression-associated fatigue symptoms

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Objective: To evaluate the effects of levomilnacipran extended-release (ER) on fatigue symptoms associated with major depressive disorder (MDD).

Methods: Data were pooled from 2 fixed- and 3-flexible-dose, randomized, double-blind, placebo-controlled studies (8 or 10 weeks) of levomilnacipran ER 40–120 mg/day in adults with MDD. Items from the MADRS (item 7 [lassitude]) and HAMD17 (items 7 [work and activities], 8 [retardation], and 13 [somatic symptoms general]) were used to assess fatigue-related impairment. Analyses included change from baseline to end of treatment (least squares mean difference [LSMD] vs. placebo) and percent of patients without residual fatigue symptoms after treatment (score <2 on MADRS item 7 or HAMD17 item 7; score <1 on HAMD17 items 8 or 13). Additionally, mean improvements in MADRS total score and MADRS response rates (⩾50% improvement) were evaluated in patients stratified by baseline fatigue (with or without high fatigue, MADRS item 7 score of ⩾4 or <4, respectively).

Results: LSMD analyses indicated significantly greater improvement with levomilnacipran ER (n=1566) vs. placebo (n=1032) on all fatigue-related items: (MADRS item 7, −0.3; HAMD17 item 7, 0.3; HAMD17 item 8, −0.1; HAMD17 item 13, −0.1; all P<0.001). At end of treatment, the percent of patients without residual fatigue symptoms was significantly higher with levomilnacipran ER vs. placebo (MADRS item 7, 35% vs. 28%, P<0.001; HAMD17 item 7, 43% vs. 35%, P<0.001; HAMD17 item 8, 46% vs. 39%, P=0.002; HAMD17 item 13, 26% vs. 18%, P<0.001). Significant mean improvements vs. placebo in MADRS total score were found in patients with high baseline fatigue (n=1916; LSMD=−3.1, P<0.001) and without high fatigue (n=681; LSMD=2.8, P=0.002). Response rates were significantly greater for levomilnacipran ER vs. placebo in both groups (high fatigue, 43% vs. 33%, OR=1.6, P<0.001; without high fatigue, 50% vs. 39%, OR=1.6, P=0.002).

Conclusion: Levomilnacipran ER may improve fatigue symptoms associated with MDD.

Policy of full disclosure: This study was funded by Forest Laboratories, Inc.

P-05. Schizophrenia A

P-05-001 Switching to antipsychotic monotherapy can improve attention and social activity in chronic schizophrenia patients

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Objective: This study sought to examine whether switching polypharmacy therapy to monotherapy would improve the cognitive function and social function of patients with schizophrenia.

Methods: Thirty-nine patients with schizophrenia who were receiving therapy with two antipsychotics were randomly divided into a switch to monotherapy group (switching group) and a polypharmacy continued group (continuing group). For the patients allocated to the switching group, the dose level of one of the two antipsychotic drugs was gradually reduced to zero. Psychotic symptoms, cognitive function and social function scale scores were assessed immediately before and 24 weeks after

switching, and the time courses of these scores were compared between the two groups.

Results: Compared with the continuing group, the switching group demonstrated significantly greater improvement in attention after switching ($p=0.02$). Furthermore, the improvement in daily living ($p=0.038$) and work skills ($p=0.04$) was significantly greater in the switching group. In an analysis of the correlation among sub-items with respect to the degrees of improvement, a significant correlation was noted between improvement in executive function and improvement in daily living ($r=-0.64$, $p=0.005$) and between improvement in work skills and improvement in attention ($r=-0.51$, $p=0.038$).

Conclusion: In patients with schizophrenia receiving polypharmacy, switching to monotherapy resulted in improvements in attention. Furthermore, improvements in executive function led to improvements in daily living, and improvements in attention led to improvements in work skills. Thus, switching to monotherapy is a useful option.

Policy of full disclosure: Professor Nakamura has received grant support from Astellas Pharma, Janssen Pharmaceutical, Eli Lilly, Glaxo Smith Kline, Pfizer, Dainippon Sumitomo Pharma Co. Ltd., Otsuka Pharmaceutical Co. Ltd., and Chugai Pharmaceutical Co. Ltd. The other authors report no financial relationships with commercial interest.

P-05-002 Efficacy of aripirpazole once-monthly in Asian patients with schizophrenia: Secondary efficacy outcomes in a multicenter, randomized, double-blind, non-inferiority study versus oral aripiprazole

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Objective: Non-inferiority of aripiprazole once-monthly (AOM), the first long-acting injectable dopamine partial agonist, was confirmed in a randomized, double-blind, non-inferiority study versus oral aripiprazole in Asian patients with schizophrenia. Here we report the secondary efficacy outcomes.

Methods: This study consisted of a screening phase and three treatment phases: an oral conversion phase (<12 weeks), an oral stabilization phase (<12 weeks) and a double-blind phase (52 weeks) in which patients were randomized to AOM 400 mg or oral aripiprazole (6–24 mg/day). Secondary outcomes from the randomized phase were mean changes in PANSS total score and each subscale score, and CGI-S, mean CGI-I score, the proportion of patients meeting exacerbation of psychotic symptoms/relapse criteria, and stabilization of psychotic symptoms/maintenance criteria, time to discontinuation due to any reason.

Results: Of 455 patients randomized in the double-blind phase, 228 received AOM and 227 received oral aripiprazole. Mean PANSS total scores at baseline of the double-blind phase were 54.4 for AOM and 53.3 for oral aripiprazole. At Week 52, changes from baseline in PANSS total score were −2.3 for AOM and −2.7 for oral. Mean CGI-I scores at Week 52 were 3.5 in both groups. The proportion of patients meeting exacerbation of psychotic symptoms/relapse criteria was 6.6% in both groups and the proportion of patients meeting stabilization of psychotic symptoms/maintenance criteria was high (92.5% in both groups). Discontinuation due to all reasons was 25.9% for AOM and 33.5% for oral aripiprazole (Hazard ratio: 0.74, 95%CI: 0.52–1.0).

Conclusion: The results show that AOM is effective in maintenance treatment of stabilized patients with schizophrenia, with comparable efficacy and tolerability to oral aripiprazole.

Policy of full disclosure: This study was funded by Otsuka Pharmaceutical Co., Ltd. Dr. Ishigooka has received research support or speakers honoraria from, or has served as a consultant to, Yoshitomi, Pfizer, Astellas, Glaxo SmithKline, Meiji Seika Pharma, Eli Lilly, Novartis Pharma, Otsuka, Mochida, Chugai, Takeda, Shionogi, Dainippon Sumitomo, and Tanabe Mitsubishi.

P-05-003 Hyperprolactinemia during antipsychotics treatment has a risk of venous thromboembolism

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Objective: Objective: The strong association between psychiatric patients receiving antipsychotics (APs) and venous thromboembolism (VTE) is well recognized. Although some reports suggests that hyperprolactinemia often causes a rise coagulation factors, there are few studies on examine the direct relationship between prolactin (PRL) elevated by APs and activated coagulation factors.

Methods: The subjects were 227 psychiatric patients (male=109, female =118) receiving APs for at least 3 months. Markers of VTE (D-dimer, fibrin/fibrinogen degradation products (FDP) and thrombin-antithrombin complex (TAT)) and serum prolactin concentrations were measured. The study was approved by the Ethics Committee of Hirosaki University Hospital, and written informed consent to participate in this study was obtained from the patients and their families.

Results: PRL levels were significantly correlated with logarithmic transformation of D-dimer ($r=0.311$, $p=0.001$) and FDP levels ($r=0.289$, $p=0.002$), but not TAT level ($r=0.131$, ns) in males. In females, however, any correlation was not found between the markers of VTE and prolactin levels. The same tendencies were confirmed using multiple regression analyses including demographics factors and APs dosage

Conclusion: This study indicates that hyperprolactinemia is associated with a rise coagulation factors in only male patients receiving APs. This finding has a clinical implication that monitoring and/or modulation of PRL level for male patients is important to decrease risk of VTE.

Policy of full disclosure: None.

P-05-004 Microglial activation in first-episode and drug-naïve schizophrenia

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Objective: A growing body of evidence suggests that neuroinflammation underlie the pathophysiology of schizophrenia. However, to our knowledge, no information is available on the alteration of microglial activation in the brain of schizophrenia without influences of antipsychotic drugs. We investigated activated microglia in the brain of drug-naïve schizophrenia, and then to examine correlation of the microglial activation and severity of psychotic symptom.

Methods: Twenty-two first-episode and drug-naïve patients with schizophrenia (age range, 18-40 years; 14 men and 8 women) and 22 age- and sex-matched normal controls participated in this study. Activation of microglia was quantified using positron emission tomography (PET) and a radiotracer for microglia, [11C](R)-(1-[2-chrorophynyl]-N-methyl-N-[1-methylpropyl]-3 isoquinoline carboxamide)([11C](R)-PK11195). PET data were analyzed by simplified reference tissue model. Clinical symptoms were assessed using the Positive and Negative Symptom Scale (PANSS).

Results: [11C](R)-PK11195 binding potential (BP) values were significantly higher in multiple brain regions in first-episode and drug-naïve patients with schizophrenia as compared to those of controls ($P<0.05$, corrected). Furthermore, there was a negative correlation between positive score of PANSS and BP of [11C](R)-PK11195 in the deep white matter of patient's brain (Pearson's $r=-0.44$, $P=0.041$).

Conclusion: Excessive microglia activation was present in multiple brain regions of first-episode and drug-naïve patients with schizophrenia. The microglial activation in the deep white matter also showed a negative correlation with severity of psychotic symptom. The present study suggests that microglia may play a protective role in the pathophysiology of schizophrenia.

Policy of full disclosure: None.

P-05-005 Association study of H2AFZ with schizophrenia in a Japanese case-control sample

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Objective: It is widely accepted that malfunction of the NMDA type glutamate receptor may be involved in the pathophysiology of the major serious mental disorder, schizophrenia, because NMDA receptor antagonists cause positive, negative and cognitive symptoms indistinguishable from those of schizophrenia. Several recent studies on brain miRNAs have demonstrated that expression of the glutamate system-related miR-132 and miR-212 is changed in post-mortem schizophrenic brains. In order to obtain further insight into the relationships among the NMDA receptor, the molecular cascades controlled by these miRNAs and schizophrenia, of commonly predicted target genes of the two miRNAs, we focused on the H2AFZ (encoding H2A histone family, member Z) gene whose expression has been shown to be modified by a schizophrenomimetic NMDA antagonist, phencyclidine, by our screening study using a DNA microarray technique.

Methods: In this study, we examined 4 tag single nucleotide polymorphisms (SNPs) (SNP01-04) located within the 10 kb up- and downstream regions of the H2AFZ gene for genetic association with

schizophrenia in a case-control study of Japanese cohort with 2012 cases and 2170 control subjects.

Results: We did not detect any significant genetic association of these SNPs with schizophrenia in this sample set. However, we observed a significant association of SNP02 in the male schizophrenia subjects (allelic P=0.003, genotypic P=0.008). Based on a haplotype analysis, haplotypes consisting of SNP02-SNP03-SNP04 also showed a significant association in the male schizophrenia subjects (P=0.018). These associations remained significant even after correction for multiple testing.

Conclusion: The present findings suggest that the H2AFZ gene may be a susceptibility factor in male schizophrenics, and that modification of the H2AFZ signaling pathway warrants further study in terms of the pathophysiology of schizophrenia.

Policy of full disclosure: None.

P-05-006 Functional role of serotonin 5-HT5A receptors in cognition: Mechanism of action study with a selective antagonist ASP5736

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Objective: We recently identified ASP5736, a novel antagonist of 5-HT5A receptor, and reported that it had the potential for the treatment of schizophrenia by mono-therapy or combination therapy with commercially available antipsychotics. We then examined the effect of ASP5736 on executive functions, which were impaired in schizophrenia.

Results: Sub-chronic administration of phencyclidine (PCP) to rats selectively impaired extradimensional shifts in the attentional set-shifting task, and ASP5736 significantly ameliorated the deficits at 0.003–0.01 mg/kg, p.o. To elucidate mechanism of action of the compound, we performed multiple pharmacological studies 1) In an in vivo receptor occupancy study, ASP5736 replaced binding of [125I]-lysergic acid diethylamide (LSD) to 5-HT5A receptor in olfactory bulb of rats at the behaviorally effective doses. 2) ASP5736 dose-dependently antagonized the 5-carboxamidotryptamine (5-CT)-induced decrease in cAMP levels in HEK293 cells stably expressing the 5-HT5A receptor. 3) Immunohistochemical study showed that 5-HT5A receptors were expressed in dopaminergic (DAergic) neurons in the ventral tegmental area (VTA), a nucleus of origin of DAergic neurons, and in parvalbumin-positive interneurons in the medial prefrontal cortex (mPFC). 4) In in vivo brain microdialysis study, the extracellular levels of DA and GABA were decreased in sub-chronically PCP-treated rats.

Conclusion: From these data we have made a hypothesis that ASP5736 might increase DA and GABA releases in the mPFC by blocking 5-HT5A receptors existing on DAergic neurons in VTA projecting to mPFC and of GABAergic interneurons on mPFC, respectively.

Policy of full disclosure: None.

P-05-007 ASP5736, a novel serotonin 5-HT5A receptor antagonist, ameliorates positive symptom, cognitive impairments and mood dysfunction in animal models of schizophrenia

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Objective: The 5-HT5A receptor is a G-protein-coupled seven-transmembrane receptor and expressed predominantly in neural tissues such as hippocampus, thalamus, amygdala and cerebral cortex with little expression in peripheral tissues. In addition, increased exploratory behavior in novel environments displayed by 5-HT5A receptor KO mice compared to wild-type mice, has suggested that the 5-HT5A receptor is assumed to be involved in mood, affective disorder, and cognitive function, while it remains largely uncovered. We recently identified ASP5736, a novel antagonist of 5-HT5A receptor and showed it has potential for the treatment of Alzheimer's disease. We then evaluated and report here that its effects on positive symptom, cognitive impairments and mood dysfunction in several animal models of schizophrenia.

Results: ASP5736 reversed phencyclidine (PCP)- and methamphetamine (MAP)-induced hyperactivity in mice at 0.01–0.1 mg/kg, p.o. and improved PCP-induced prepulse inhibition deficit in rats at 0.01–0.1 mg/kg, p.o. Furthermore, working memory deficit in MK-801-treated mice and visual learning deficit in neonatally PCP-treated mice were both ameliorated by 0.001–0.003 mg/kg, p.o. and 0.003 mg/kg, p.o. of ASP5736, respectively. In addition we evaluated the effect of ASP5736 on depression model (forced swim test) using DBA/2 mice. ASP5736 significantly decreased immobility time at doses of 0.1–0.3 mg/kg, p.o. On the other hand, ASP5736 didn't cause sedation, catalepsy, or increase in plasma prolactin.

Conclusion: These results collectively suggest that ASP5736 may benefit not only positive symptom but also cognitive impairments and mood dysfunction, with less concerns on adverse effects in schizophrenia patients.

Policy of full disclosure: None.

P-05-008 ASP5736, a novel serotonin 5-HT5A receptor antagonist, ameliorates positive symptom and cognitive impairments in animal models of schizophrenia: Combination studies with olanzapine

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Objective: We recently identified ASP5736, a novel antagonist of 5-HT5A receptor. In our previous study, we reported that ASP5736 ameliorated positive symptom and cognitive impairments in animal models of schizophrenia. We then evaluated the effects of ASP5736 on positive symptom, cognitive impairments and adverse effects in several animal models of schizophrenia in combination with olanzapine.

Results: Although olanzapine itself failed to improve MK-801-induced working memory deficit, ASP5736 with olanzapine significantly attenuated the deficit to the same degree as ASP5736 administered alone. Furthermore, the sedative effect of olanzapine was not enhanced by ASP5736 at 0.003 mg/kg, p.o., which is an effective dose against MK-801-induced working memory deficit. Methamphetamine (MAP)-induced hyperactivity was also significantly ameliorated by ASP5736 alone, and the inhibitory effect on MAP-induced hyperactivity of olanzapine was enhanced approximately three-fold following administration of ASP5736 from ID50=1.18 mg/kg to ID50=0.37 mg/kg, p.o. Of note, the adverse effect (catalepsy) of olanzapine was not worsened by the co-administration of ASP5736.

Conclusion: These results collectively indicate that co-administration of olanzapine had no influence on the memory improvement by ASP5736, and that while the effect of olanzapine on positive symptom model was enhanced by the treatment of ASP5736, the adverse effects of olanzapine were not worsened by ASP5736. Present studies suggest that a novel and potent 5-HT5A receptor antagonist ASP5736 might have the potential to be used for the treatment of cognitive impairment associated with schizophrenia (CIAS) in combination with commercially available antipsychotics.

Policy of full disclosure: None.

P-05-009 Cariprazine demonstrates greater potency than aripiprazole in animal models of psychosis, cognitive impairment, and negative symptoms

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Objective: Dopamine D_3 receptors are thought to play a role in the regulation of cognition and mood and blockade of this receptor may be beneficial in treating the negative, cognitive, and mood symptoms associated with schizophrenia. This analysis compared the potencies of aripiprazole, a dopamine D_2 receptor partial agonist, and cariprazine, a dopamine D_3 and D_2 receptor partial agonist with preference for D_3 receptors, across a number of animal paradigms that model different symptom domains of schizophrenia.

Methods: The effects of different doses of cariprazine and aripiprazole were evaluated in established rodent (rat) models of psychosis, cognitive impairment, and negative symptoms/depression. Differences in potency between the 2 compounds in each model were estimated using ED_{50} values or minimal effective doses (MED).

Results: Cariprazine occupied D_2 receptors in rats with approximately 30-fold greater potency than aripiprazole (ED_{50}: cariprazine, 0.23 mg/kg; aripiprazole, 7.7 mg/kg); potency for D_3 receptor occupancy in rats was >70-fold higher for cariprazine vs. aripiprazole. In models of antipsychotic-like activity, cariprazine demonstrated 20 to 30-fold greater potency than aripiprazole (ED_{50} for conditioned avoidance response: cariprazine, 0.8 mg/kg, aripiprazole, 18 mg/kg; ED_{50} for amphetamine-induced motor activity: cariprazine, 0.12 mg/kg; aripiprazole, 3.9 mg/kg). In comparison, cariprazine showed much greater differences in potency relative to aripiprazole in the models of cognitive impairment (cariprazine was 25 to >250-fold more potent) and negative symptoms/depression (cariprazine was 85 to 100-fold more potent).

Conclusion: Cariprazine showed greater potency than aripiprazole across a number of animal models that represent different symptom

domains of schizophrenia. The greatest differences in potency between cariprazine and aripiprazole were seen in paradigms of cognitive impairment and negative symptoms/depression. The high affinity of cariprazine at D_3 receptors may underlie the greater potency relative to aripiprazole in models of cognitive impairment and negative symptoms.

Policy of full disclosure: Nika Adham is an employee of Forest Research Institute.

P-05-010 The outcome of acute transient psychotic disorders according to 5-year follow-up

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Objective: To study the clinical, dynamic and prognostic aspects of acute transient psychotic disorders.

Methods: We have examined 108 inpatients (61 men and 47 women, mean age 29.3±9.7 years, range 18–55 years) with acute psychotic states (F 23, ICD-10). Group 1: 55 inpatients with acute polymorphic psychotic disorders without symptoms of schizophrenia (F 23.0). Group 2: 53 inpatients with acute polymorphic psychotic disorders with symptoms of schizophrenia (F 23.1). Methods used: clinical-psychopathological, clinical follow-up, statistical. Follow-up observations period was 5 years from the moment of psychotic symptomatology reduction.

Results: Repeated psychotic attacks over a 5-year period were observed for 15 patients in group 1 (27.3%) and 16 patients in group 2 (30.1%). The single relapse of illness was observed in 46.7% of cases (7 patients) of group 1. In 8 inpatients (53.4%) of this group from 2 to 5 psychotic episodes were recorded. All relapses of the disease in group 1 were characterized by schizophrenic structure psychotic episodes with the identification of specific deficit symptoms in postpsychotic period. In the group of acute transient psychotic disorders with symptoms of schizophrenia, single exacerbation of schizophrenia was noted in 43.7% of cases (n=7) and for 56.3% of inpatients (n=9) from 2 to 4 psychotic episodes were recorded.

Conclusion: Psychotic states in both groups were characterized by the tendency of recurrence. The obtained preliminary data allow us to refer 27.3% of F 23.0 cases to the atypical debut of schizophrenia that presumes supporting therapy after clinical reduction of first episode psychosis.

Policy of full disclosure: None.

P-05-011 Prefrontal GABA modulation of working memory processes

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Objective: Reduced expression of markers for GABA within the prefrontal cortex (PFC) is consistently observed in schizophrenia, and may lead to cognitive deficits associated with the disorder. Recent studies have shown that blockade of prefrontal GABAA receptors increased response latencies but did not impact accuracy in the delayed-response task conducted on a radial maze. However, the possibility remains that tasks which place higher demands on attention and requiring resistance to 'proactive interference' may be more sensitive to PFC GABA dysfunction. Thus, the goal of this study was to explore the contribution of PFC GABA transmission these different aspects of working memory.

Methods: Separate groups of rats were trained on one of two tasks. In the massed-trials reference/working memory task, rats were trained to retrieve a food from the same 4 arms of an 8-arm radial maze, where they received massed training designed to increase proactive interference (5 trials per day, 1–2 min ITI). The delayed non-match to position (DNMTP) task consisted of a sample phase, in one of two levers was extended, and a choice phase, requiring selection of the opposite lever, separated by a variable delay (1–24 s). Well-trained rats received intra-mPFC infusions of saline and either the GABAA antagonist, bicuculline (12.5 or 50 ng), or the GABA agonists baclofen and muscimol (100 ng each).

Results: Blockade of PFC GABAA receptors caused a pronounced increase in working and reference memory errors in both the first and subsequent trials of the radial arm maze task, as has been observed in schizophrenic patients. In contrast, PFC inactivation did not affect performance of this task. PFC GABA blockade also induced delay-independent impairments in accuracy on the DNMTP task.

Conclusion: Reducing PFC GABA transmission blockade produces impairments in working memory accuracy that are distinct from the effects of PFC inactivation, and resemble those observed in schizophrenia.

Policy of full disclosure: None.

P-05-012 Aripiprazole once-monthly for long-term maintenance treatment of schizophrenia: A 52-week open-label study

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Objective: To evaluate the safety, tolerability, and maintenance of the therapeutic effect of aripiprazole once-monthly (AOM) in long-term treatment of schizophrenia.

Methods: This study (NCT00731549) enrolled new subjects or subjects who participated in one of the pivotal studies (NCT00705783 Kane et al. 2012 or NCT00706654 Fleischhacker et al. 2013). The study comprised a screening phase (if applicable), a conversion phase to oral aripiprazole (Phase 1, if applicable), an oral stabilization phase (Phase 2), and an AOM maintenance phase (Phase 3). New subjects who did not participate in the pivotal studies entered at screening, proceeded to Phase 1 or 2, depending on current treatment. Subjects who completed one of the pivotal studies, were re-stabilized on oral aripiprazole in Phase 2. Only subjects meeting stability criteria entered Phase 3, where they received open-label AOM administered every 4 weeks for a maximum of 52 weeks.

Results: 1,081 subjects entered Phase 3 (464 from NCT00705783, 474 from NCT00706654) and 143 new subjects]. Of these, 79.4% (858/1081) completed 52 weeks of treatment. The most frequent primary reasons for discontinuation were withdrawal of consent (8.2%), impending relapse (4%) [3.4% with AEs plus 0.6% without AEs], and adverse events (2.9%). AEs (>=5% of patients) were headache (7.6%) nasopharyngitis (7%), anxiety (6.8%), and insomnia (6.6%). The proportion of subjects in Phase 3 meeting impending relapse criteria was 8.25% (89/1079).

Conclusion: Over a 52-week period, subjects participating in an open-label trial of AOM had a high completion rate and a low rate of discontinuation due to impending relapse. The safety and tolerability profile was similar to that observed in the pivotal studies, with no new safety signals arising during long-term treatment. The results suggest that aripiprazole once-monthly maintains effectiveness throughout long-term treatment.

Policy of full disclosure: Supported by Otsuka Pharmaceutical Development & Commercialization, Inc. and H. Lundbeck A/S. Timothy Peters-Strickland, Ross Baker, Robert D. McQuade, Na Jin, Pamela P. Perry, Brian R. Johnson, Anna R. Duca, and Raymond Sanchez are employees of Otsuka Pharmaceutical Development & Commercialization, Inc. Anna Eramo is an employee of H. Lundbeck A/S.

P-05-013 Disrupted effective connectivity of emotional circuitry in schizophrenia

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Objective: Impaired emotional processing is a core feature of schizophrenia (SKZ). Consistent findings suggested that this impairment could be paralleled by a disrupted functional and structural integrity of frontolimbic areas. Moreover several studies using some connectivity techniques, such as Psycho-physiological Interaction, confirmed an alterated connectivity in SKZ. Nevertheless these techniques didn't allow to explore the causal relationships among the involved regions. For this reason, using Dynamic Causal Modeling (DCM), we explored in SKZ and healthy controls (HC) the effettive connectivity between crucial areas for emotional processing: Amygdala, dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex (ACC).

Methods: A 3.0 Tesla fMRI was used to study 24 SKZ patients and 38 HC during an emotional task. Six competitive DCM models were constructed: the ACC-Amy connection was bidirectional and DLPFC-Amy unidirectional. We tested all the possible combinations in ACC/DLPFC connectivity. The input enter the network from Amy and DLPFC or from Amy only. Bayesian model selection was used to determine the best model from a structural perspective, whereas Bayesian Model Averaging was performed to extract DCM parameters. Afterwards the parameters were included in a second level analyses to assess (1) differences between groups (ANOVA) and (2) correlations (Person correlation) with scores of Positive and Negative Symptoms Scale (PANSS).

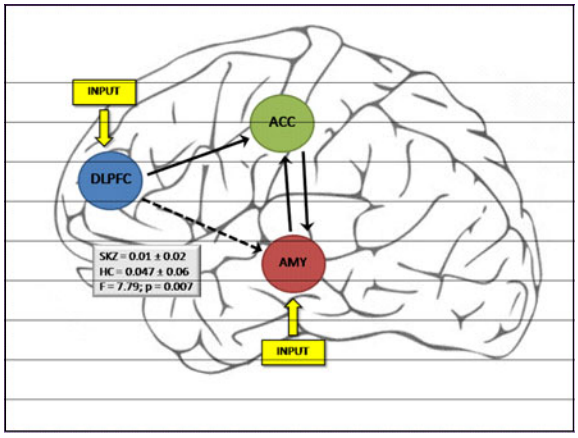
Results: In both groups the best model showed a forward connection from DLPFC to Amy and to ACC, and a bidirectional connection between ACC-Amy. DLPFC-Amy connection was significantly reduced in SKZ compared to HC. The strength of ACC-Amy connection correlated significantly with PANSS positive symptomatology rating.

Conclusion: To our knowledge this is the first study which explore the causal relationships of the neural system involved in emotional regulation in SKZ. Our results suggest a functional disconnection in the social brain

network of these patients. This may contribute to the behavioral and symptomatic outcome of the disorder and may be proposed as a possible biomarker of treatment efficacy.

Policy of full disclosure: None.

Result DCM:



P-05-014 Risk factors for new episode of schizophrenia

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Objective: The goal of this research is the registration of risk factors for new schizophrenic episodes.

Methods: The study was prospective, comparative, analytical and descriptive, and was carried out in the Psychiatric Clinic University Clinical Center Sarajevo. Subjects were divided into experimental and control group with 50 subjects. The experimental group patients had more than one schizophrenic episode, while the control group had only one schizophrenic episode which should be at least a year ago. The survey questionnaire, designed by the authors of the study, examined the following factors: Compliance with taking prescribed therapy, interruption of therapy, the absence of psychoeducation, age of first schizophrenic episode and number of previous episodes.

Results: Compliance with therapy shows that the respondents in the control group was taking medications more regularly, did not stop taking the medication when they felt better (only 4% compared to 96% of the experimental group), did not stop taking their medication if they felt worse after taking medications (30% compared to 96% of the experimental group) and are more familiar with the long-term benefits of the medications. Termination of antipsychotic therapy was registered in 98% of patients in experimental and only 2% of the control group. The absence of psychoeducation is registered in 4% of the control group and in 32% of the experimental group patients. The respondents in the control group, on average, later experienced first schizophrenic episode, compared to the experimental group. All these differences were statistically significant. Experimental group had an average of 6.88 schizophrenic episodes.

Conclusion: The study demonstrated that the risk factors have a significant impact on relapse of schizophrenic episodes. Non-compliance with taking prescribed therapy, interruption of therapy, the absence of psychoeducation and earlier age of first schizophrenic episodes are significant risk factors for recurring schizophrenic episodes.

Policy of full disclosure: None.

P-05-015 Efficacy and safety of adjunctive bitopertin (10 and 20 mg) versus placebo in subjects with sub-optimally controlled symptoms of schizophrenia treated with antipsychotics – Results from the Phase III TwiLyte study

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Objective: Current dopamine-acting antipsychotics do not work uniformly for all patients. NMDA receptor hypofunction has been implicated as a potential factor in psychosis. In this study we evaluated the safety and efficacy of bitopertin, a glycine reuptake inhibitor thought to indirectly enhance NMDA receptor function, in patients with schizophrenia who continued to show sub-optimally controlled psychotic symptoms despite ongoing treatment with antipsychotics (TwiLyte; NCT01235520).

Methods: Key inclusion criteria were: age >=18 years, DSM-IV-TR diagnosis of schizophrenia; Positive and Negative Syndrome Scale (PANSS) score >=70; score >=4 on >=2 psychotic PANSS items; and clinical and antipsychotic treatment stability. Following the 4-week observation period, patients were randomized 1:1:1 to bitopertin 10 mg, 20 mg or placebo once daily for 12 weeks.

Results: 560 patients (94% randomized) were included in the ITT population. Treatment arms were comparable at baseline with PANSS total scores and Positive Symptoms Factor Scores (PSFS; transformed to a 0 [absent] to 6 [extreme] scale) of ~55 and ~19 respectively for all groups, corresponding to moderately severe ongoing psychosis. Over 80% patients in each group completed 12 weeks of treatment. All groups showed equivalent improvement at Week 12 on the PSFS (primary endpoint) and on PANSS total (secondary endpoint), without any statistical separation. PSFS improvements were: bitopertin 10 mg -4.67 (SE, 0.329; p=0.2169), 20 mg −4.81 (SE 0.330; p=0.3572), placebo −5.25 (SE 0.334). PANSS total scores changed in a similar direction and magnitude. The adverse event (AE) profile was similar to placebo with >=1 AE reported by 30.3%, 35.6% and 34.7% for bitopertin 10 mg, 20 mg and placebo groups, respectively. There were no effects on vital signs, weight or metabolic parameters, and there was an expected dose-dependent reduction in haemoglobin.

Conclusion: Bitopertin was well tolerated, but we found no evidence for efficacy against sub-optimally controlled positive symptoms. This is the first study in this population, further studies are underway.

Policy of full disclosure: This study was supported by F. Hoffmann-La Roche Ltd. DB-K, TB, CJE, SM-R, FL and SS are all employees of Roche. WWF has received research grants from Otsuka, Janssen, Alkermes and Reckitt-Benckiser, consulting honoraria from Lundbeck, Roche, BMS, Otsuka, Janssen, Pfizer, MedAvante, Sunovion, Amgen, Endo and Vanda, Speaker honoraria from Lundbeck, Janssen, Otsuka, Astra Zeneca, Richter and Roche, and owns stocks in MedAvante. SK has received grant support from GSK, GW and Roche and has served as a one-off consultant and/or speaker for AstraZeneca, Bristol Meyers Squibb, Eli Lilly, Envivo, Janssen – Johnson and Johnson, Otsuka, Pfizer, Takeda and serves on the Scientific Advisory Boards for Lundbeck and Roche.

P-05-016 Minocycline add-on to haloperidol: Brain topography of glutamatergic signaling transcripts and implications for psychosis treatment

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Objective: In this study, we investigated whether the second-generation tetracycline minocycline add-on to haloperidol may affect the expression of two early genes, Homer1a and Arc, implicated in glutamatergic signaling. The investigation was carried out in rats exposed or not to ketamine, thus mimicking N-Methyl D-Aspartate receptor (NMDA-R) hypofunction or naturalistic conditions, respectively.

Methods: The first group of rats received the following treatments: 1) Vehicle+Vehicle (VEH+VEH); 2) Vehicle+Haloperidol 0.8 mg/kg (VEH +HAL); 3) Vehicle+Minocycline 45 mg/kg (VEH+MYN); 4) Vehicle+ Haloperidol 0.8 mg/kg+Minocycline 45 mg/kg (VEH+HAL+MYN). The second treatment group received Ketamine 30 mg/kg (KET) instead of Vehicle, resulting in the following treatment subgroups: KET+VEH; KET+HAL; KET+MYN; KET+HAL+MYN. The topography of transcripts expression was evaluated by means of in situ hybridization.

Results: Homer1a – Vehicle-experiment. Haloperidol and minocycline, alone or in combination reduced gene expression in the insular cortex compared with vehicle. In striatum, Homer1a expression was induced by haloperidol in almost all subregions. – Ketamine-experiment. Haloperidol+minocycline reduced Homer1a expression in the medial agranular cortex and in the motor cortex compared with vehicle. In striatum, haloperidol induced Homer1a expression in the ventrolateral caudate-putamen only. Minocycline limitedly reduced haloperidol-mediated Homer1a expression. Arc – Vehicle-experiment. Haloperidol +minocycline reduced Arc cortical expression compared with vehicle and haloperidol or minocycline alone increased Arc cortical expression compared with their combination. In striatum, both haloperidol and haloperidol+minocycline induced Arc expression compared with vehicle, while minocycline alone significantly reduced it. – Ketamine-experiment. The expression pattern observed in the Vehicle-experiment was confirmed also in the Ketamine- experiment. No significant differences in Homer1a and Arc baseline expression where observed (i.e. VEH+VEH vs. KET+ VEH).

Conclusion: Minocycline add-on blunted haloperidol-mediated cortical Arc expression and cortico-striatal Homer1a expression. Minocycline has been described to attenuate the increase in dopamine levels after NMDA-R blockade. Therefore, minocycline may attenuate haloperidol's acute effect on dopaminergic and glutamatergic signaling, which may be relevant for therapeutic efficacy and side effects.

Policy of full disclosure: None.

P-05-017 Reduced expression of both brain-derived neurotrophic factor and reelin sensitizes to the long-term effects of glucocorticoid stimulation on memory in mice: relevance to schizophrenia

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Objective: Schizophrenia is a neurodevelopmental disease likely caused by a combination of multiple genetic factors and environmental influences such as stress exposure during adolescence/young- adulthood. Reelin and brain-derived neurotrophic factor (BDNF) play an important role during brain development and reduced levels of both proteins have been found in schizophrenia. We then study the Reelin x BDNF x stress exposure interaction in schizophrenia.

Methods: First we used Western blot to quantify mature BDNF (mBDNF) and full-length (FL) reelin and its N-R6 and N-R2 cleavage fragments in the dorsal hippocampus (DH) and ventral hippocampus (VH) of 6 week old wild-type (WT) and BDNF heterozygous (HET) mice. In a parallel cohort, we then simulated adolescent/young-adult stress by chronic treatment with corticosterone (CORT) from 6–9 weeks of age. In adulthood at 11–12 weeks of age, we assessed short-term spatial memory and social behaviour in a Y-maze and 3 chamber social interaction task (SI), respectively.

Results: As expected, mBDNF levels were about 50% lower in DH and VH of HET compared to WT. Moreover, mBDNF levels were approximately 50% lower in males compared to females. Reelin FL and N-R2 were reduced by 30% in DH of male HET compared to male WT and females, with no differences in VH. CORT-treated HET males, but not females, showed a significant reduction of spatial memory in the Y maze but there were no group differences in the SI task.

Conclusion: Our results suggest that reduced levels of reelin against a background of low BDNF expression, as observed here in the DH of young-adult male HET, may sensitize to the effects of developmental stress to result in cognitive deficits in adulthood. Because reduced levels of both reelin and BDNF have been found in schizophrenia, our results may be relevant for some of the cognitive deficits commonly observed in this illness.

Policy of full disclosure: None.

P-05-018 Gender differences in the pharmacotherapy of schizophrenia

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Objective: To compare male and female patients participating in the EUFEST (European First-Episode Schizophrenia Trial), focusing on response to treatment.

Methods: The EUFEST trial compared four second generation antipsychotics (amisulpride, olanzapine, quetiapine and ziprasidone), against treatment with low doses of haloperidol in patients with first-episode schizophrenia. Patients were randomly assigned by a centralized, computerized online randomization system to open-label treatment. The data were collected at baseline and then prospectively for 1 year. Treatment response was evaluated using the PANSS (the Positive and negative syndrome scale).

Results: All patients from EUFEST study for whom both baseline and 12 assessment were available (n=498; 298 men and 200 women) were included. Baseline characteristics (age and proportion of patients assigned to individual antipsychotics) were the same between the male and female patients with exception of ziprasidone: significantly less men than women were assigned to ziprasidone. The total PANSS and all PANSS subscales scores did not differ between the both groups After 3 months of treatment a significantly more robust improvement in the total PANSS and all PANSS subscales scores was seen in women. After 6 months the women improved significantly more in the total PANSS and the PANSS positive subscale, after 9 months significantly more pronounced improvement was seen in the total PANSS and all the PANSS subscale scores with exception of negative subscale, no differences after 12 months were seen. Among all given antipsychotics only olanzapine led to significantly greater improvement in all domains of psychopathology, the total PANSS all the PANSS subscale scores, in women during all the follow-up period.

Conclusion: The gender differences should be more intensively studied and should be taken into consideration in guidelines. Strategies to deal with these gender differences need to be considered in early intervention program.

Policy of full disclosure: Supported by the project CEITEC (CZ.1.05/1.1.00/02.0068) from European Regional Development Fund.

P-05-019 Genetic association between GRIA2, GRIA4 gene polymorphisms and clinical phenotypes of schizophrenia

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Objective: A glutamate dysfunction hypothesis has been proposed to explain the pathogenesis of schizophrenia. There are increasing evidences that AMPA receptors dysfunction may be related to increased susceptibility to schizophrenia. The aim of this study was to determine whether genetic polymorphisms of the glutamate receptor, ionotropic, AMPA receptor (GRIA) are associated with schizophrenia in the Korean population.

Methods: Three SNPs of the GRIA2 and five SNPs of the GRIA4 gene were genotyped. The allelic and genotypic associations between 219 schizophrenia patients and 380 healthy controls were examined. Possible associations between these polymorphisms and the clinical symptoms of schizophrenia such as hallucinations and delusions were also investigated. Multiple logistic regression models (co-dominant, dominant, and recessive) were performed to estimate odds ratios and p values. A Bonferroni correction was used for multiple testing.

Results: There was significant differences in the genotype frequencies of rs672673 of the GRIA4 gene were found between schizophrenia and controls [p=0.047 in the co-dominant model (AA vs. GG), p=0.035 in the recessive model (AA vs. GG/AG)]. In analysis of clinical symptoms, significant differences were found between schizophrenia patients with hallucinations and schizophrenia patients without hallucinations in the GRIA4 gene [rs672673 (G/A), p=0.0034 in the recessive model (AA vs. GG/AG)].

Conclusion: The results from the present study support the relationship between AMPA receptor gene polymorphisms and schizophrenia symptoms. GRIA4 polymorphisms may be contribute to the development of hallucinations in schizophrenia in the Korean population.

Policy of full disclosure: None.

P-05-020 Association between promoter polymorphism (-1572 T/C) in 5-hydroxytryptamine receptor 3B and poor concentration in schizophrenia

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Objective: Previous studies have shown the involvement of 5-hydroxytryptamine receptor 3 (HTR3) in schizophrenia. In addition, the variants of HTR3 genes have been associated with treatment outcomes of antipsychotics in schizophrenia. In this study, we investigated the associations of the HTR3 genes with schizophrenia by analyzing the single nucleotide polymorphisms (SNPs) of the HTR3A and HTR3B.

Methods: A total of 222 Korean schizophrenia patients and 381 control subjects were recruited at Kyung Hee Medical Center in Seoul, Republic of Korea. SNPs located in the promoter or exon of the HTR3B and HTR3A were selected from the dbSNP database. Seven SNPs (rs10789970, rs11214763, rs3758987, rs1176744, and rs2276305 in HTR3B; rs1062613 and rs1176713 in HTR3A) were selected, and genotyped using direct sequencing. The operational criteria checklist was used to measure general psychopathology. Multiple logistic regression analysis using codominant, dominant, and recessive models was performed with SNPStas, adjusting age and gender.

Results: In our study, no SNPs of the HTR3A and HTR3B were associated with schizophrenia. However, in analysis according to the clinical symptoms of schizophrenia, we found that rs10789970 of HTR3B was significantly associated with poor concentration in schizophrenia patients in the additive [TC vs. CC vs. TT; P=0.0016, odds ratio (OR)=1.95, 95% confidence interval (CI)=1.27–2.99) and dominant models (TC/CC vs. TT; P=0.0024, OR=2.46, 95% CI=1.37–4.42). In allele frequency analysis, rs10789970 was also associated with poor concentration (P=0.0020, OR=1.88, 95% CI=1.26–2.81).

Conclusion: In conclusion, these findings imply that HTR3A and HTR3B genes may not be directly involved in the incidence of schizophrenia. But we found association with HTR3B and poor concentration in schizophrenia patients. These results suggest that the HTR3B may be involved in the attention problem of schizophrenia in Korean population.

Policy of full disclosure: None.

P-05-021 Preference for long-acting injectable antipsychotics of community-dwelling patients with schizophrenia and their caregivers in Korea

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Objective: The prescription rates of long-acting injectable antipsychotics are very low around 1% in Korea. This study was aimed to explore the preference of long-acting injectable antipsychotics in patients with schizophrenia, who are currently living in community, and their caregivers.

Methods: The patients who were diagnosed with schizophrenia and were registered in the 31 mental health centers of Gyeonggi province and their caregivers were inquired the knowledge of the long-acting injectable antipsychotics. The questionnaires contained informations such as demographic characteristics, history of psychiatric treatment, and knowledge and preference of long-acting injectable antipsychotics and so on.

Results: About 8,960 subjects were registered in the community mental health centers of Gyeonggi province in February 2012. Among them, 5,318 patients were diagnosed with schizophrenia. A total of 980 subjects (614 of patients and 365 of caregivers) answered the questionnaires. The mean ages (SD) of patient responders (n=604) and caregiver responders (n=352) were 42.0 (±10.2) and 62.2 (±13.4) years old respectively. A considerable number of patients (44.6% of patient responder and 43.6% of caregiver responders) have experienced discontinuation of medications without doctor's consent. Only 35.9% of patient responders (n=605) and 27.1% of caregiver responders (n=358) did know about the long-acting injectable antipsychotics. Tentative preference for long-acting injectable antipsychotics were 35.2% and 46.8% for the patients and caregivers, respectively. More analyzing results will be represented in the poster.

Conclusion: There is the huge discrepancy between the preference and the real prescriptions of long-acting injectable antipsychotics in Korea. Both patients and their caregivers registered in the CMHCs have a strong commitment to live in the community. The obstacles against the benefits of long-acting injectable antipsychotics need to be resolved.

Policy of full disclosure: None.

P-05-022 Metabolic syndrome in chronic antipsychotic treatment of schizophrenia

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Objective: Metabolic syndrome (MetS) in patients with schizophrenia has been reported widely, mostly in a cross-sectional data. We were aimed to evaluate MetS changes during the maintenance antipsychotic treatment in Korean patients with schizophrenia.

Methods: The retrospective chart review was conducted in order to explore the natural course of metabolic effects in the clinical practice of antipsychotic treatment. Through the review of the electronic medical record of patients with schizophrenia of Seoul National University Hospital from June 2007 to October 2010, patients who were measured more than twice for all MetS components were recruited. One hundred and eighty one patients with schizophrenia were analyzed for the metabolic data of the American Heart Association and the National Heart, Lung and Blood Institute adaptation of National Cholesterol Education Program Adult Treatment Panel III#s (ATP-IIIA) definition of MetS, waist circumference criterion of the Korean Society for the Study of Obesity.

Results: Men were 98 patients (54.1%) and mean age of patients was 34.4 (SD=9.1) years. Mean durations of illness and of antipsychotic treatment were 11.2 (SD=6.5) years and 9.9 (SD=6.3) years, respectively. Mean interval of measurements for metabolic data was 12.5 (SD=5.4) months and the prevalence of MetS changed from 33.7% at baseline to 44.8% at follow-up. The incidence of MetS was 30.0% and the reversal rate of that was 26.2% between two measurement time-points. Incidence and reversal by clozapine were 39.0% (23/59), 31.0% (13/42) and those by other antipsychotics were 21.3% (13/61) and 15.8% (3/19), respectively.

Conclusion: MetS was continuously increased during chronic antipsychotic treatment. Simultaneously, substantial numbers of patients showed reversal to state of no MetS in routine practice. Clozapine showed prominent and dynamic change of metabolic syndrome compared to other antipsychotics.

Policy of full disclosure: None.

P-05-023 Efficacy and safety of paliperidone ER in patients with first episode psychosis: An open-label, prospective, multi-center study

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Objective: The aim of our study was to evaluate the efficacy and safety of paliperidone extended-release (paliperidone ER) in patients with first-episode psychosis.

Methods: This was an 8-week, open-label, prospective, multicenter trial. The study population consisted of 75 patients of first-episode psychosis. The initial recommended dose of paliperidone ER was 3–6 mg/day, increasing to 12 mg/day depending on treatment response. The primary outcome measures were the PANSS and CGI-SCH; secondary measures included the SANS and Cognitive Assessment Interview (CAI).

Results: Total 51 patients(68.0%) completed the study. Treatment with paliperidone ER resulted in significant improvement in the PANSS, CGI and SANS scores over time. The response rate (defined as >=30% decrease in PANSS total score from baseline to last observation) was 55.3%. Using the definition of treatment response as 20% reduction in PANSS total scores, NPV and specificity at week-2 was higher than those of week-3. When using 30% reduction in PANSS total scores, there was no difference in NPV and specificity between week 2 and week-3. Overall, the most frequent adverse events were akathisia (41.3%), somnolence (24.0%), EPS (22.7%) and sedation. Adverse events were primarily observed early in the course of treatment, at 1 or 2-weeks. No significant changes in the scales measuring extrapyramidal symptoms (SARS, AIMS, BAS) were observed. After 8-week treatment, there was significant increase in fasting triglyceride, total cholesterol, prolactin level, and significant weight gain was observed.

Conclusion: These results indicate that paliperidone ER is effective in the treatment of first-episode psychosis and has a modest side effect burden. According to the definition of treatment response, response at week-2 or 3 is shown to be a good predictor of subsequent response at week 8, demonstrating high NPV and high specificity.

Policy of full disclosure: None.

P-05-024 Differential effects of the potential antipsychotic d, l-govadine and its isomers on behavioural flexibility; comparison with D1 and D2 selective compounds

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Objective: Schizophrenia is associated with positive and negative symptoms as well as cognitive deficits. Dopamine D2 (DA D2) receptor antagonists are effective at treating positive symptoms yet fail to improve cognitive impairments of the disorder. We recently described the potential antipsychotic efficacy of the tetrahydroprotoberberine D,L-govadine, that appears to exert both D2-antagonist and possibly D1-partial agonist properties. This compound increases DA efflux in forebrain regions, shows antipsychotic properties in preclinical assays relevant to schizophrenia and also enhances cognitive function assessed with a delayed response task. The current study investigated the effects of the racemic mixture of D,L-govadine and its D and L isomers on behavioural flexibility, an executive function impaired in schizophrenia.

Methods: Rats were tested on an operant strategy-shifting task, wherein they first learned a visual-cue discrimination. The next day, drugs were administered prior to the set-shift, where rats learned to disregard the visual-cue and learn a novel response discrimination strategy. The effects of the 3 govadine compounds (0.3–1 mg/kg) were compared to those induced by the D1 agonist SKF81297 and the D2 antagonist, haloperidol.

Results: A low dose of haloperidol (0.1 mg/kg) caused non-perseverative impairments in set-shifting, whereas a higher dose

(0.2 mg/kg) impaired retrieval of the initial rule. Low doses of SKF81297 (0.1 mg/kg) improved shifting by decreasing perseveration. In comparison, D,L-govadine generally did not affect set-shifting, although the high dose increased non-perseverative errors. L-govadine induced dose-dependent, non-perseverative impairments, similar to haloperidol. In contrast, D-govadine improved performance at all doses and reduced perseveration.

Conclusion: These data suggest that antipsychotic properties of D, L-govadine may be attributable to the L-isomer while the cognitive enhancing effects may be due to D1 agonist-like actions of the D-isomer. Further development of these types of compounds may prove useful in devising therapies to treat both psychotic and cognitive symptoms of schizophrenia.

Policy of full disclosure: None.

P-05-025 N-Propynyl analogs of beta-phenylethylidenehydrazine increase brain levels of glycine and inhibit its uptake by brain slices

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Objective: There has been a great deal of interest in recent years in inhibitors of glycine reuptake as potential antipsychotic drugs. Two analogs of the novel neuroprotective drug beta-phenylethylidenehydrazine (PEH) (a metabolite of phenelzine (PLZ), namely the N-bis-(2-propynyl) and N-mono-(2-propynyl) analogs, were synthesized by us and compared ex vivo to PEH with regard to their effects on rat brain levels of glycine.

Methods: Glycine levels were measured using high performance liquid chromatography with fluorescence detection after derivatization. The analogs were also studied in vitro in rat frontal cortex brain slices to compare their effects to those of PEH and PLZ with regard to their ability to inhibit the uptake of glycine; the results were compared to those of two known inhibitors of the glycine transporter, namely sarcosine and Org-24598.

Results: The two synthetic analogs caused marked increases in brain levels of glycine at 3, 6 and 12 hrs post-injection whereas PEH had no effect on these levels. All drugs were injected i.p. into male Sprague Dawley rats at a dose of 0.22 mmol/kg. In the uptake studies in vitro, the N-bis-(2-propynyl) analog caused a concentration-dependent inhibition of 3H-glycine uptake at 100, 200 and 400 microM compared to controls. The N-mono-(2-propynyl) analog and PEH caused inhibition of 3H-glycine uptake at 200 and 400 microM, however, not to the extent seen with the N-bis-(2-propynyl) analog. PLZ caused no inhibition of 3H-glycine uptake at 50, 100, 200 or 400 microM. Although the two analogs were weaker than sarcosine and Org-24598, they nonetheless produced significant inhibition of 3H-glycine uptake.

Conclusion: This effect combined with their marked effect on brain levels of glycine indicate that further studies on them as potential antipsychotics are warranted. The authors are grateful to the CIHR and to Alberta Health Services for funding.

Policy of full disclosure: None.

P-05-026 Disruption of regulated AMPA receptor endocytosis enhances latent inhibition of two-way avoidance

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Objective: The attentional deficit observed in schizophrenia can be modeled in animals using a latent inhibition paradigm in which the pre-exposure to a neutral stimulus (NS) retards subsequent learning of the association between the NS and an unconditional stimulus (UCS). Interfering with this learning could highlight important aspects of the neurobiological processes involved in latent inhibition. This study assessed the role of long-term depression (LTD) in latent inhibition.

Methods: LTD can be disrupted by an interference peptide, Tat-GluA2-3Y which blocks alpha-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid (AMPA) receptor endocytosis. This peptide was first administered intravenously (2.25 nmol/g) 60 min. prior to the acquisition of two-way avoidance. In a separate experiment, Tat-GluA2-3Y (15 pmol) was then administered into different brain regions including the prefrontal cortex, amygdala and nucleus accumbens.

Results: Tat-GluA2-3Y had no effect on learning the association of NS-UCS when animals had not been pre-exposed to the NS. However, disruption of LTD by interference with AMPA receptor endocytosis significantly disrupted 2-way avoidance learning signaled by a CS to which the rat had been pre-exposed This effect was replicated when Tat-GluA2-3Y has been microinjected into the central nucleus of amygdala but not in other structures.

Conclusion: These findings suggest that LTD in the central nucleus of amygdala plays a crucial role in switching the diminished salience of a pre-exposed neutral stimulus to a conditioned stimulus.

Policy of full disclosure: None.

P-05-027 Safety and tolerability of cariprazine in long-term treatment of schizophrenia: Integrated summary of safety data

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Objective: Pooled data from 2 studies were analyzed to evaluate the long-term safety and tolerability of cariprazine, a potent dopamine D3 and D2 receptor partial agonist with preferential binding to D3 receptors, in patients with schizophrenia.

Methods: Integrated summary of safety/tolerability data from two 48-week studies of open-label, flexible-dose cariprazine in adult patients with schizophrenia. In the first study (NCT01104792), new patients and patients who completed double-blind treatment in 1 of 2 lead-in studies (NCT01104766 or NCT01104779) received cariprazine 3–9 mg/day. In the second study (NCT00839852), patients who completed a double-blind lead-in trial (NCT00694707) received cariprazine 1.5–4.5 mg/day. Safety evaluations included adverse events, laboratory and vital signs, ECG, ophthalmologic examinations, and assessments on the Barnes Akathisia Rating Scale (BARS) and Simpson-Angus Scale (SAS).

Results: Of 679 patients, 40.1% completed open-label treatment. Mean duration of treatment (days±SD) was 188.4±136.8; 211 patients (31.1%) were exposed to cariprazine for $\geqslant$1 year. In patients continuing from double-blind studies, PANSS and CGI-S scores further decreased during open-label treatment. Treatment-emergent AEs (TEAEs) were reported in 553 patients, the most common of which were akathisia (15.5%), insomnia (13.1%), headache (12.7%), and weight increase (10.5%). Serious AEs, including 1 suicide, were reported in 79 patients (11.6%). The most common were worsening of schizophrenia (4.4%) and psychotic disorder (2.1%). Mean increase in body weight was 2.46 kg. No clinically significant mean changes in laboratory values (including metabolic parameters), blood pressure, or ECGs were noted. Mean prolactin levels decreased from baseline to the end of study. Incidences of parkinsonism (SAS >3) and akathisia (BARS >2) were 10.7% and 17.8%, respectively. Ophthalmologic testing revealed no clinically meaningful changes.

Conclusion: Cariprazine administered for up to 48 weeks in adults with schizophrenia was generally safe and well tolerated, with relatively few new AEs compared with acute treatment.

Policy of full disclosure: Supported by funding from Forest Laboratories, Inc. and Gedeon Richter Plc. Suresh Durgam is an employee of Forest Research Institute.

P-05-028 Effect of antipsychotic drugs on bone density and cortisol level in schizophrenia

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Objective: The aim of the work was to study the long term effects of antipsychotics on bone density and cortisol level in schizophrenic patients.

Methods: The study was conducted on 50 schizophrenic patients in Alexandria university hospital. They were divided into two groups. Group A: 30 patients under antipsychotic medication for more than 2 years but less than 10 years. And group B: 20 patients, medication naïve (no medication). All patients were subjected to: Clinical psychiatric examination to diagnose schizophrenia (DSM-IV-TR); medical and neurological examination; brief psychiatric rating scale; measurement of serum prolactin level; measurement of cortisol level; measurement of bone density by dual- energy-X ray Absorptiometry.

Results: The result showed that bone mineral density (BMD) was inversely correlated with hyper-prolactinemia caused by antipsychotic, and also affected by cortisol level in unmedicated schizophrenics, while antipsychotics affect cortisol level through normalizing or lowering it.

Policy of full disclosure: None.

P-05-029 The efficacy and safety of aripiprazole once-monthly in obese and non-obese patients with schizophrenia; a post-hoc analysis

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Objective: To evaluate efficacy and safety of aripiprazole once-monthly (AOM), an extended release injectable suspension of aripiprazole, in obese (BMI>=30 kg/m^2) and non-obese (BMI<30 kg/m^2) patients with schizophrenia.

Methods: Data from a 38-week, double-blind, active-controlled, non-inferiority study (NCT00706654); randomisation (2:2:1) to aripiprazole once-monthly 400/300 mg (AOM-400/300 mg), oral aripiprazole (10–30 mg/day) (ARI), or aripiprazole once-monthly 50/25 mg (AOM-50/25 mg) in stable patients were analyzed post-hoc. Relapse rates in the 38-week randomized phase were compared using the Chi-squared test.

Results: 662 patients were randomized to: AOM-400/300 mg (n=265; obese n=95 [36%]); ARI (n=266; obese n=95 [36%]); or AOM-50/25 mg (n=131; obese n=43 [33%]). In obese patients, the relapse rate was significantly (p=0.0012) lower with AOM-400/300 mg (7.4%) than with AOM-50/25 mg (27.9%). Relapse rates with AOM-400/300 mg and ARI (8.4%) were similar. In non-obese patients, the relapse rate was significantly (p=0.0153) lower with AOM-400/300 mg (8.8%) than with AOM-50/25 mg (19.3%). Relapse rates with AOM-400/300 mg and ARI (7.6%) were similar. For AOM-400/300 mg, the most common treatment emergent adverse events (>=10%) were insomnia (obese 12.6%, non-obese 11.2%), headache (obese 12.6%, non-obese 8.2%), injection site pain (obese 11.6%, non-obese 5.3%), akathesia (obese 10.5%, non-obese 10.6%), upper respiratory tract infection (obese 10.5%, non-obese <5%). Increased weight was reported in 10.5% of obese patients and 8.2% of non-obese patients. The incidence of shifts from non-obese at baseline to obese during the randomized phase was 7.6% (13/170) and from obese to non-obese was 17.9% (17/95).

Conclusion: The efficacy and tolerability of AOM 400/300 mg were similar in both the obese and non-obese subgroups.

Policy of full disclosure: Supported by Otsuka Pharmaceutical Development & Commercialization, Inc., and H. Lundbeck A/S. Dr. De Hert has been a consultant for, received grant/research support and honoraria from, and been on the speakers/advisory boards of Astra Zeneca, Bristol-Myers Squibb, Eli Lilly, Janssen-Cilag, Lundbeck JA, Pfizer, Sanofi Aventis and Takeda. Dr. Eramo is an employee of H. Lundbeck A/S. Dr. Landsberg, L.-F. Tsai, and Dr. Baker are employees of Otsuka Pharmaceutical Development & Commercialization, Inc.

P-06. Neurodegeneration A

P-06-001 ASP5736, a novel, selective and brain-penetrable serotonin 5-HT5A receptor antagonist, ameliorates cognitive deficits in rodent models of Alzheimer's disease

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Objective: Although human 5-HT5A receptor was cloned 20 years ago, very little has been unraveled about the function of the receptor in native tissues. Findings from mRNA localization and immunolabeling studies have revealed widespread expression in the CNS, and have provided clues to the potential functional roles of the receptor. The lack of understanding of the role of the receptor has been, at least in part, caused by the lack of available selective 5-HT5A receptor ligands. Therefore, we have chemically optimized the functional properties of a series of compounds and identified ASP5736 as a novel antagonist of 5-HT5A receptor. In the present study, we describe our in vitro and in vivo characterization of this compound.

Results: ASP5736 exhibited high affinity for the human 5-HT5A receptor (Ki=3.6 nM) and potently antagonized 5-carboxamidotryptamine-induced Ca2+ influx in human cells stably expressing the 5-HT5A receptor (IC50=1.0 nM). It showed more than 200-fold selectivity over other receptors, including other 5-HT receptor subtypes, enzymes and channels except for human 5-HT7 receptor (Ki=122.9 nM). The compound penetrated into the brain after oral administration to mice and rats. We then evaluated the effects of ASP5736 on rodent models of cognitive deficits in Alzheimer's disease. Working memory deficit in scopolamine-treated mice was attenuated by ASP5736 treatment (0.001–0.003 mg/kg, po) as well as by donepezil (0.25–0.5 mg/kg, po). Moreover, spatial learning deficit in aged rats was also attenuated by ASP5736 treatment (0.001–0.03 mg/kg, po), but not by donepezil (0.1–3 mg/kg, po).

Conclusion: These studies provide compelling evidence that ASP5736 is a novel, selective and brain-penetrable 5-HT5A receptor antagonist that is useful to elucidate the physiological function of 5-HT5A receptor in the brain. Furthermore, they also suggest that 5-HT5A receptor antagonist might have utility for the symptom relief of Alzheimer's disease.

Policy of full disclosure: None.

P-06-002 Aripiprazole for the treatment of psychotic symptoms in patients with Lewy bodies: A case series

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Objective: Dementia with lewy bodies (DLB) is commonly considered the second most common form of dementia. The purpose of this study is to investigate the treatment effects of aripiprazole in patients with DLB.

Methods: Eleven patients who had meet the criteria for DLB participated in this study. The presence of psychotic symptoms was confirmed by scores of either the delusions or hallucinations items of the Neuropsychiatric Inventry (NPI) score. Patients who had 25 or more on the Mini-mental State Examination Scale (MMSE) at the entry or having brain damage were excluded. Aripiprazole was initiated at a low dose (3 or 6 mg/day) and titrated to higher doses at 2-weeks intervals or more rapidly based on investigator's judgment. Reductions from higher doses were permitted for tolerability. Previous medications prior to aripiprazole administration were not changed through this trial. Patient's clinical status was assessed at baseline, then 2-weeks during the study by using NPI, Clinical Global Impression (CGI) and Brief Psychiatric Rating Scale (BPRS) to measure psychotic behavioral symptoms, and Simpson-Angus Scale (SAS) to measure parkinsonism symptoms. Clinical Dementia Rating (CDR) and MMSE were carried out at screening and end point to evaluate cognitive function.

Results: All patients who completed the study had a favorable response, with a decline of more than 50% in NPI. All patients who completed the study exhibited improvement of CGI score from 4 or 5 or 6 to 1 or 2. BPRS score showed a marked decrease in psychosis and agitation at week 2, and 5 of 7 responded at week 10. Three of nine patients who completed the study exhibited improvement of CDR score, and the other 6 patients exhibited no change.

Conclusion: This open-label trial shows that aripiprazole may be effective and well tolerated for the treatment of psychotic symptoms and agitation in the patients of DLB.

Policy of full disclosure: None.

P-06-003 Studies of the mechanism of action in protective effect against neuronal cell death of 4-phenylbutyrate and its derivatives for therapeutic agents of neurodegenerative disease

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Objective: Antiaggregation molecules are expected to be novel therapeutics for neurodegenerative diseases such as Alzheimer and Parkinson. Therefore, we focused on 4-phenylbutyrate (4-PBA) as a chemical chaperone that ensures functional folding of proteins. However, the optimization of 4-PBA is important for better therapeutic application because currently the high doses requirement appears to be a problem. To solve this problem, we investigated minor structural change dependent increase in biological activity dependent of 4-PBA.

Methods: We initially prepared 4-PBA derivatives by altering the number of carbons in the fatty acids on 4-PBA. Four compounds (3-Phenylpropionic acid: 3-PPA, 4-PBA, 5-Phenylbutyric acid: 5-PVA, and 6-hexanoic acid: 6-PHA) showed a chemical chaperone activity in vitro, and aggregation inhibition activity increased with an increase in the number of carbons in the fatty acid moiety. Cytoprotective effects against endoplasmic reticulum (ER) stress-induced neuronal death correlated with the in vitro chemical chaperone activity. 3-PPA and 4-PBA significantly reduced the neuronal death caused by the overexpression of Parkin-associated endothelin receptor-like receptor (Pael-R).

Results: With 3-PPA or 4-PBA treatment, localization of the overexpressed Pael-R shifted away from the endoplasmic reticulum toward the cytoplasmic membrane. We hypothesized that inhibition of human histone deacetylase (HDAC) by 3-PPA and 4-PBA is involved in this effect. Next, we investigated the mechanism underlying the protective effect of 4-PBA against ER stress-induced neuronal death using three simple 4-(p-substituted phenyl) butyric acids.

Conclusion: Here, we found highly active derivatives from the prototype 4-PBA, which we expect to be useful for therapeutic agents of neurodegenerative disease.

Policy of full disclosure: None.

P-06-004 Role of vesicular release in l-DOPA-evoked increases in extracellular dopamine in the 6-OHDA lesioned striatum

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Objective: Extracellular levels of dopamine (DA) derived from exogenous l-DOPA is largely determined by the dose of l-DOPA and severity of nigrostriatal denervation. In earlier studies, both excessive l-DOPA doses (+50 mg/kg) and extensive terminal loss (+90%) resulted in enhanced DA efflux that was tetrodotoxin-independent and/or unaffected by DA transporter inhibition, suggesting a non-dopaminergic, possibly non-neuronal, origin of DA synthesis and release. However, recent evidence suggests that l-DOPA-derived DA can indeed be sequestered into vesicles within striatal DA terminals, raising the possibility of a vesicular mechanism of release in the denervated striatum. Specifically, we assessed in 6-OHDA-lesioned rats whether DA derived from a relatively lower dose of l-DOPA is sequestered into vesicles and released by Ca2 +-dependent exocytosis.

Methods: Microdialysis was used to monitor changes in DA efflux in the dorsal striatum of rats with unilateral 6-OHDA lesions of substantia nigra and/or medial forebrain bundle. Intra-striatal reverse-dialysis of l-DOPA (1 uM) followed by either an omission of Ca2+ or addition of the vesicular monoamine transporter 2 inhibitor tetrabenazine to the perfusate.

Results: Based on prior analyses, extracellular DA concentration of 0.5 nM was indicative of a threshold lesion severity for inducing both qualitative and quantitative differences in response to experimental manipulations. In moderately lesioned rats (>0.5 nM), l-DOPA infusion resulted in a significant increase in DA efflux. This increase was attenuated significantly by depletion of Ca2+ or exposure to tetrabenazine, reaching values consistently below pretreatment baseline. Rats with severe DA depletion (<0.5 nM) also showed a significant increase in l-DOPA-evoked DA efflux. In contrast to moderate lesions, however, both Ca2+ omission and tetrabenazine application failed to attenuate (i.e., maintained) the increase in DA following l-DOPA.

Conclusion: The present results suggest that synaptic regulation of DA derived from exogenous l-DOPA is dependent on the severity of lesion. In rats with moderate lesions, extracellular DA derived from l-DOPA is mediated by Ca2+-dependent exocytosis of vesicles. Importantly, once the extent of lesion crosses a threshold severity, efflux of DA is mediated by a non-vesicular mode of release.

Policy of full disclosure: Supported by operating grants from Canadian Institutes of Health Research to AGP.

P-06-005 Effect of the timing of acetylcholinesterase inhibitor ingestion on sleep

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Objective: Many patients with Alzheimer's disease experience sleep disturbances, and donepezil is usually prescribed for night-time administration. However, increased acetylcholine is associated with cortical arousal. We evaluated whether subjective sleep quality differed according to the timing of medication administration.

Methods: Ninety-two patients with mild to moderate Alzheimer's disease who had taken donepezil at night (n=54) or galantamine in the morning (n=38) were recruited for this study. Scores on the sleep visual analogue scale (VAS) for sleep quality and daytime drowsiness were obtained.

Results: The mean sleep-quality and daytime-drowsiness VAS scores of the donepezil and galantamine groups differed significantly at baseline (44.0±26.4 vs. 55.2±27.3, respectively; P<0.001 and 48.8±28.8 vs. 38.8 ±25.3, respectively; P<0.001). The patients taking donepezil were then randomly assigned to take donepezil in the morning (n=24) or at night (n=30). Eight weeks later, VAS scores also differed among the three groups (P<0.001 for both sleep quality and daytime drowsiness). The VAS scores of patients taking galantamine and donepezil in the morning were different from those taking donepezil at night at week 8. Significant changes in VAS scores emerged only in the group taking donepezil in the morning (4.6±26.5, P=0.046 for sleep quality; #7.1±26.1, P<0.001 for daytime drowsiness).

Conclusion: These results suggest that taking acetylchlinesterase inhibitors in the morning can improve the sleep states of patients with Alzheimer's disease.

Policy of full disclosure: None.

P-06-006 Catechin attenuates post stroke neurological complications by suppressing NF-KB signalling pathway in collagenase treated rats

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Objective: The aim of the present study was to explore the effect of catechin (12.5 mg/kg, 25 mg/kg, 50 mg/kg) and catechin loaded nanoparticles (12.5 mg/kg, 25 mg/kg, 50 mg/kg) on neurological scoring, memory, mechanical hyperalgesia, allodynia, depression,oxidative-nitrosative stress inflammation and NF-kB in collagenase-induced hemorrhagic stroke.

Methods: Catechin possesses strong neuroprotective potential but limited brain penetration. Therefore, we have also used catechin loaded in solid lipid nanoparticles, a technology to enhance brain delivery, and compared the neurological effects with plain catechin. Neurological scoring was tested on the battery of behavioral paradigms (cylinder test, spontaneous motility, righting reflex, horizontal bar test, tilted cage top, placing reaction, forelimb flexion) to evaluate neurological deficits on 3rd, 7th, 14th and 21st day after collagenase administration in caudate nucleus. In addition, memory (Morris water maze), mechanical hyperalgesia (Randall Sellitto), Allodynia (von Frey hairs), depression (forced swim test), biochemical tests (lipid peroxidation, nitrite, superoxide dismutase, reduced glutathione and catalase in brain homogenate) and cytokines (TNF-alpha & IL-1β) and NF-kB were also assessed in collagenase treated rats.

Results: Chronic treatment with plain catechin and catechin loaded in solid lipid nanoparticles for 4 weeks starting from 2nd day after collagenase injection significantly attenuated neurological, behavioral, biochemical and molecular changes associated with hemorrhagic stroke. Catechin loaded in solid lipid nanoparticles produced a pronounced effect as compared to plain catechin.

Conclusion: The major finding of the study is that catechin alone ameliorated the post stroke neurological complications but only when it is delivered across the blood brain barrier. Moreover, catechin not only attenuated the neurological deficits associated with stroke but also reversed post stroke neurological complications through modulation of NF-kB signaling pathway in the collagenased rats and thuscatechin may find clinical application to treat neurological complications in the stroke patients.

Policy of full disclosure: None.

P-06-007 Spontaneous head twitches in aged rats: A correlate of late-onset psychosis?

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Objective: Although Behavioral and Psychological Symptoms of Dementia (BPSD) are recognized as one of the major unmet medical needs in geriatric psychiatry, medications targeting BPSD receive little attention in drug development programs. The apparent contrast between the unmet needs and research activities may be explained, at least partially, by a paucity of age-specific animal models, which could be used to screen compounds targeting BPSD.

Methods: Head twitches (HTs) are thought to be 5-HT2A/2C receptor-mediated responses induced by serotonin receptor agonists in mice and rats. Spontaneous head twitches (SHTs) were consistently observed in male Wistar rats from our colony of aged animals (>18 month-old).

Results: Large individual differences in SHTs were found with 25% of aged rats showing <2 twitches/10 min. and another 25% showing >12 twitches/10 min. The mean number of SHTs was 7.6±6.2 twitches/10 min. Individual differences in SHTs were stable over time with Pearson#s r values >0.9. A 5-HT2A receptor antagonist, ketanserin (3.0 mg/kg, i.p.) antagonized SHTs in aged rats. On the other hand, SHTs made the observation of HTs induced by a 5-HT2A/2C agonist, DOI impossible. The presence of SHTs in aged animals was associated with enhanced locomotor responses to amphetamine and heightened sensitivity to MK-801-induced stereotypies. SHTs were rarely observed in 3 month-old Wistar rats (the mean number: 0.2 twitches/10 min., n=72). When scored by blind observers, SHTs in aged rats were indistinguishable from DOI-induced HT in young animals.

Conclusion: Although exact pharmacological mechanisms standing behind SHTs remain unclear, our pilot study may indicate that SHTs are a marker of 'propsychotic' state in a subgroup of aged Wistar rats.

Further studies are needed to find psychotropic medications which could inhibit SHTs and reverse sensitized responses to amphetamine and MK-801.

Policy of full disclosure: The study was supported by Adamed Ltd., Pienkow, Poland and Polish Agency for Enterprise Development (PARP project no. UDA-POIG.01.04.00-14-055/10-00).

P-06-008 Impact of oxidative stress on cognition and depressive symptoms in mild cognitive impairment in the elderly

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Objective: Oxidative stress is one of the most recognized hypotheses in the theory of aging. Brain tissue is vulnerable to oxidative stress, which proposed to lead various neurodegenerative disorders. Cognitive impairment and depression are common in the elderly population. We aimed to examine the oxidative stress impact on cognition and depressive symptoms in nursing home residents.

Methods: Demographic data, mini mental state examination (MMSE), clock drawing test (CDT) and geriatric depression scale (GDS) scores of nursing home residents were examined retrospectively. Participants were divided into two groups as healthy controls and patients with mild cognitive impairment. Superoxide (SPO), superoxide dismutase (SOD) and malondialdehyde (MDA) levels were determined in previously collected and −80 C stored serum samples, using enzyme-linked immunosorbent assay (ELISA) method.

Results: A total of 72 participants were recruited 22.2% (n=16) of them were male, and 77.8% of them (n=56) were female. Patients were 82±6.9 years old (mean±SD). Mean MMSE scores were 24.8±4.6 and 22.3±3.9 for healthy controls and MCI group, respectively ($p<0.05$). Mean GDS scores were 11.1±3.7 and 10.7.3±2.1 for healthy controls and MCI group, respectively ($p>0.05$). We found a strong correlation between CDT scores and SOD levels ($p<0.01$). We also found similar correlation between GDS scores and SPO levels ($p<0.01$). But we did not find any significant difference in oxidative stress markers levels between groups.

Conclusion: In a relatively small sample size our findings partially support oxidative stress relation with cognitive functioning and depressive symptoms. We believe oxidative stress hypotheses deserve to be investigated in cellular level.

Policy of full disclosure: None.

P-06-009 Impact of drug burden on cognition and depressive symptoms in older people

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Objective: Polypharmacy is common among elderly population, which may lead risk of adverse drug reactions. Drug Burden Index was proposed as useful tool to assess functional effect of drug exposure in older population. We aimed to examine the drug burden impact on cognition and depressive symptoms in nursing home residents.

Methods: Demographic data including medication history, mini mental state examination (MMSE), clock drawing test (CDT) and geriatric depression scale (GDS) scores of nursing home residents were examined retrospectively. Drug Burden Index was used for total (TDB), and anticholinergic drug burden (AchDB) calculations. Correlation coefficients and their significance between descriptive data, TDB, AchDB, MMSE, CDT, GDS scores were analyzed using Pearson test.

Results: A total of 56 participants were recruited 21.4% (n=12) of them were male, and 78.6% of them (n=44) were female. Patients were 80.1±6.7 years old (mean±SD). Mean scores for MMSE, CDT and GDS were 23.2±4.9, 2.46±1.45, and 11.4±3.5 (mean±SD), respectively. Mean TDB and AchDB were 0.37±0.38 and 0.48±0.45 (mean±SD), respectively. We did not find any significant correlation between drug burden and cognitive functioning. Also correlation analysis between depressive symptoms and drug burden did not reveal any relationship.

Conclusion: In a relatively small sample size our findings did not support previous evidence for utility of Drug Burden Index to assess functional effect of drug exposure in older population. Drug interactions may be subtle that we could not predict by available methods. We believe new biological methods to detect subtle drug interactions are highly needed in older people who are at risk for adverse reactions.

Policy of full disclosure: None.

P-07. Epilepsy

P-07-001 Missense mutation of the gene encoding synaptic vesicle protein 2A (SV2A) facilitates the kindling epileptogenesis

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Objective: Synaptic vesicle glycoprotein 2A (SV2A) is the prototype protein specifically identified in synaptic vesicles and mediates the action potential-dependent exocytosis of neurotransmitters. In addition, SV2A serves as a specific binding site for the racetam-derivative antiepileptics (e.g., levetiracetam), suggesting that SV2A is involved in pathogenesis or treatment of epilepsy. Here, in order to elucidate the functional role of SV2A in epileptogenesis, we created a novel rat model (SV2A mutant rat) carrying a Sv2A-targeted mutation (L174Q) by ENU mutagenesis and analyzed behavioral phenotypes.

Results: SV2A mutant rats exhibited normal appearance under ordinary condition; however, they showed a significantly higher susceptibility to the amygdala kindling, yielding higher seizure severity score and longer afterdischarge duration. In addition, SV2A mutant rats were remarkably susceptible to the PTZ kindling with higher seizure incidence. Western blot analysis revealed no alteration in SV2A expression in any region of the brain. However, in vivo microdialysis studies showed that the depolarization (high K+)-induced GABA release in the amygdala was significantly reduced by the SV2A mutation whereas the glutamate release remained unaltered.

Conclusion: These findings suggest that the SV2A mutation impaired the function of SV2A and specifically reduced the depolarization-induced release of GABA in the amygdala, which facilitates the kindling epileptogenesis in rats.

Policy of full disclosure: None.

P-07-002 Limbic kindling impairs retrieval of fear memories and promotes hippocampal neurogenesis and plasticity of NPY signaling

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Objective: Temporal lobe epilepsy is often accompanied by severe cognitive, and psychiatric comorbidities that have a negative impact on quality of life. Previous research using the kindling model of epilepsy has shown that limbic seizures, but not non-limbic seizures, produce behavioral comorbidities representative of the human condition. In this work, we examine the neurobiological correlates of kindling-induced deficits in cognition.

Methods: We characterized differences between limbic (i.e., amygdala and hippocampus) and non-limbic (i.e., caudate nucleus) seizures on conditioned fear behavior and hippocampal plasticity. Hippocampal plasticity was measured through immunohistochemical analyses of the neuronal activity marker Fos, the endogenous anticonvulsant neuropeptide Y (NPY), and the NPY Y2 receptor (NPY2R), which presynaptically inhibits glutamate release. We also assessed adult neurogenesis using bromodeoxyuridine (BrdU) and doublecortin (DCX).

Results: Although kindling did not affect learning of a hippocampal-dependent fear-conditioning task, limbic but not non-limbic kindling did impair subsequent retrieval of these fear associations. Impaired memory coincided with a general reduction of Fos protein and dramatically increased NPY and NPY2R immunoreactivity throughout the hilus and CA3. Further, limbic but not non-limbic kindling dramatically increased the number of BrdU+ cells and enhanced dendritic complexity within immature DCX+ neurons.

Conclusion: Limbic seizures impair retrieval of fear memories, decrease neural activity within the hippocampus, enhance NPY signaling, and enhance the rate of adult neurogenesis. When combined with our previous finding that new neurons born under conditions of recurrent seizures are unable to functionally integrate into memory circuits, and the fact that GABA plays an important regulatory role in neurogenesis, the overall picture suggests that seizures may impair cognition by enhancing GABAergic mechanisms, which subsequently promotes abnormally intensified hippocampal cell proliferation and maturation that can interfere with memory circuits. These findings have implications for the development of novel therapeutic targets for treating the behavioral comorbidities associated with epilepsy.

Policy of full disclosure: None.

P-08. Neuropathology; from ion channels to cortical EEG

P-08-001 Intra-accumbal administration of endomorphin-2 decreases acetylcholine efflux via mu receptors and increases dopamine efflux independent of mu receptors in the nucleus accumbens of freely moving rats

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Objective: We have shown that local administration of the putative endogenous mu receptor agonists endomorphin (EM)-1 and EM-2 into the nucleus accumbens (NAc) increased accumbal dopamine (DA) with and without stimulating mu receptors, respectively (Okutsu et al., 2006). Accumbal mu receptors are suggested to exert an inhibitory role on accumbal cholinergic activity (Britt & McGehee, 2008). Therefore, we analysed the effects of EM-1 and EM-2 on extracellular acetylcholine (ACh) and DA in the NAc using in vivo microdialysis. In order to monitor basal ACh levels, a low concentration of physostigmine (50 nM) was added to the perfusate.

Methods: Male Sprague-Dawley rats were used. ACh and DA levels in accumbal perfusate samples taken every 20 min were measured by HPLC-ECD. Drugs were administered intracerebrally through the microdialysis probe.

Results: The addition of physostigmine (50 nM) into perfusates allowed detection of ACh without affecting basal DA levels. Local administration of either EM-1 or EM-2 (6 and 30 nmol) into NAc decreased ACh in a dose-related manner. The EM-1- and EM-2 (30 nmol)-induced reductions in ACh were prevented by co-administration of the mu receptor antagonist CTOP (3 nmol), which failed to alter basal ACh. While intra-accumbal administration of either EM-1 or EM-2 (30 nmol) increased DA efflux, EM-1- but not EM-2-induced DA efflux was inhibited by CTOP (3 nmol), which failed to affect basal DA.

Conclusion: These results suggest that activation of accumbal mu receptors by EM-1 or EM-2 inhibits accumbal ACh efflux. This study also supports our notion that EM-1 and EM-2 enhance accumbal DA efflux by different mechanisms when they are infused into NAc (Aono et al., 2008). Thus, in contrast to intra-accumbal infusion of EM-1, which increases accumbal DA efflux through mu receptors, intra-accumbal infusion of EM-2 increases accumbal DA without activating mu receptors.

Policy of full disclosure: None.

P-08-002 Reduced oscillatorynatural frequencies of the frontal cortex in schizophrenia, bipolar disorder and major depressive disorder

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Objective: Recent studies have demonstrated that cortical brain areas tend to oscillate at a specific natural frequency when directly perturbed by transcranial magnetic stimulation (TMS). Fast electroencephalographic (EEG) oscillations, which typically originate from prefrontal regions, have been reported to be markedly reduced in schizophrenia.

Methods: Here we employed TMS/EEG to assess the natural frequency of prefrontal areas in a sample of 48 age-matched participants (12 each in major depression disorder (MDD), bipolar disorder (BD), schizophrenia (SCZ) and healthy controls). Event related spectral perturbations (ERSP) were obtained for each subjects using wavelet decomposition.

Results: TMS resulted in a significant activation of the Beta/gamma band response (21–50 Hz) to prefrontal cortical perturbation in healthy control subjects. By contrast, the main frequencies of prefrontal EEG responses to TMS were significantly reduced in patients with SCZ, BPD and MDD (11–27 Hz) relative to healthy subjects.

Conclusion: These results support our previous findings and demonstrate that patients with schizophrenia, bipolar disorder and major depression showed a slowing in the natural frequency of prefrontal cortico/thalamocortical circuits, suggesting a common neurobiological impaired mechanism, which may involve GABAergic interneurons neurotransmission.

Policy of full disclosure: None.

P-09. Pain

P-09-001 Reduced supraspinal nociceptive responses and distinct gene expression profile in CXBH recombinant inbred mice

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Objective: Considerable variability exists in the sensitivity to analgesic opioids across individuals, which has been an unresolved clinical issue in pain management. CXBH mice, known as an "opioid receptor-rich" strain, are a recombinant inbred mouse strain established by crossing the C57BL/6By and BALB/cBy strains. In the present study, we investigated nociceptive and antinociceptive sensitivity in CXBH mice and elucidated the underlying molecular mechanisms.

Methods: The behavioral responses to nociceptive stimuli were examined in the tail-flick test hot-plate test, Randall-Selitto test, and abdominal constriction test. Whole-genome gene expression profiles in the brains of each mouse strain were analyzed with illumina Expression BeadChips. Northern blot analysis was performed to estimate the expression levels of the μ, δ and κ opioid receptors.

Results: CXBH mice exhibited slightly higher morphine-induced antinociception compared with C57BL/6J and BALB/cBy mice in the hot-plate test but not tail-flick test. CXBH mice exhibited a marked reduction of nociceptive sensitivity, regardless of the type of nociceptive stimulus, with the exception of tail stimulation. Changes in gene expression that corresponded to reduced nociceptive sensitivity in the brains of CXBH mice were observed in 62 transcripts, including pain- and analgesia-related transcripts, in a whole-genome expression assay. The total mRNA expression of opioid receptors was higher in CXBH mice than in C57BL/6J and BALB/cBy mice. However, the expression levels of MOR-1 mRNA, a major transcript of the μ opioid receptor gene, were not different among the C57BL/6J, BALB/cBy, and CXBH mice.

Conclusion: Supraspinal nociceptive responses but not antinociceptive responses were reduced in the CXBH mice, and the expression levels of transcripts were altered in the brain of this strain.

Policy of full disclosure: None.

P-09-002 Vascular endothelial growth factor signaling in injured nerves mediates peripheral sensitization in neuropathic pain

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Objective: Chronic neuroinflammation may be a critical component of incurable inflammatory diseases, including neuropathic pain. Because angiogenesis due to vascular endothelial growth factor (VEGF) signaling plays a crucial role in inflammatory response, we focused on the mechanisms of VEGF-regulated neuropathic pain in mice.

Methods: Neuropathic pain model was produced by partial sciatic nerve ligation (PSL) in mice. Tactile allodynia and thermal hyperalgesia were evaluated by von Frey test and Hargreaves test, respectively. Blood vessels in the sciatic nerve (SCN) were visualized by ex vivo fluorescence imaging and immunohistochemistry using DiI fluorescence.

Results: The mRNA and protein expression of VEGFA were upregulated in the injured SCN after partial sciatic nerve ligation (PSL). VEGFA was localized to infiltrating macrophages and neutrophils derived from bone marrow. Upregulation of VEGFA was epigenetically mediated by histone H3 acetylation and trimethylation in its promoter region. The receptors of VEGF, VEGFR1 and VEGFR2, were localized to vascular endothelial cells or macrophages. Progression of angiogenesis was observed in the injured SCN after PSL and confirmed by the upregulation of CD31. Perineural administration of pharmacological inhibitors of VEGFA or VEGFR-associated tyrosine kinases attenuated tactile allodynia and thermal hyperalgesia, which were caused by PSL. Moreover, we determined the contribution of VEGF- and CXC-chemokine receptor 4-expressing angiogenic macrophages to neuropathic pain.

Conclusion: Taken together, epigenetically upregulated VEGFA in injured peripheral nerves participates in angiogenesis and prolongs pain behaviors through its receptors. We propose that VEGFA-related components may underlie peripheral sensitization leading to neuropathic pain.

Policy of full disclosure: None.

P-09-003 Distinctive spontaneous neural activity in patients with somatoform pain disorder: A resting state fMRI study

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Objective: Patients with somatoform pain disorder suffer from long lasting pain. Various neuroimaging studies have examined the mechanisms underlying somatoform pain disorder. However, there have been few resting-state functional magnetic resonance imaging (R-fMRI) studies of such patients.

Methods: We examined distinctive functional network in terms of regional homogeneity (ReHo) during the resting state, assessing nine patients with somatoform pain disorder and 20 healthy controls. All participants gave their written informed consent before participation, according to a protocol approved by the Hiroshima University ethics committee.

Results: We found 1) significant ReHo increases for the left precentral gyrus in somatoform pain disorder patients relative to healthy controls and 2) a positive correlation between pain ratings and ReHo values for the left precentral gyrus in patients. It has been reported that precentral gyrus activation is associated with the amelioration of various chronic pain syndromes.

Conclusion: These findings suggest that constant stronger resting-state left precentral gyrus activity in patients with somatoform pain disorder may be in some way compensatory, possibly serving to relieve the hypersensitivity of pain intensity, with this linkage possibly representing a distinctive neural mechanism in somatoform pain disorder.

Policy of full disclosure: None.

P-09-004 Treatment of skin cancer pain with naltrexone in mice locally transfected with a mutant mu-opioid receptor gene in spinal cord

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Objective: The opioid antagonists, such as naloxone or naltrexone, exhibited full agonistic properties in the mutated mu-opioid receptor, MORS196ACSTA, in which the conserved Ser196, Thr327, Cys330 were mutated to Ala, Ala, and Ser, respectively. In our previous study, systemic naltrexone (10 mg/kg, s.c.) elicited anti-allodynic effect without the induction of dependence and rewarding effect in mice with neuropathic pain after the expression of MORS196ACSTA in the spinal cord by intrathecal administration of lentivirus (LV)-MORS196ACSTA-EGFP. The objective of this study was to further investigate whether this antinociceptive paradigm could be effective in mice with skin cancer pain.

Methods: LV-MORS196ACSTA-EGFP was injected intrathecally into the male C57BL/6 mice and allowed the gene expression for 4 weeks. B16-F1 melanoma cells were then subcutaneously injected into the plantar region of left hind paw to induce skin cancer pain. The volume of paw, spontaneous pain and mechanical allodynia (determined by von Frey test) were assessed before and after systemic naltrexone (10 mg/kg, s.c.) or local naltrexone (10 nmol, i.t.) from day 5 to 18 after injection of melanoma cells.

Results: The injection of melanoma cells into a hind paw of mice increased the paw volume and induced spontaneous pain and allodynia (decrease of paw withdrawal pressure) in the ipsilateral paw from day 5 to day 18. Naltrexone (10 mg/kg, s.c. or 10 nmol, i.t.) elicited significant anti-allodynic effect and improved the spontaneous pain on ipsilateral hind paws of mice which expressed MORS196ACSTA in the spinal cord.

Conclusion: These data imply that naltrexone may have therapeutic potential for skin cancer pain after the gene expression of MORS196ACSTA in the spinal cord.

Policy of full disclosure: None.

P-10. Biomarkers (incl. Pharmacogenomics and brain imaging) for diagnosis and treatment response A

P-10-001 Serotonin transporter ubiquitynation is a potential biomarker for major depressive disorder

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Objective: Major depressive disorder is characterized by fatigue, diminished interest or pleasure in every day's activities and despair. Serotonin transporter (SERT) plays a critical role in the termination of synaptic transmission, SERT is related to vulnerability to depression and important targets for antidepressants. But, the metabolism of SERT and its contribution to the depression are still unclear. Melanoma antigen gene-D1 (MAGE-D1) plays a role of adaptor molecule in ubiquitin-dependent degradation pathway. In vivo and in vitro immunoprecipitation studies revealed that MAGE-D1 binds to SERT via necdin homology domain. Transfection of MAGE-D1 into CHO cells expressing SERT stably displayed intracellular colocalization of MAGE-D1 with SERT and decrease of serotonin reuptake and SERT protein expression with increase of SERT ubiquitination. MAGE-D1 knockout mice showed depressive endophenotypes without any anxiety, cognitive or motor dysfunction, which were attenuated by antidepressants. The high potassium-induced release of serotonin was reduced in the prefrontal cortex and hippocampus of the MAGE-D1 knockout mice, which were accompanied with hyperexpression of SERT by decrease of its ubiquitination. Thus, decrease in SERT ubiquitination has been implicated as a causative mechanism in depression.

Methods: In the present experiment, we used lymphoblasts derived from the peripheral blood lymphocytes in fluvoxamine-responsive and -resistant depression patients to quantitatively examine SERT protein expression and its ubiquitination.

Results: SERT protein was increased in the fluvoxamine-resistant depression patients. Ubiqutinated SERT protein was decreased in the fluvoxamine-resistant depression patients. The proteasome inhibitor increased the expression of the SERT protein in healthy volunteer, but failed to increase that in both fluvoxamine-responsive and -resistant depression patients. Further, ubiqutinated SERT expression in platelet of healthy subject is associated with depression-related personality trait as harm avoidance in some indexes (anticipatory worry in men, and shyness in women).

Conclusion: These data suggests that SERT ubiquitynation could be a potential biomarker for major depressive disorder.

Policy of full disclosure: None.

P-10-002 The potential of DNA methylation of the SLC6A4 gene as a surrogate index of the important characteristics in the diagnosis and the treatment of major depression

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Objective: Establishing biological markers for major depression (MD) could be important for improving patient care and providing more effective treatment. Since gene-environmental interactions are closely involved in the etiology of MD, DNA methylation profiles might serve as a useful diagnostic biomarker. We examined the utility of DNA methylation profiles at the CpG island of SLC6A4 (DMS) as a diagnostic biomarker for MD. In addition, the relationship between DMS and the serotonin transporter gene-linked polymorphic region (5-HTTLPR) allele, the severity of symptoms, number of early adversities, and therapeutic responses to antidepressants were examined.

Methods: Genomic DNA was extracted from peripheral blood of Japanese healthy controls and patients with MD before and after treatment. DMS was analyzed using a MassARRAY Compact System. The severity of depression was evaluated using the Hamilton Rating Scale for Depression, and early adversity was evaluated using the Early Trauma Inventory.

Results: We were unable to distinguish between and healthy controls, or between unmedicated patients and medicated patients using DMS. The 5-HTTLPR allele had no significant effect on DMS. The methylation rates for several CpGs differed significantly after treatment. Notably, the methylation rate of CpG 3 in patients with better therapeutic responses was significantly higher than that in patients with poorer responses.

Conclusion: Although further studies examining the function of specific CpG units of SLC6A4 are required, these results suggest that the methylation rate of SLC6A4 is a useful surrogate index for therapeutic responses to antidepressants in unmedicated patients with MD.

Policy of full disclosure: None.

P-10-003 Fronto-limbic disconnection in bipolar disorder

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Objective: Bipolar disorder (BD) is a severe, disabling and life-threatening illness. Several lines of evidence, coming both from neuropsychological and brain imaging studies, suggest that disruptions in neural connectivity could play a key role in the mechanistic explanation of the cognitive and emotional symptoms typical of this disorder. In literature only few studies evaluated effective connectivity (EC) with Dynamic causal modeling technique (DCM) in BD. In the present study we performed DCM of functional neuroimaging data to investigate the EC in a specific cortico-limbic network in a sample of bipolar depressed patients.

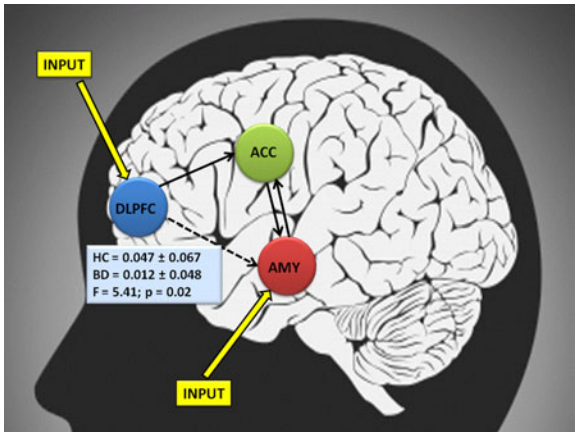
Methods: DCM was performed on fMRI activation to a face-matching paradigm task of 52 bipolar patients during a major depressive episode, without psychotic features, and 40 healthy subjects. EC was estimated with DCM in a trinodal neural model including anatomically defined regions of dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC) and the amygdala (AMY). Six alternative bilinear and stochastic models were defined for each subject.

Results: The best model was the same across all subjects, and consists in a forward connection from DLPFC to AMY and from DLPFC to ACC and with a bidirectional connection between ACC and AMY. However patients with BD showed a significantly reduced endogenous connectivity between DLPFC and Amy during the emotional processing task. There was no significant group effect upon the others endogenous connection.

Conclusion: Both DLPFC and ACC are part of a network involved in emotion regulation and share strong reciprocal connections with the amygdalae. These regions are fundamental in voluntary emotion regulation strategies, including reappraisal and redirection, and previous findings showed that their irregular functioning might be involved in the cognitive and emotional deficits characteristic of BD. Thus, our finding of a reduced DLPFC-amygdala connectivity may reflect abnormal modulation of mood and emotion typical of bipolar patients.

Policy of full disclosure: None.

DCM result:



P-10-004 Cortico-limbic dysfucntion in borderline personality disorder: Adverse childhood experiences and treatment with clozapine

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Objective: Several studies identified a dysregulation of fronto-limbic circuit during social cognition tasks in borderline personality disorder (BPD). Clozapine successfully treats the major behavioural abnormalities associated with BPD [2], but its effects on neural activity have never been investigated in BPD. Here we assessed the activation of cortical and limbic structures with BOLD fMRI, during implicit processing of faces expressing emotions of anger and fear,exploring the effects of 6 months of combined treatment with clozapine and psychotherapy, and also of adverse childhood experiences.

Methods: A 3.0 Tesla fMRI acquisition was used to study 30 female subjects: 18 healthy control (HC), 12 BPD. At the individual level we first compared face vs shape conditions to isolate regions engaged. Than we performed an ANOVA with two factors: diagnosis (BPD vs. HC) and ACE (high vs. low) to compare neural activations; controlling for age, education and medications. We performed a second analysis ANOVA in 10 subjects (5 BPD and 5 matched controls), BPD were tested before and after treatment.

Results: In both groups higher ACE were associated with a greater activation of left amygdala, with BPD showing baseline hyperactivity of left amygdala and dorsolateral prefrontal cortex. Integrated treatment caused a broad symptomatic improvement, paralleled by a normalization of amygdala reactivity with a further increase of DLPFC activity in BPD.

Conclusion: Results suggest an effect of ACE on fronto-limbic neural response, which was influenced by BPD diagnosis. Greater activation in DLPFC suggested a request for a greater control on cortico-limbic areas which resulted, after successful treatment, in a normalization of amygdala reactivity to aversive stimuli.

Policy of full disclosure: None.

P-10-005 Chronotherapeutic treatment efficacy and white matter integrity: A tract-based spatial statistics study in bipolar patients

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Objective: Bipolar disorder (BD) is a progressive and disabling psychiatric condition. A growing body of literature suggests that bipolar symptomatology may be influenced by dysfunctions in white matter (WM) integrity. Nevertheless chronotherapeutic treatments prompt a rapid and stable antidepressant response in bipolar depression by combining total sleep deprivation and light therapy. Diffusion tensor imaging (DTI) allows a non-invasive, in vivo study of the integrity of WM microstructure. The aim of this study is to investigate a possible correlation between WM microstructure and the response to chronotherapeutic treatment in BD.

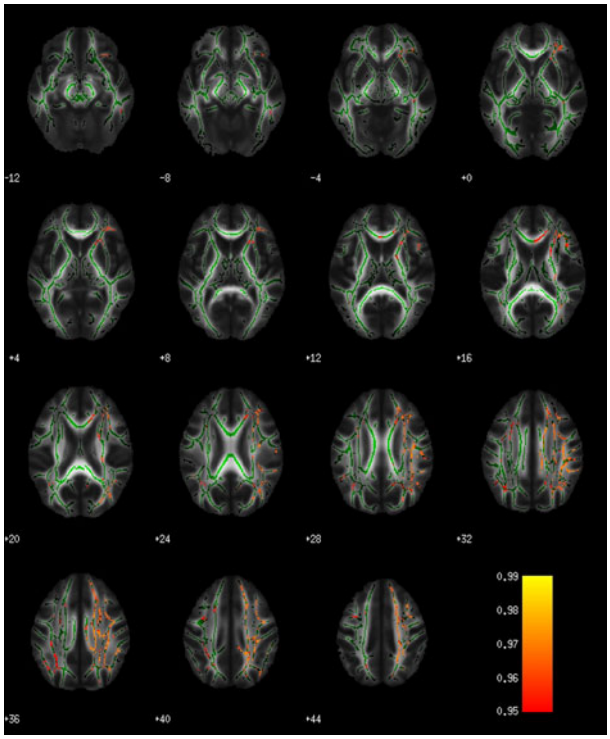
Methods: We studied 73 patients affected by a major depressive episode with a diagnosis of BD type I. Patients who shown a reduction of 50% to Hamilton Rating Scale for Depression ratings were identified as responders to chronotherapeutic. We compared the DTI measures of WM integrity of responder (n=47) and no-responder (n=26) to the treatment using tract-based spatial statistics on DTI measures: axial, radial, and mean diffusivity, and fractional anisotropy. Scans were analyzed using FSL and recorded before treatment. We accounted for the effects of nuisance covariates that could influence WM structure.

Results: No-responder patients showed increased mean diffusivity compared to responders in several WM fiber tracts including corpus callosum, corona radiata, superior longitudinal fasciculus, inferior longitudinal fasciculus, cingulum bundle, localized especially in the right hemisphere.

Conclusion: Mean diffusivity reflects the presence of boundaries to the free diffusion of water in each voxel, and correlates with membrane density and myelin degeneration. Damages of the myelin sheaths cause disruption in structural connectivity, with a reduction of the signal speed and could affect the capability of neurons to communicate with each other efficiently, thus leading to a compromised functional connectivity. Our results suggest that WM integrity may contribute to the efficacy of chronotherapeutic treatment, and it may represent a relevant marker for treatment response in this disorder.

Policy of full disclosure: None.

White matter areas where no-responder patients showed significantly higher values of mean diffusivity than responders:



P-10-006 Imaging of high-risk adolescent myelin integrity using DTI

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Objective: Adverse childhood experiences slow the development of white matter axon diameter and microtubule structure, and decrease the ratio of myelinated to unmyelinated fibers in the brain's white matter tracts. The brain is becoming viewed more as a complex network of networks, with each network relying on white matter integrity to function optimally. Diffusion Tensor Imaging (DTI) provides a means of visualizing the integrity of these white matter tracts. DTI scans were used to investigate whether complex psychiatric symptoms are correlated with impaired white matter development in adolescents.

Methods: Single DTI scans from 20 adolescent inpatients from CASA House Edmonton were compared to 20 pair-matched (age/gender/handedness) controls. Patients were diagnosed with at least two Axis-I (DSM-IV TR) disorders; patients with a diagnosis of Fetal Alcohol Syndrome (FAS) or Tourette's at the time of scanning were excluded from analysis. Tract integrity analysis was carried out using Tract-Based Spatial Statistics, part of Oxford's FSL software for MRI analysis. This approach extracts Fractional Anisotropy (FA) maps from the brain, which show white matter tracts. FA maps are combined by group and compared for differences along the core of each tract. Differences between groups suggest a large difference in tract integrity.

Results: Following statistical corrections and confirmation of tract locations from a neurologist, we saw decreases in patient white matter integrity, localized to three tracts ($p<0.05$): superior fronto-orbital fasciculus, genu of the corpus callosum, and corticospinal tract.

Conclusion: Adolescent inpatients had significantly impaired white matter development in three tracts compared to control subjects. This suggests underdeveloped white matter could act as a marker for complex psychiatric disorders. More research is needed to determine what proportion of psychiatric symptoms can be accounted for by these differences in white matter development.

Policy of full disclosure: None.

P-10-007 Analysis of serotonin transporter and 5-HT2A receptor clusters in peripheral lymphocytes as putative biomarkers of therapeutic efficacy in major depressive disorder

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Objective: To analyze the clustering of the serotonin transporter (SERT) and the 5-HT2A receptor in the plasma membrane of lymphocytes from non-psychiatric subjects and naive depression patients, and in these same patients after 8 weeks of antidepressant medication; and to compare changes in these parameters in relation to the degree of response to pharmacological treatment.

Methods: We collected blood samples from 38 untreated and newly diagnosed depression patients at the time of diagnose and after 8 weeks of pharmacological treatment, and of 38 non-psychiatric subjects. We used the Hamilton Scale to quantify the level of depression in patients both before and after pharmacological treatment. We then used immunocytochemistry to assess SERT and 5-HT2A clusters in lymphocytes.

Results: SERT clusters size, and 5-HT2A clusters size and number are increased in lymphocytes in depression. These parameters are partially reversed after pharmacological treatment. Analysis of the distribution of SERT and 5-HT2A clusters size allowed the differentiation of two subpopulations of naive depression patients (D-I and D-II). Initially, naive D-I and D-II depression patients showed similar Hamilton scores. However, D-II patients showed a better therapeutic outcome after 8 weeks of pharmacological treatment than D-I patients, with many D-II patients showing remission of symptoms. Pharmacological treatment alters the distribution of SERT and 5-HT2A clusters size in D-II patients but not in D-I patients.

Conclusion: SERT and 5-HT2A clusters in peripheral lymphocytes are altered in major depression, partially reversed by antidepressant treatment, and may be considered a putative biomarker of therapeutic efficacy in major depression.

Policy of full disclosure: None.

P-10-008 Kynurenine production is reduced by acute typtophan depletion: Implications for cognitive impairment in brain-gut axis disorders

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Objective: The specificity of acute tryptophan depletion (ATD) as a challenge of the serotonergic system has been questioned. We propose alterations in the production of kynurenine, a candidate biomarker of cognitive dysfunction in brain-gut axis disorders such as irritable bowel syndrome, as an alternative mechanism through which ATD exerts its effects.

Methods: In a double-blind, crossover design, age-matched females with irritable bowel syndrome (IBS; N=9) and healthy controls (HC; N=14) were administered a tryptophan-depleting amino acid mixture or control drink containing tryptophan. Cognitive performance was assessed 5 hours post-drink using tests the Cambridge Neuropsychological Test Automated Battery (CANTAB).

Results: In addition to reductions in plasma tryptophan availability, ATD also reduced plasma kynurenine concentrations (HC: pre-drink: 580.78±44.49[ng/ml], post-drink: 210.05±29, $p<0.001$; IBS: pre-drink: 474.64±32.65, post-drink: 141.84±7.93, $p<0.001$). The control drink increased kynurenine (HC: mean kynurenine pre-drink=480.67±41.82, post-drink=1105.56±141.16, $p<0.001$; IBS: pre-drink=498.76±43.91, post-drink=1732.78±424.37, $p<0.05$) and impaired memory performance in the IBS cohort (paired associate learning mean errors: HC: 2.43±0.87, IBS: 7.78±1.85, $p=0.016$), although ATD did not (HC: 3±0.96, IBS: 3.89±1.81, $p>0.05$).

Conclusion: ATD can alter not only tryptophan but also kynurenine production, which may regulate visuospatial memory performance in brain-gut axis dysfunction. Targeting the kynurenine pathway may represent a viable therapeutic option to restore normal cognitive performance in IBS.

Policy of full disclosure: The Alimentary Pharmabiotic Centre is a research centre funded by Science Foundation Ireland (SFI), through the Irish Government's National Development Plan (NDP). The authors and their work were supported by SFI (grant nos. 02/CE/B124 and 07/CE/B1368, and currently via grant number SFI/12/RC/2273). GC is supported by a NARSAD Young Investigator Grant (Grant no 20771) from the Brain and Behavior Research Foundation. GC, JFC, TD and APA are also funded by the Irish Health Research Board (HRB) Health Research Awards

(grant no HRA_POR/2011/23). The authors (TD, JFC, GC and EMMQ) received support from UCC's Strategic Research Fund towards the purchase of CANTAB software licenses. The authors wish to acknowledge the facilities provided by the HRB Clinical Research Facility at UCC, Mercy Hospital, Cork.

P-11. Clin. Investigator, Nat. Funding Agency, Public-Private Partnership initiated clinical trails

P-11-001 Mirtazapine treatment can become a preventive measure against the long-term usage of benzodiazepines

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Objective: Mirtazapine (MIR) is the first noradrenergic and selective serotonergic antidepressant. It is known to improve sleep and appetite, particularly in patients with depression. We evaluated improvements in sleep and appetite from the start of MIR therapy to up to 60 days.

Methods: Sleep improvement was evaluated based sleep time and the daily dose of benzodiazepines (BZPs), as a converted-to-diazepam equivalent, and the numbers of different BZP agents used. Quantity of meals and body weight were measured to see changes of their appetite. The protocol was approved by the ethics review board of Tokyo Women's Medical University (No. 2875).

Results: There were 51 patients with major depressive disorder (DSM-IV) who started MIR therapy during hospitalization between September 2009 and December 2012. When we compared the sleep time on the first day and its average on the other days the patients received the 15-mg dose, sleep time was extended from 4.6±2.0 to 6.3±1.9 h ($P<0.05$). The difference from the other doses was not significant. The dose of BZPs and the numbers of BZPs were decreased from 6.6±4.2 to 2.0±2.2 mg and 1.2±0.7 to 0.49±0.5 drugs, respectively ($P<0.05$). Twenty-two of the 51 patients were able to withdraw their BZPs. The patients gradually began to eat more, but their body weights did not increase from the baseline measurement.

Conclusion: MIR treatment allowed to extend sleep time immediately without increasing body weight. Almost all the patients could withdraw or decrease BZPs. This study suggests that MIR treatment can become a preventive measure against the long-term usage of BZPs.

Policy of full disclosure: None.

P-12. Use of traditional medicine to guidenovel CNS drug development

P-12-001 Differential effects of d- and l-tetrahydropalmatine on dopamine efflux in the rat nucleus accumbens

S. Ahn[1], A. Phillips[1]. [1]*University of British Columbia, Vancouver, Canada*

Objective: Tetrahydroprotoberberines (THPBs), including stepholidine, govadine, and tetrahydropalmatine (THP), are key compounds found in plant-derived traditional medicines. A growing interest in the pharmacotherapeutic potential of THPBs is linked to direct effects on brain dopamine (DA) receptors and other key neurotransmitters. The l-enantiomers of each of the parent racemic compounds have been shown to act as DA D2 receptor antagonists and this in turn has been linked to the possible antipsychotic effects of l-stepholidine and l-Govadine, as well as the sedative and analgesic properties of l-THP in humans. Preclinical assessment of the d- isomer of THP indicates that it may serve as a selective depleter of synaptic vesicles containing DA, raising the possibility that it may act as a vesicular monoamine transporter blocker. The present study sought to extend the examination of the pharmacological and neurochemical properties of the d- and l-isomers of THP by employing in vivo brain microdialysis to assess their effects on the mesolimbic DA system.

Methods: In vivo microdialysis and high pressure liquid chromatography with electrochemical detection was used to monitor changes in DA efflux in the nucleus accumbens (NAc; AP +1.7 mm, ML +/−1.1 mm, DV −8.0 mm) of rats. All experiments involved intra-NAc reverse-dialysis of d- or l-THP (50 uM).

Results: Intra-NAc administration of the d- and l-isomers of THP had opposite effects on DA efflux. l-THP evoked a significant increase in DA efflux (~+40% relative to baseline). In contrast, d-THP initially evoked a small short-lasting increase (+30%) which then decreased below baseline (~−40%).

Conclusion: The present findings compliment earlier studies by confirming that each isomer of THP can differentially modulate extracellular levels of DA in the NAc. The increase in DA efflux induced by d-THP is entirely consistent with reports that it is a selective D2 antagonist. The profile of a short-term elevation in DA efflux followed by a decrease to levels significantly below baseline values, is very similar to that observed with other VMAT2 antagonists including tetrabenazine and reserpine. On-going electrophysiological studies are assessing the effects of the stereo-isomers on DA cell firing in the ventral tegmental area.

Policy of full disclosure: Supported by operating grants from the Canadian Institutes of Health Research to AGP.

P-13. Psychoneuroimmunology and neuroinflammation A

P-13-001 Mood-modulating drugs alter prostaglandin E2 levels in rat brain in a region-dependent manner

A. Azab[1], A. Nassar[1], Y. Sharon-Granit[1]. [1]*Ben-Gurion University of the Negev, Beer-Sheva, Israel*

Objective: Accumulating evidence suggests that mood-modulating drugs exhibit anti-inflammatory properties. However, many contradicting findings have been reported, probably due to different experimental conditions under which the drugs were investigated. This study was undertaken to examine the effects of chronic treatment with four different mood-modulating drugs – valproate, carbamazepine, olanzapine and imipramine – on lipopolysaccharide (LPS)-induced production of prostaglandin E2 (PGE2) in rats' hypothalamus and hippocampus.

Methods: Rats were treated with valproate (100 mg/kg), carbamazepine (40 mg/kg), olanzapine (10 mg/kg) and imipramine (20 mg/kg) for 4 weeks by a single daily intraperitonteal (ip) injection. On day 29, at 2 h post drug treatment, rats were injected (ip) with saline or LPS (1 mg/kg). At 2 h post LPS injection, rats were sacrificed and hypothalamus and hippocampus were quickly excised. Hypothalamus and hippocampus were homogenized and centrifuged. Supernatants were separated for determination of PGE2 levels by ELISA.

Results: Treatment with LPS resulted in a significant increase in hypothalamic PGE2 levels. Pretreatment with carbamazepine, olanzapine and imipramine significantly reduced LPS-induced elevation in hypothalamic PGE2 levels, while valproate led to a non-significant reduction. On the other hand, LPS did not significantly alter PGE2 levels in the hippocampus. Overall, none of the tested drugs significantly affected hippocampal PGE2 levels.

Conclusion: These results suggest that mood-modulating drugs exert similar anti-inflammatory properties and that their effects on PGE2 production are region-specific.

Policy of full disclosure: None.

P-13-003 Chronic LPS administration induces prolonged sickness behavior in rats

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Objective: Acute inflammation, e.g. by exposure to lipopolysaccharide (LPS), produces an adaptive motivational state termed sickness behavior, to cope with inflammatory mediators and the subsequent negative energy balance. This response is short acting, whereas prolonged sickness behavior manifest with a different survival response. Physical activity is known to exert anti-inflammatory effect, and could serve as a unique modulator of the immune system during chronic inflammation. The objective of this study was to investigate the behavioral, metabolic and brain cytokine changes following chronic administration of a low dose LPS in rats, and to explore the modulatory effects of exercise.

Methods: Sprague-Dawley rats were injected with LPS (600 µg/kg) or saline, once or for eight weeks. Half of the rats in the chronic study had free access to a running wheel. Sickness behavior was evaluated, including body weight, food intake, locomotor-activity, depressive-like behavior, together with cytokine and chemokine levels in frontal cortex and hypothalamus. Energy related parameters including fasting glucose, fat mass and liver weight was also measured.

Results: Chronic LPS administration resulted in reduced body weight and food intake, decreased activity level and depressive-like behavior,

similar to a single LPS injection. However, contrasting acute inflammation, chronic LPS administration induced hyperglycemia, decreased fat mass and increased liver weight. Chronic LPS induced a specific elevation of proinflammatory cytokines (IL-1β and IFN-γ) and chemokines (MIP-1α and MCP-1) in frontal cortex. Exercise did not reverse the LPS-induced sickness behavior or the altered cytokine levels.

Conclusion: Chronic administration of LPS produced prolonged sickness behavior, distinct from the syndrome following a single LPS injection, which could be caused by the specific energy demand during a chronic inflammatory disease. Exercise did not reduce the LPS-induced sickness behavior or brain cytokine levels, suggesting that the immunemodulatory effects of exercise are not sufficient to overcome the LPS-induced immune response.

Policy of full disclosure: None.

P-13-005 Effects of haloperidol on lipolysaccharide-induced inflammation in rats

A. Nassar[1], Y. Sharon-Granit[1], A. N. Azab[1]. [1]*Ben-Gurion University of the Negev, Beer-Sheva, Israel*

Objective: The therapeutic mechanisms of mood-modulating drugs (mood stabilizers, antipsychotic and antidepressant drugs) are not fully understood. Accumulating evidence suggests that inflammation plays a role in the pathogenesis of bipolar disorder and that mood-modulating drugs exhibit anti-inflammatory properties. This study was undertaken to examine the effects of the antipsychotic drug haloperidol on lipopolysaccharide (LPS)-induced inflammation in rats.

Methods: Rats were treated with haloperidol (2 mg/kg) for 4 weeks by a single daily intraperitonteal (ip) injection. On day 29, at 2 h post haloperidol treatment, rats were injected (ip) with saline or LPS (1 mg/kg). At 1.5 h post LPS injection body temperature (BT) was measured. Immediately thereafter, rats were sacrificed, blood was collected, and liver and brain regions (hippocampus, hypothalamus and frontal cortex) were excised. Hippocampus, hypothalamus, frontal cortex and liver were homogenized and centrifuged. Supernatants were separated for determination of inflammatory mediators. Levels of inflammatory mediators in plasma and supernatants of liver and brain regions were measured by ELISA.

Results: Treatment with LPS resulted in a significant decrease in BT (hypothermia). Pretreatment with haloperidol significantly reduced LPS-induced hypothermia. Moreover, haloperidol significantly decreased levels of tumor necrosis factor (TNF)-alpha, interleukin (IL)-6 and interferon (INF)-alpha in the hippocampus and hypothalamus. On the other hand, haloperidol differently affected TNF-alpha (increased) IL-6 (decreased) and INF-alpha (not changed) levels in the frontal cortex. Haloperidol did not alter hepatic levels of all three cytokines while it significantly reduced plasma IL-6 levels.

Conclusion: These results suggest that haloperidol possess potent anti-inflammatory properties, however, its effects on inflammatory mediators production vary in different tissues.

Policy of full disclosure: None.

P-13-006 The expression of dopaminergic receptor D5 mRNA is increased in circulating lymphocytes of children and adolescents with tic disorders and/or obsessive-compulsive disorder

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Objective: Tic disorders and obsessive-compulsive disorder (OCD) are neuropsychiatric disorders in which dopaminergic dysfunction and immune system abnormalities seem to coexist.

Methods: Using real-time PCR, we determined the mRNA expression of dopamine receptors (DRs) D1-5 in peripheral blood lymphocytes (PBLs) from 22 children and adolescents with tic disorders and/or OCD and 6 healthy controls (HCs).

Results: Overall, we found that the levels of these mRNA expressions were low or undetectable. Although it was not statistically significant, the expression levels of DRD2 and DRD3 appear to be lower in the lymphocytes isolated from patients compared to the ones from healthy subjects. Most of DRD4 expressions were undetectable so that it is not evident the role of this receptor in developing this disease. Lastly, 7 of 22 patients (32%) showed the expression of DRD5 mRNA, while no healthy control expressed this receptor.

Conclusion: These data may suggest that DRD5 mRNA upregulation in PBLs from children and adolescents with tic disorders and/or OCD may represent a peripheral marker of dopaminergic dysfunction and supports the involvement of the immune system in tic disorders and/or OCD.

Policy of full disclosure: None.

P-13-007 Fc alpha/mu receptor (Fc alpha/mu R) mRNA upregulation in tic disorders and/or obsessive-compulsive disorder

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Objective: The pathogenesis of tic disorders and obsessive-compulsive disorder (OCD) is still unknown. In addition to genetic factors, autoimmune mechanism may play an important role, as a sequela of preceding streptococcal upper respiratory infections. Although it has been suggested that Fc alpha/mu receptor (Fc alpha/mu R) may be associated with the pathogenesis of tic disorder and/or OCD in children and adolescents, it has not been found that this receptor is expressed in peripheral blood lymphocytes (PBLs) of children with tic disorder and/or OCD.

Methods: Using real-time PCR, we determined the mRNA expression of Fc alpha/mu R in PBLs of tic and/or patients and compared to healthy controls.

Results: To our surprise, almost half of patients (15 of 34) expressed this receptor in their PBLs at least in the mRNA level. In addition, the mRNA level of Fc alpha/mu R in the lymphocytes of tic and/or OCD patients is higher than the one of healthy subjects, suggesting that this receptor is important to the pathogenesis of tic disorders and OCD.

Conclusion: We found that the mRNA of Fc alpha/mu receptor (Fc alpha/mu R) was present in PBLs of children and adolescents with tic disorders and/or OCD, and this finding may lead to new therapeutic avenue to treat these patients.

Policy of full disclosure: None.

P-14. Autism spectrum disorders A

P-14-001 The endoplasmic reticulum stress may contribute to the pathogenesis of the autism spectrum disorders

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Objective: It was not elucidated the pathogenic mechanism of the autism spectrum disorders (ASD). On the other hands, it have been previously reported that some type of ASD might be caused by deficient of specific genes, which regulate the synaptic development. In this study, we focused on the endoplasmic reticulum (ER) stress, and we investigated whether the ER stress affects the neuronal maturation such as dendrite outgrowth.

Methods: In vivo experiments, the pregnant mice were injected with 500 mg/kg valproic acid (VPA) on E9.5 for establishment of animal model of ASD. Offspring born from VPA-treated mothers were subjected to the experiments. In vitro experiments, the neurons were differentiated from the mouse embryonic carcinoma P19 cells using all-trans retinoic acid. The cells were cultured in the absence or presence of tunicamycin during differentiating for 8 days.

Results: In the animals treated with VPA, behavioral analysis of the offspring showed a decrease in the locomotor activity, a decrease in the cognitive ability and an increase in the aggressive social behavior. In the cerebral cortex of the offspring, the expression of ER stress marker GRP94 was increased. In addition, the mRNA levels of the proneural factor Hes1 and Pax6, which negatively regulate the neuronal differentiation, were decreased in the cortex. Furthermore, the level of Math1, which positively regulates the differentiation, was increased in the cortex. In the P19 cells, tunicamycin led to an increase in the expression of GRP78/94 during the differentiation to neuron. The number of the neuronal marker Tuj-1-positive cells was increased by the ER stress in the differentiated cells. On the other hands, the dendrite outgrowth of the differentiated cells was inhibited by the ER stress.

Conclusion: We found that the brain in the animal model of ASD was under the ER stress condition, and that ER stress induced abnormal differentiation and neuronal maturation.

Policy of full disclosure: None.

P-14-002 Efficacy and safety of aripiprazole used for impulsiveness in 22q11.2 deletion syndrome with autism spectrum disorder

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Objective: 22q11.2 deletion syndrome (22q11.2DS) has an incidence estimated at 1:4-5,000 and an increased risk of developing mental illnesses. They were usually regarded as schizophrenia, but we considered it as autism spectrum disorder (ASD) and that medical treatment may be useful for its impulsiveness. Aripiprazole is indicated overseas to use for excitability in children with ASD. We treated 3 patients with ASD symptoms and studied its efficacy and safety.

Methods: Out of patients with 22q11.2DS seen in our hospital, three patients with ASD symptoms were consisted of men aged 14 and 17 years and a woman aged 23 years. Detailed life history and present illness were taken and diagnosis was made according to DSM-5 along with Autism Diagnostic Interview-Revised (ADI-R). The outcome was evaluated by ABC-J, CGI-S, and CGI-I before aripiprazole administration, at 2, 4, and 8 weeks after that.

Results: At baseline prior to the dose, the mean of ABC-J irritability was 33.3+/−2.9, lethargy 30.3+/−3.3, stereotypy 2.7+/−0.4, hyperactivity 22.3+/−10.3, and inappropriate speech 5.7+/−2.9. At the end point, the mean of ABC-J irritability was 5.0+/−1.4, lethargy 14.0+/−3.7, stereotypy 0.7+/−0.3, hyperactivity 4+/−1.8, inappropriate speech 2.3+/−1.6, showing improvement as well as with CGI. The three patients did not have any adverse effects including insomnia, hypersomnia, and akathisia.

Conclusion: Aripiprazole appears to be effective for impulsiveness and irritability in 22q11.2DS. Developmental disorder should be kept in mind in evaluating 22q11.2DS patients in case of treatment, along with environmental adjustment provided including social development assistance and psychological education if necessary, it is important to select better medical treatment for them. For the limited number of such cases, further study is warranted in the future.

Policy of full disclosure: None.

P-14-003 Lurasidone ameliorates a ketamine-induced joint visual attention dysfunction as a possible disease model of autism spectrum disorders in common marmosets

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Objective: Joint visual attention (JVA) is defined as following another person's pointing gesture and gaze, and the performance of JVA generally enables infants to socially coordinate their attention with other people. It is said that infants with autism spectrum disorders (ASD) find it difficult to perform JVA. We have already evaluated that common marmosets, small monkeys, were capable of performing JVA, and ketamine, an NMDA receptor antagonist, impaired the JVA function. So, this ketamine-induced JVA impaired model with common marmosets could be a possible disease model of some aspects of ASD. Recently we have reported that lurasidone, the latest antipsychotic agent, increased the cortical efflux of glutamate. Several investigations showed that NMDA receptor hypofunction was associated with ASD, so lurasidone might be effective on JVA impairment induced by ketamine. Therefore, the present study investigated whether lurasidone ameliorates the ketamine-induced JVA impairment.

Methods: Five common marmosets were used. The apparatus was constructed using 4 white acrylic boxes (4×4×4 cm) which were attached to 4 corners of a square frame (10×10 cm). All of the boxes had a door with a hinge and the marmoset could easily get a reward by pushing the door. The marmoset was informed which box contained the reward by the experimenter pointing to it. We scored in accordance with the number of incorrect choices they made.

Results: Ketamine significantly decreased JVA score as we previously reported, and lurasidone significantly reversed the ketamine-induced JVA impairment.

Conclusion: We showed that ketamine induced JVA dysfunction and that lurasidone ameliorated the impairment. These findings suggest that this experimental system could be a useful animal model of ASD and lurasidone might be effective on some aspects of ASD.

Policy of full disclosure: None.

P-14-004 Associations between NFKB and NFKBIL1 polymorphisms and autistic-like traits in a Swedish population of twins

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Objective: Autism spectrum disorders are a complex group of neurodevelopmental disorders which are characterized by impairments in social interactions and both verbal and nonverbal communication. The immune system has been suggested to be of importance for the development of neuropsychiatric symptoms; for example, elevated levels of cytokines and the inflammation-related transcription factor nuclear factor kappa-B (NFKB) have been reported in autistic individuals. The aim of this study was to investigate possible associations between single nucleotide polymorphisms (SNPs) in NFKB and NFKB inhibitor-like protein 1 (NFKBIL1) and autistic-like traits in a Swedish population of twins.

Methods: The subjects in this study (n=12426, 9–12 years old) are from "The Child and Adolescent Twin Study in Sweden" (CATSS). Their parents participated in a telephone interview where the children were assessed by the Autism-Tics, ADHD, and Other Comorbidities Inventory (A-TAC) where autistic-like traits are measured using a continuous scale. DNA was extracted from saliva samples and polymorphisms were genotyped. Statistical analyses were performed in the SAS 9.3 (SAS Institute, Inc., Cary, NC) softwear.

Results: Four out of the five investigated SNPs (NFKB: rs4648022; NFKBIL1: rs2230365, 2239797 and rs2857605) showed significant associations with the A-TAC total autistic-like traits score.

Conclusion: To our best knowledge, polymorphisms in the genes encoding NFKB and NFKBIL1 have not been studied previously in relation to autism. These proteins may be involved in neuronal development and our findings support the hypothesis of the immune system being important in the aetiology of neuropsychiatric symptoms.

Policy of full disclosure: None.

P-15. Attention deficit disorders A

P-15-001 Adolescent exposure to methylphenidate attenuates successive negative contrast and evoked dopamine efflux in the rat nucleus accumbens

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Objective: Repeated exposure to and subsequent withdrawal from psychostimulants may mimic specific psychological symptoms of depression, including decreased interest in normally rewarding stimuli. The growing use of the psychostimulant methylphenidate (MPH) to treat attention-deficit/ hyperactivity-disorder, especially in young children, has raised concerns of safety and long-term consequences in adulthood. However, to date, there is sparse evidence of mood disorders or increased incidents of addictive behavior in individuals treated previously with MPH. The present study examined the effects of adolescent exposure to MPH on successive negative contrast in rats trained to lick for sucrose solutions. Microdialysis was employed to assess any latent effects of MPH treatments on dopaminergic responses evoked by a challenge dose of MPH.

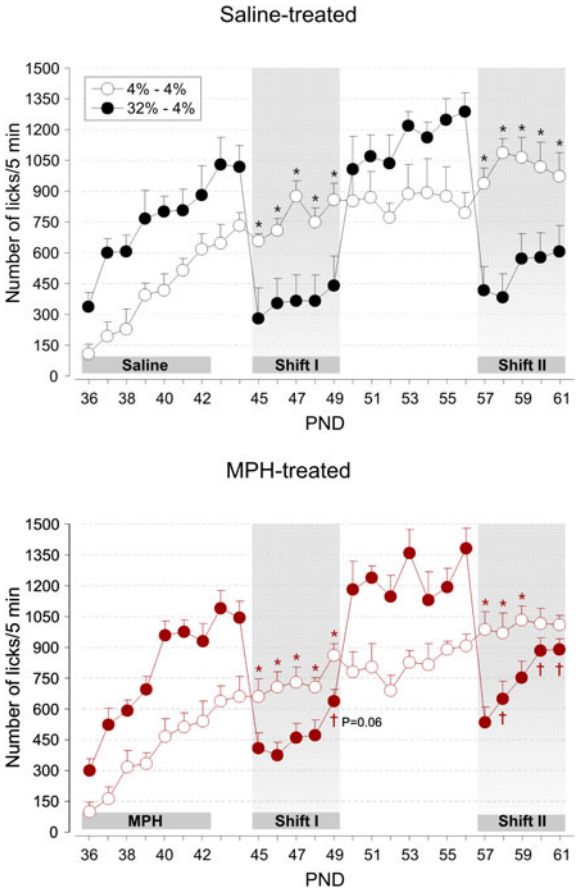
Methods: Adolescent rats were trained to drink either a 4% or 32% sucrose solution from postnatal day (PND) 36–61. During the first week (PND 36–42), rats were also treated with daily MPH (2 mg/kg, ip). For a period of 5-days, starting at 3 days and then at 2 weeks post-MPH treatment, we compared consumption of 4% sucrose in rats trained to drink 4% with those that experienced a downshift from 32% to 4% sucrose. Microdialysis was employed 10-days later to examine the effects of MPH (2 mg/kg, ip) on DA efflux in the nucleus accumbens.

Results: An unexpected change from a 32% to 4% sucrose solution during the first downshift period elicited more licks in MPH-treated rats than saline-controls, with the negative contrast effect becoming further diminished during the second period of downshift (i.e., sucrose ingestion returned to control values more quickly in rats pre-treated with MPH). MPH-evoked increases in DA efflux in the NAc were significantly attenuated in MPH-treated rats compared to saline-controls.

Conclusion: Repeated exposure of rats to MPH during adolescence lead in adulthood to an attenuated negative contrast effect. This finding differs from an enhancement of 'negative contrast', observed in adult rats. Furthermore, the attenuation in the magnitude of MPH-evoked DA efflux in rats pre-exposed to MPH, suggests a long-lasting change in activation of the mesolimbic DA system that may influence motivational responses to natural and drug rewards.

Policy of full disclosure: Supported by operating grants from Canadian Institutes of Health Research to AGP.

Effect of adolescent exposure to MPH on successive negative contrast:



P-15-002 Evaluation of self-perception of individuals with ADHD before and after the use of lisdexamfetamine dimesylate (Vyvanse)

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Objective: This study sought to evaluate the impression of ADHD patients in the areas of work/school, social and family life of the Sheehan Disability Scale before and after the use of dexamphetamine dimesylate.

Methods: Fifty eight pacients that had been previously diagnosed with ADHD through screening, application of the SNAP-IV or ASRS-18 questionnaire and psychiatric interview and that were under treatment withdexamphetamine dimesylate in doses of 30 or 50 mg/d for at least one month have participated on the evaluation. The questionnaires (SNAP IV and ASRS 18), the same utilized on the inicial screening for the ADHD diagnostic, were sent by e-mail with questions regarding the perception of the pacient and/or the caretaker, after the use of dexamphetamine dimesylate, on matters related to work and/or study as well as social and family life, and Sheehan Disabity Scale was used for analysis of the answers.

Results: In our sample of 22 patients, we observed that patients, 30 days after initiation of treatment with lisdexamfetamine, reported improvement in symptoms measured by the scores of the spheres of the Sheehan Disability Scale. There was a reduction in scores work/school in 82% of cases, social life in 77% and family life 55%. Analyzing the total, work/school sphere was the one with a higher percentage of symptoms reduction in their perception (82%).

Conclusion: In our sample of 58 patients, we observed that patients, 30 days after initiation of treatment with lisdexamfetamine, reported improvement in symptoms measured by the scores of the spheres of the Sheehan Disability Scale. There was a reduction in scores work/school in 82% of cases, social life in 77% and family life 55%. Analyzing the total, work/school sphere was the one with a higher percentage of symptoms reduction in their perception (82%).

Policy of full disclosure: None.

P-15-003 Treatment of attention in children with mild intellectual disability

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Objective: Attention deficit in children with mild intellectual disability is being considered fundamental cognitive deficit that endangers activities of daily living.

Methods: Aim of this research is to determine the quality of attention components in children with mild intellectual disability and to suggest several modes to treat this ability. Sample includes 105 subjects with mild intellectual disability, age 10 to 15, both genders, absence of somatic, neurological and emotional disturbances.

Results: For selectivity of attention development level assessment, Stroop test is being used. Pearson's coefficient of linear correlation is determined, r=+0.73 (words) and r=+0.71 (colors), which is significant at level 0.01. We find that longer time needed to complete the test causes larger number of mistakes that are made. Attention flexibility research in children with mild intellectual disability is conducted with Trail Making Test. Low level of positive correlation is determined (r=+0.40, level 0.01) between test variables, so we conclude that examinees that do the test more quickly, make less mistakes.

Conclusion: Treatments for improving quality of attention in children with mild intellectual disability should be made according to symptomatology of each individual. There are two basic treatment approaches: pharmacological and behavioral. Methylphenidate therapy can efficiently reduce attention problem in children with mild intellectual disability. Discontinuation of medical treatment leads to interruption of benefits that are achieved in improving this ability. Using alternative treatments such as behavioral therapy and neurofeedback has advantages. Symbiosis of medical and behavioral treatment gives best results in treating attention in children with mild intellectual disability.

Policy of full disclosure: Abstract represents the result of two projects: "Creating Protocol for assessment of educational potential in children with development difficulties as criteria for creating an individual educational programs" (No. 179025) and "Social participation of persons with intellectual disability" (No. 179017), which are being funded by The Ministry of education, science and technological development, Republic of Serbia.

P-15-004 Acoustic noise benefit a common feature of the attention deficit hyperactivity disorder phenotype? – Evidence from motor learning in spontaneously hypertensive rats

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Objective: In addition to attention deficits and hyperactivity it is common for children with ADHD to display impaired fine and gross motor skills which increases the burden further in an academic setting. Recent findings indicate that acoustic loud white noise (80 dBA) improves cognitive performance in children with low attention. In this study, we explored if the ADHD rat model the Spontaneously Hypertensive Rat (SHR) displayed similar noise benefit as that observed in children with low attention.

Methods: Effects of acoustic white noise compared to ambient silence on skilled reach and Rotarod running were investigated in male SHR (noise n=15, silence n=16) and Wistar SCA controls (noise n=12, silence n=16). Each animal were trained 15 minutes in the Montoya staircase and ran a total of four trials on the Rotarod each day for a total of 10 days. In parallel experiments the effect of methylphenidate (MPH, SHR n=12, Wistar n=8) compared to NaCl (SHR n=12, Wistar n=12) on motor learning was investigated using the same motor learning paradigms. The number of pellets consumed each day and the latency to fall of the Rotarod was used in the statistical analysis.

Results: As previously reported SHR displayed impaired acquisition of skilled reach and Rotarod running compared to Wistar controls. Acoustic noise restored motor learning in the SHR learning skilled reach and Rotarod running but had no influence on learning in Wistar rats. MPH completely restored the performance on the Rotarod but had no effect on skilled reach learning in the SHR.

Conclusion: Results from this study suggests that rats with the ADHD phenotype share the noise benefit previously reported in children with low attention, the effect was in the same range as MPH medication. Acoustic noise may be useful as an alternative treatment to stimulant medication in the management of ADHD.

Policy of full disclosure: Göran Söderlund is the co-founder of a company that develops a noise improvement tool to utilize the positive effects of noise.

P-16. Anxiety disorders and phobias

P-16-001 Dependence on benzodiazepines in patients with panic disorder: A cross-sectional study

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Objective: The aim of this cross-sectional study was to examine the prevalence of psychological dependence on benzodiazepines in outpatients with panic disorder and elucidate demographic and clinical characteristics associated with this condition.

Methods: This study was conducted in four outpatient clinics in Tokyo, Japan from November, 2012 to November, 2013. Subjects were eligible if they were outpatients aged 18 years or older and met the diagnostic criteria for panic disorder according to the International Classification of Diseases, 10th edition (ICD-10). The subjects received the following assessments: the Severity of Dependence Scale, Japanese Version (SDS), the Self-Report Version of Panic Disorder Severity Scale, Japanese Version (PDSS-SR), and the Quick Inventory of Depressive Symptomatology-Self Report, Japanese Version (QIDS-SR). The following information was also collected: age, sex, ethnicity, duration of illness, physical and psychiatric comorbidities, and details of prescribed psychotropic medications.

Results: Fifty-one patients participated in this study; of these, 31 patients (60.8%) showed psychological dependence on benzodiazepines (i.e. a total score of #5 in the SDS). The proportion of patients with dependence (i.e. a total score of #4 in the PDSS) was significantly lower in remitted patients (44.1%, N=15/34) than those who were not in remission (94.1%, N=16/17) (Pearson chi-squares=11.9, $p<0.001$). A multiple regression analysis showed that the PDSS scores showed a positive correlation with the SDS total scores (#=0.60, 95% confidence interval=0.17–0.50, $p=0.0001$), while other factors failed to show any significant association.

Conclusion: These findings emphasize the need of enhanced awareness toward benzodiazepine dependence in both patients and psychiatrists as well as close attention especially to patients with panic disorder who present severe symptomatology.

Policy of full disclosure: Dr. Fujii has nothing to disclose. Dr. Suzuki has received manuscript or speaker's fees from Astellas, Dainippon Sumitomo, Eli Lilly, Elsevier Japan, Meiji Seika, Novartis, Otsuka, and Weily Japan within the past three years. Dr. Mimura has received grants and/or speaker's honoraria from Asahi Kasei Pharma, Astellas Pharmaceutical, Daiichi Sankyo, Dainippon-Sumitomo Pharma, Eisai, Eli Lilly, GlaxoSmithKline, Janssen Pharmaceutical, Meiji-Seika Pharma, Mochida Pharmaceutical, MSD, Novartis Pharma, Otsuka Pharmaceutical, Pfizer, Shionogi, Takeda, Tanabe Mitsubishi Pharma, and Yoshitomi Yakuhin within the past three years. Dr. Uchida has received grants from Pfizer, Astellas Pharmaceutical, Eisai, Otuka Pharmaceutical, GlaxoSmithKline, Shionogi, Dainippon-Sumitomo Pharma, Eli Lilly, Mochida Pharmaceutical, Meiji-Seika Pharma, Janssen Pharmaceutical, and Yoshitomi Yakuhin and speaker's honoraria from Otuka Pharmaceutical, Eli Lilly, Shionogi, GlaxoSmithKline, Yoshitomi Yakuhin, Dainippon-Sumitomo Pharma, Meiji-Seika Pharma, Abbvie, and Janssen Pharmaceutical within the past three years.

P-16-002 Establishment of a social interaction test using a 3-chamber system for rats

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Objective: Social interaction test has been generally evaluated as index of social behaviors performed between two experimental animals. In this study, we established a new social interaction test using a 3-chamber openfield system to examine the social behavior of a rat.

Methods: A rat had been acclimated for 2 days in the square-shaped open-field system in which two stranger cages (SCs) without rats were installed. After acclimation to the open-field system, we measured the time required for the rat to approach the SC in which a rat was placed by visual observation or video tracking analysis in the test trial.

Results: To evaluate the effects of lighting, social behavior was examined under dark (5 lux) and bright conditions (350 lux). Under the dark condition, the time required for the rat to approach the SC in which a rat was placed based on active contact was significantly longer than that measured by visual observation under the bright condition. In addition, video tracking analysis using imaging data also showed a similar tendency. Briefly, this result was similar to that obtained by visual observation. In the social interaction test using the 3-chamber system, the time required for the rat to approach the SC in which a rat was housed (social interaction time), which was measured by visual observation, was correlated with that by video tracking analysis. On the other hand, anxiolytics, tandospirone (3 mg/kg, i.p.) and diazepam (0.3 mg/kg, i.p.), significantly increased the time required to approach the SC in which a rat was housed, without influencing spontaneous locomotor activity.

Conclusion: In conclusion, this study showed the behavioral-pharmacological validation of this social interaction test to measure innate anxiety and social behavior using a 3-chamber system in rats. In addition, this evaluation system may contribute to the development of new therapeutic drugs for psychiatric diseases, including anxiolytics.

Policy of full disclosure: None.

P-17. Transcultural psychopharmacology

P-17-001 Effects of antidopaminergic intervention on catecholamine metabolites in plasma and urine in healthy volunteers

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Objective: The need for a better understanding of the effects of antipsychotic drugs on monoaminergic neurotransmission have led to several examinations of their influence on the relatively easily accessible catecholamine metabolites in plasma and urine as possible markers for psychosis and antipsychotic response. Up to now, such examinations, mainly performed in patients with schizophrenia, resulted in inconsistent, partially opposed results.

Methods: In this single-blind, randomized, placebo-controlled, parallel group study we investigated the changes of the peripherally measurable catecholamine metabolites following seven days administration of three antipsychotics with entirely different mechanism of action (aripiprazole, haloperidol and reserpine), and their relationship to physiology and behaviour in 72 healthy volunteers.

Results: A repeated measures ANOVA revealed a statistically significant time*group interaction for homovanillic acid (HVA) ($p=0.008$) and vanillic mandelic acid (VMA) ($p=0.019$) in urine and 3-methoxy, 4-hydroxyphenylglycol (MHPG) in plasma ($p=0.003$). In detail, reserpine caused the strongest increase of HVA and MHPG, while aripiprazole caused a most pronounced VMA increase. Further, strong positive associations, remaining statistically significant even after Bonferroni adjustment, were found for the HVA plasma concentration measured after the pharmacological challenge and PANSS scores (PANSS total: $r=0.570$, $p<0.001$; PANSS negative: $r=0.498$, $p<0.001$; PANSS cognitive: $r=0.553$, $p<0.001$) as well as the HAMD score ($r=0.423$, $p=0.003$). Furthermore, we found a strong negative correlation between the HVA concentration and the self-assessment (rated using the visual analogue scale) of achievement potential ($r=-0.466$, $p=0.001$), the ability to concentrate ($r=-0.569$, $p<0.001$), and the general well-being ($r=-0.550$, $p<0.001$).

Conclusion: Our results point to a robust association between different aspects of psychopathology and catecholamine metabolites after antidopaminergic intervention in healthy volunteers. Those metabolites represent the central monoaminergic neurotransmission only to a limited extent. However, our observation, requiring further replication, could be a valuable contribution to a better understanding of the neurobiological basis of different psychopathological phenomena.

Policy of full disclosure: None.

P-18. Neuroimaging A

P-18-001 Neural basis of embarrassment of self-face recognition in patients with social anxiety disorders: A functional magnetic resonance imaging study

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Objective: Although social anxiety disorder (SAD) is highly prevalent, the neural mechanism is yet unknown. We conducted a functional magnetic resonance imaging (fMRI) study, using tasks involving self-conscious emotions. In an earlier study, it was proven that, in healthy individuals,

the emotion of embarrassment, upon viewing self-face images, increased when they were exposed to observations by others, and the activation in the right anterior insula was consequently increased. We had expected that, in patients with SAD, the emotion of embarrassment would become larger than that of healthy individuals and be further increased during exposure to other's observations, and that increases of activation in the right anterior insula would appear more prominently.

Methods: Five patients with SAD and eight healthy individuals participated. Brain activities were measured with Siemens 3T MRI when photographic images of self-face and other-faces, which had been randomly preselected from a video image, were presented and the subjects rated the degree of embarrassment they felt upon viewing each image. We created two comparison conditions, in one the participants were exposed to other's observations, and in the other without observations. This study was approved by the ethic committee of Nagoya City University and all the participants gave written informed consent.

Results: This study demonstrates that patients with SAD have stronger emotion of embarrassment upon viewing self-face images. As a result, self-face related brain activities increased (self-face related activities minus other-face related activities) in the regions involved with emotion of embarrassment (such as insula, cingulate cortex, and so on), while we observed, by contrast, reduction in activities in the right premotor regions involved in self-face recognition process.

Conclusion: Our data indicates that patients with SAD have strong emotion of embarrassment of their own faces, and their abilities in the self-face recognition process may be decreased.

Policy of full disclosure: None.

P-18-002 Structural magnetic resonance imaging study in patients with social anxiety disorder in Japan

T. Kawaguchi[1], A. Kawaguchi[1]. [1]*Nagoya City University, Nagoya, Japan*

Objective: Despite the fact that social anxiety disorder (SAD) is highly prevalent, few structural imaging studies have been conducted. Studies using the method of region-of-interest have reported decreases of hippocampal/amygdala volumes in patients with SAD. We have also reported cases in which increases of right hippocampal volumes were observed in comparison before and after group cognitive behavioral therapy. On the other hand, a study using the vosel-based morphometry (VBM) (Potts et al. 1994) concluded that no significant difference was found. However, Talati et al. reported abnormalities in the volumes of gray matters based on VBM. As described above, there has been no fixed theory obtained in the structural imaging studies. Moreover, these studies were conducted in European and North American subjects, although there are cultural differences in the characteristics of SAD between Asians and Europeans/North Americans. In the present research, we made comparison between Japanese patients with SAD and healthy individuals based on VBM.

Methods: The subjects of our research were 13 patients who had been diagnosed with SAD and 13 healthy individuals. We obtained magnetic resonance images with Siemens 3T for VBM analysis using Statistical Parametric Mapping 8 (SPM8). This study was approved by the ethics committee of the Nagoya City University, and conducted with written consent provided by all the participants.

Results: From this analysis, we did not find a significant statistical difference at the cluster level, or observe remarkable differences in hippocampus-amygdala regions, which had been reported in earlier studies.

Conclusion: The fact that no significant difference was found in this study conforms to the research result presented by Potts et al. We, however, assume that it may be because of the number of cases being small, and that more number of cases need to be collected for reanalysis in the future.

Policy of full disclosure: None.

P-18-003 Silexan (WS® 1265) reduces serotonin-1A receptor binding in vivo

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Objective: Silexan (WS® 1265)*, a patented active substance comprised of an essential oil produced from Lavandula angustifolia flowers, has been authorized in Germany as herbal medicinal product for the treatment of states of restlessness related to anxious mood and its effectiveness has been shown in several forms of anxiety disorders. The serotonin-1A receptor (5-HT1A) was shown to play a major role in the pathogenesis and treatment of anxiety disorders.

Methods: To elucidate the effect of Silexan on 5-HT1A receptor binding, 17 healthy men (mean age±SD=25.1±3.6 years) underwent 2 positron emission tomographies (PET) using the radioligand [carbonyl-11C] WAY-100635 following the daily intake of 160 mg Silexan or placebo over a minimum of 8 weeks, respectively (randomized, double-blind, cross-over design). PET scans were normalized to MNI-space (SPM8). Quantification of 5-HT1A receptor binding potential was carried out in PMOD 3.3 using SRTM2 and the cerebellar grey as reference region.

Results: Voxel-wise repeated-measures ANOVA including the sequence (Silexan-placebo versus placebo-Silexan) as co-variate revealed a significant decrease of 5-HT1A receptor binding potential following the intake of Silexan compared to placebo in two large clusters encompassing the temporal gyrus and the fusiform gyrus, the hippocampus on one hand ($k=5334$, peak t value=6.64, $p<0.05$, FWE corrected at cluster-level) as well as the insula and the anterior cingulate cortex on the other hand ($k=4812$, peak t value=6.08, $p<0.05$, FWE corrected at cluster-level).

Conclusion: This PET study shows a reduced 5-HT1A receptor binding in healthy subjects following the daily administration of 160 mg of Silexan compared to placebo. This is in agreement with SSRI- or ECT-induced reduction in 5-HT1A binding. These findings propose an involvement of the 5-HT1A receptor in the anxiolytic effects of Silexan. *Silexan is the active substance of Lasea®, manufacturer: Dr. Willmar Schwabe GmbH&Co.KG, Karlsruhe, Germany.

Policy of full disclosure: None.

P-18-004 Effect of early stress on hippocampal gray matter is influenced by a functional polymorphism in EAAT2 in bipolar disorder

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Objective: Current views on the pathogenesis of psychiatric disorders focus on the interplay between genetic and environmental factors, with individual variation in vulnerability and resilience being part of the development of illness. The aim of the present study is to investigate the effect of glutamate transporter polymorphism and exposure to adverse childhood experiences (ACE) on hippocampal gray matter volume of patients with bipolar disorder (BD).

Methods: Eighty-six subjects affected by BD were genotyped for EEAT2 -181A>C and severity of ACE was rated on the Risky Families Questionnaire. An analysis of variance, limited to the hippocampus, with genotype and ACE as factors was performed, with age, sex, duration of illness, number of episodes and handedness as possible confounding factors. Statistical threshold was $P<0.05$ corrected for multiple comparisons with whole-brain family-wise error (FWE) correction.

Results: Patients exposed to higher levels of ACE had lower gray matter volume. The effect of SLC1A2-181A>C revealed itself only among patients exposed to lower levels of ACE, among whose T/T homozygotes showed the lowest, and G/G the highest, gray matter volume.

Conclusion: This is the first study to show a joint effect of both ACE and SLC1A2-181A>C on hippocampal volume. The greatest difference between high and low exposure to ACE was observed in carriers of the G allele which reported significantly higher gray matter volume when exposed to less stress. Since the mutant G allele has been associated with a reduced transcriptional activity and expression of the transporter protein, we could hypothesize that after exposure to highest levels of ACE G/G homozygotes are more vulnerable to stress and report the highest damage to brain volume as a consequence of an excess of free glutamate.

Policy of full disclosure: None.

P-18-005 Reduced insulin sensitivity is related to less endogenous dopamine at D2/3 receptors in the ventral striatum of healthy non obese humans: Preliminary findings with [11C]-(+)-PHNO

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Objective: The conceptualization of obesity in relation to food addiction remains a widely debated topic in neuroscience. Rodent models of diabetes suggest reduced basal dopamine levels in the nucleus accumbens, similar to that seen in models of drug addiction. However, it is not known whether insulin sensitivity is related to endogenous dopamine levels in the ventral striatum (VS) of humans. Using the agonist dopamine

D2/3 receptor (D2/3R) radiotracer [11C]-(+)-PHNO, and an acute dopamine depletion challenge, we sought to determine whether baseline D2/3R availability and estimated endogenous dopamine levels at D2/3R in VS are related to estimates of insulin sensitivity in otherwise healthy persons.

Methods: Eleven healthy, non-obese and non-diabetic persons (3 female) participated in the study. Eleven participants provided a baseline [11C]-(+)-PHNO scan, while nine of these subjects also provided a scan under acute dopamine depletion, allowing estimates of endogenous dopamine occupying D2/3R at baseline. Acute dopamine depletion was achieved via oral administration of alpha-methyl-para-tyrosine (64 mg/kg) as previously described by our group. The insulin sensitivity index was estimated for each subject from fasting plasma glucose and insulin using the Homeostasis Model Assessment II (HOMA2).

Results: Baseline [11C]-(+)-PHNO BPND in the right VS was negatively correlated with estimated insulin sensitivity ($r(10) = -0.65$, $p=0.02$). Notably, [11C]-(+)-PHNO BPND in the left VS was not correlated with insulin sensitivity ($r(10) = -0.35$, $p=0.29$). In the nine subjects who also provided a scan under dopamine depletion, estimated baseline dopamine occupancy at D2/3R in the VS was positively correlated with insulin sensitivity ($r(8)=0.84$, $p=0.005$). This relationship was driven primarily by dopamine occupancy in the right VS ($r(8)=0.75$, $p=0.01$), but not in the left VS ($r(8)=0.41$, $p=0.28$).

Conclusion: In keeping with previous rodent studies, we demonstrate novel findings which suggest that a decreased index of insulin sensitivity is associated with reduced baseline endogenous dopamine levels at D2/3R in the ventral striatum of healthy persons. Given our small sample size, it will be important to replicate these findings in healthy persons, as well as persons with co-morbid metabolic and neuropsychiatric diseases.

Policy of full disclosure: None.

P-18-006 Of pig and man: Analogy of response to electroconvulsive therapy (ECT): Most do, a few don't

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Objective: ECT although recognized as the most effective treatment for depression, still has positive response rates between 70 and 80 percent. Reasons for this differential response rate range from the nature of the seizure to patient presentation. We aimed to evaluate in parallel, in a controlled setting and in normal minipigs, the response of the dopaminergic (DA), noradrenergic (NA) and serotonergic (5HT) systems, to a clinical course of ECT by PET.

Methods: Seven isofluorane-anesthetized Gottingen minipigs underwent PET scanning with 11C-SCH23390 (tracer of DA D1 receptors), 11C-yohimbine (tracer of alpha2 adrenergic receptors) and 11C-MDL100,907 (tracer of 5HT2 serotonergic receptors) at baseline, 24–48 hrs post and 8–10 days after the end of ECT. The animals received a clinical course of 10 bilateral ECT (Thymatron device), 3 times a week, under ketamine sedation followed by intravenous thiopental and succinyl choline. PET data were routinely analyzed (Logan linear analysis for SCH23390 and yohimbine and ratio striatum/cerebellum for MDL100,907.) For yohimbine and MDL100,907, binding was evaluated in 7 regions: frontal, temporal and occipital cortices, thalamus, striatum, hippocampus and amygdala. Only striatal binding was considered for SCH23390.

Results: Binding data were analyzed using a standard repeated measures design with polynomial contrasts to determine differences in mean levels pre- and post-ECT. However, for all three tracers, the data violated the assumptions of the general linear model. Subsequent examination of the data indicated that two animals (28%) had almost opposite responses to ECT in comparison to the other five (72%) for the 5HT and NA systems. In contrast, for the DA system, all seven animals had similar responses but varied markedly in the magnitude of response.

Conclusion: These data suggest that even in a very controlled setting, differential responses in neurotransmitter systems to ECT are common and may not entirely reflect stimulation parameters, seizure characteristics or individual pathology but innate sensitivities of the monoaminergic systems.

Policy of full disclosure: None.

P-18-007 Early changes in neural responses to emotional information predict clinical response to antidepressant treatment in depression

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Objective: To test whether early changes in emotional bias are predictive of response to antidepressant treatment. Antidepressant treatment has been shown to modulate behavioural and neural markers of negative affective bias, before therapeutic changes in mood are seen. It has been hypothesised that early changes in emotional processing are an important mechanism which mediates clinical improvement over time by allowing a more positive response to on-going environmental stimuli.

Methods: 32 unmedicated patients meeting DSMIV criteria for major depression were treated with escitalopram 10 mg over 6 weeks. The neural response to emotional facial expressions was assessed both before and after 7 days of treatment. Depression severity was measured before treatment, 7 days and after 6 weeks using the Beck Depression Inventory (BDI). Small volume correction was applied during fMRI analysis to assess if early change in key areas identified through previous studies predicted clinical change after 6 weeks.

Results: BDI scores fell an average of 17.5 points after the 6 weeks treatment. This response was predicted by decreased amygdala response to fearful facial expressions after 7 days of treatment. The decreased amygdala response was predictive of 6 week clinical response and survived entering baseline or one week change in BDI scores as a co-variate.

Conclusion: SSRIs have previously been reported to decrease amygdala response early in treatment in depressed patients and compared to a placebo control. The current study shows that these early changes are predictive of later clinical response as supported by the cognitive neuropsychological model of antidepressant drug action. These data therefore add support to the idea that early changes in emotional processing have clinical significance which is expressed with a time delay, following environmental exposure and a period of learning in the context of a reduced negative bias.

Policy of full disclosure: None.

P-19. Others A

P-19-001 The importance of anesthetic algorism of modified ECT, focused on strict control of intravenous anesthetic concentration

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Objective: It is important to induce qualitatively effective convulsive brain waves under proper sedation and cardiovascular stability during modified electroconvulsive therapy (mECT). However, many anaesthetic agents such as propofol and thiopental used for mECT have anti-convulsant properties and their sedative doses were differences among individuals. We prepared an algorism to modify anesthetics dose-setting and a level of electrical stimulus (ES energy) correlatively under the qualitative appraisal of convulsive brain waves, and assessed the usefulness.

Methods: Subjects included 53 patients who went through the first one Kur of mECT between April 2013 and October 2014 after obtained approval from institutional ethical committee. 450 mECT sessions were evalated. Anesthesia was induced with propofol and remifentanil target-controlled-infusion (TCI) using TIVA-trainer ver. 8 and monitored with bispectral index (BIS). Following rocuronium injection, pressure controlled ventilation was adjusted to maintain the end-tidal carbon-dioxide between 30 and 34 mmHg. According to the algorism, an ES was applied to elicit a seizure with monitoring electroencephalographic. Quality and duration of convulsive brain waves, their relationship with BIS values, hemodynamic change before and after ES.

Results: In 448 cases (99.6%) out of 450 cases, qualitatively effective convulsive brain waves were induced. The needed number of times of ES was 1 in 434 cases, 2 in 13, and 3 in 3. Duration of convulsive brain waves was shorter when the quality of postical suppression was high, and not correlated with BIS values. On the other hand, according to anesthetics dose-settings, significant differences were observed in hemodynamic change before and after ES, and in the frequency of cardiovascular agonists or antagonists injection before ES.

Conclusion: While countermeasures to circulation fluctuations were needed according to anesthetics dose-settings, the algorism resolved the most important pending problems on mECT for the most part.

Policy of full disclosure: None.

P-19-002 PACAP-PAC1 signaling pathway regulates internalization of serotonin 2A receptor in a protein kinase C and beta-arrestin2 dependent manner

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Objective: A growing number of human genetic and animal model studies implicate the pituitary adenylate cyclase-activating polypeptide (PACAP) signaling pathway as a risk factor for psychiatric disorders such as schizophrenia and stress-related disorders. PACAP-deficient mice show notable psychomotor abnormalities and neurological changes that are thought to be endophenotypes for psychiatric disorders. Most of them are reversed by risperidone, an atypical antipsychotic drug with serotonin (5-HT)2 receptor and dopamine D2 receptor antagonist properties, and ritanserin, a selective antagonist for 5-HT2 receptor. These findings indicate that 5-HT2 receptor signaling is involved in psychiatric conditions in which PACAP signaling is dysfunctional, although the underlying mechanisms remain unclear. Since it is known that 5-HT2A receptor functions are regulated by receptor internalization, in this study we examined whether PACAP signaling modulates the internalization of 5-HT2A receptor.

Methods: The internalization of 5-HT2A receptor expressed in HEK293T cells was investigated using the HaloTag system. The HaloTag protein labeling technology is widely used for living cell imaging and protein analysis.

Results: PACAP induced internalization of 5-HT2A as well as PAC1 receptor in a dose- and time-dependent manner. In contrast, PACAP did not affect internalization of 5-HT1A receptor. Moreover, pretreatment with the PKC inhibitor sphingosine considerably inhibited PACAP-induced internalization of 5-HT2A receptor. Furthermore, beta-arrestin2 siRNA significantly blocked PACAP-induced internalization of 5-HT2A receptor.

Conclusion: Taken together, these results suggest that the PACAP-PAC1 pathway regulates 5-HT2A receptor internalization in a PKC and beta-arrestin2 dependent manner. This functional crosstalk implies the possibility that endogenous PACAP in the brain critically regulates 5-HT2 receptor signaling, altered regulation of which may be involved in the development of psychiatric disorders. Our results give new insights into the mechanisms underlying the therapeutic effects of antipsychotic drugs.

Policy of full disclosure: None.

P-19-003 Changes in extracellular contents of D-serine and D-serine-NMDA receptor-associated amino acids by selective suppression of serine racemase expression in forebrain glutamatergic neurons

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Objective: In mammalian brains, D-serine plays a pivotal role in glutamate neurotransmission as an endogenous co-agonist for the N-methyl-D-aspartate receptor (NMDAR), which is essential for the expression of higher-order brain functions. However, the exact molecular and cellular mechanisms underlying the regulation of the extracellular D-serine contents remain unclear. Recently, Coyle and his colleagues demonstrated that the neuron-selective deletion of the gene of a D-serine synthesizing enzyme SR (SR) (nSRCKO) caused a significant reduction by 65% in the tissue SR mRNA expression in the medial prefrontal cortex (mPFC) and hippocampus (HC) and disturbed an induction of NMDA receptor-mediated LTP in the HC. Therefore, we have studied in the nSRCKO mouse the extracellular levels of D-serine and NMDA receptor function in the HC or mPFC.

Methods: Male and female nSRCKO mice (Benneyworth et al. 2012) were used. We monitored extracellular contents of various chiral and non-chiral amino acids by applying an in vivo microdialysis technique in combination with high-performance liquid chromatography with fluorometric detection.

Results: The extracellular contents of D-serine were significantly diminished by 47% in the HC, but not mPFC. In these brain regions, there were no significant alterations in tissue and extracellular contents of L-serine, a precursor for D-serine, and glycine, another co-agonist for the NMDAR. NMDA receptor function was examined by basal and NMDA-induced levels of extracellular taurine contents before and after an intra-dialysis-tubing infusion of NMDA. Basal extracellular taurine levels in nSRCKO HC (before NMDA) were significantly decreased. Furthermore, the maximum absolute value of taurine after NMDA perfusion into the HC in nSRCKO was much lower than that of control.

Conclusion: These data indicate that neuronal SR plays a substantial role in the control of extracellular D-serine levels and that decreased D-serine contents lead to hypofunction of the NMDAR, at least, in the HC.

Policy of full disclosure: None.

P-19-004 Impact of chemotherapy on subjective cognitive function in patients with breast cancer: A cross-sectional study

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Objective: Chemotherapy was reported to induce mild to moderate impairment in cognitive function in patients with breast cancer. However, they did not include any assessment of subjective cognitive function while they mainly focused on objective one. Given the fact that it is patients with breast cancer who recognized and reported this impairment for the first time, subjective cognitive function needs to be examined to elucidate the cognitive impairment potentially induced by chemotherapy.

Methods: This cross-sectional study included females with breast cancer who underwent chemotherapy within four weeks ahead of the screening. Subjective cognition was assessed using the Cognitive Failures Questionnaire (CFQ), Dysexecutive Questionnaire (DEX), and Everyday Memory Checklist (EMC). Objective cognitive measures included the Behavioral Assessment of the Dysexecutive Syndrome (BADS) and Rivermead Behavioral Memory Test (RBMT).

Results: 14 subjects were included (age=53.8±8.8 years; duration of illness=456±954 days; stage I=2, IIa=4, IIb=3, IIIa=2, IIIb=1, IV=1, unclear=1). The total BADS score (16.9±4.7) was comparable to normal data (t13.6=1.20, p=0.25). The total scores in the patient-version DEX (8.3±9.7) and family-version DEX (8.8±9.79) showed a trend correlation (r=0.50, p=0.07). The total score in the patient-version EMC (6.1±4.5) was lower than normal data (t82=2.38, p=0.02) and showed a trend correlation with that in the family-version EMC (4.8±5.0) (r=0.52, p=0.05). The total RBMT score (21.8±2.7) was comparable to normal data (t82=0.27, p=0.79). The total CFQ score (25.4±10.9) was lower than the normal (t15.5=6.80, p<0.001).

Conclusion: Patients with breast cancer did not show any significant subjective impairment in executive function, memory, and attention within four weeks after chemotherapy. Prospective studies are warranted to explore long-term changes in subjective cognitive function in this population following chemotherapy.

Policy of full disclosure: None.

P-19-005 A catatonia model as dysregulated glutamatergic cortico-thalamic-cortico neurotransmission

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Objective: Development of a parsimonious neurobiological model of the catatonic syndrome.

Methods: 1. Description and biology of catatonia associated associated with phencyclidine (PCP) intoxication and anti-NMDA Receptor (anti-NMDAR) antibody encephalitis 2. Review of cortico-thalamic-cortico circuitry 3. Review of catatonia syndrome symptoms with regard to underlying neurobiology 4. Review of catatonia treatments with regard to the described neurobiology.

Results: 1. PCP-induced catatonia and catatonia consequent to anti-NMDAR Ab encephalitis reflect conditions caused by hypoactivity of NMDA receptors (1). 2. Cortical pyrimidal cells project from the frontal cortex (FC) to the ventral tegmental area (VTA) via thalamic relays and regulate tonic dopamine (DA) activity in the receptive fields in the VTA. Recurrent mesocortical (MC) DA neurons feed back to pre-frontal cortical D1 receptors. Via a polysynaptic pathway, cortical glutamatergic (GLT) afferents project to pedunculopontine tegmental (PPT) interneurons neurons stimulate mesolimbic (ML) and nigrostriatal (NS) D2 receptors. MC DA neurons in the FC stimulate GLT projections to VTA and striato-tegmental (ST) gamma-aminobutyric acid (GABA) neurons which inhibit firing of MC and NS DA neurons (2,3). This organization provides for co-modulation of GLT, DA, and GABA pathways (Figure 1). 3. The classic symptoms of catatonia and putative neurologic localization are listed in Figure 2. In terms of its neuropsychiatry, catatonia can be understood conceptually as a psychomotor disorder. Some symptoms, such as mirror

echopraxia (4), can be understood as reflecting mainly cortical-to-subcortical dysregulation. Conversely, symptoms such as rigidity and immobility (5) may reflect subcortical-to-cortical dysregulation. Others may reflect more complex interactions. 4. The most effective treatments for catatonia are ECT and lorazepam (6). Neuroimaging with MRS has suggested that ECT results in higher cortical GLT activity (7) and enhances GABAergic function, at least in depressed patients (8). The often immediate benefits of lorazepam (9) are consistent with collateral modulation of SC DA activity with which then modulate cortical GLT through feedback loops.

Conclusion: Symptoms of catatonia are consistent with dysregulated cortico-thalamic-cortical neurotransnmission. PCP and anti-NMDAR Abs block glutamate receptors. This blockade results in disrupted co-modulation of dopamine activity, glutamate transmission, and GABA function. ECT and lorazepam directly impact these disrupted circuits and are the first line treatments for catatonia.

Policy of full disclosure: None.

P-19-006 The changes in prescription pattern of aripiprazole among psychiatric inpatients

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Objective: We aimed to investigate the changes in prescription pattern of aripiprazole among psychiatric inpatients.

Methods: We compared prescription patterns in inpatients treated with aripiprazole between 2009–2013 and 2002–2008. The subjects' charts were retrospectively reviewed to ascertain the distribution of psychiatric diagnoses and to identify other factors, such as demographic characteristics, starting/maximum doses, and treatment regimen for diagnoses.

Results: Among the patients in the 2009–2013, the most common psychiatric diagnosis was bipolar disorder, although among the patient in 2002–2008, schizophrenia and other psychotic disorder was the most common diagnosis. Patients with schizophrenia and other psychotic disorders, major depressive disorder, and bipolar disorder in the 2009–2013 had significantly lower starting doses than those in the 2002–2008. Maximum doses with schizophrenia and other psychotic disorders in 2009–2013 were significantly higher than those in the 2002–2008, whereas patients with major depressive disorder in 2009–2013 had significantly lower than those in the 2002–2008. Aripiprazole monotherapy decreased from 16.7% to 2.7% in schizophrenia and other psychotic disorder. The polypharmacy increased from 21.4% to 47.3% in bipolar disorder.

Conclusion: Treatment with aripiprazole has extended in indication beyond schizophrenia and other psychotic disorder to mood disorder and other diagnosis in recent years.

Policy of full disclosure: None.

P-19-007 Korean medication algorithm for depressive disorder: Comparisons with other treatment guidelines

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Objective: The Korean Medication Algorithm Project for Major Depressive Disorder (KMAP-MD) was developed in 2002 and then revised in 2006. In 2012 it was secondly revised to reflect current changes in pharmacotherapy for depressive disorder; Korean Medication Algorithm Project for Depressive Disorder 2012 (KMAP-DD 2012). We aimed to compare KMAP-DD 2012 with other recently published treatment guidelines for depressive disorder.

Methods: We reviewed a total of five treatment guidelines for depressive disorder that included American Psychiatric Association Practice Guideline, Canadian Network for Mood and Anxiety Treatments Clinical Guidelines, The National Institute for Health and Clinical Excellence Guideline, Texas Medication Algorithm Project Procedural Manual, and World Federation Societies of Biological Psychiatry Guidelines. We compared the recommendations of these five guidelines to those of KMAP-DD 2012.

Results: In terms of recommendations for initial treatment strategies, KMAP-DD 2012 is not significantly different from the other five guidelines. However, in case of non-response or partial response to initial treatment, the recommendations varied across treatment guidelines. For the maintenance therapy, the duration of maintenance therapy, and the doses of antidepressants and antipsychotic agents differed among the treatment guidelines. There are some discrepancies in the recommendations for each subtype of depressive disorders across treatment guidelines. For the treatment among special population such as child-adolescent depression, geriatric depression and postpartum depression, there are no significant differences in overall recommendation across guidelines. However, most guidelines other than KMAP-DD 2012 describe the potential risk of antidepressant such as increased suicidality among young population.

Conclusion: This comparison identified that, by and large, the treatment recommendations of KMAP-DD 2012 are similar to those of other treatment guidelines, and reflect current changes in prescription pattern for depression based on accumulated research data. Further studies will be needed for several issues that the treatment guidelines reviewed here cannot draw a definitive conclusion because of lack of evidence.

Policy of full disclosure: None.

P-19-008 Prescribing preferences in rapid tranquillisation. A survey in Belgian psychiatrists and emergency physicians

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Objective: The pharmacotherapeutic management of agitation is a common clinical challenge. Pharmacotherapy is frequently used, the use of published guidelines is not known. The objective of this study was twofold; to describe the prescribing patterns of psychiatrists and emergency physicians and to evaluate to which extent guidelines are used.

Methods: A cross-sectional survey in the Dutch-speaking part of Belgium is carried out in 39 psychiatric hospitals, 11 psychiatric wards of a general hospital and 61 emergency departments. All physicians are asked for demographic information, their prescribing preferences, their use of guidelines and the type of monitoring (effectiveness, safety).

Results: 550 psychiatrist and emergency physicians were invited. The overall response rate was 20% (n=108). The number 1 preferred medication classes were antipsychotics (59.3%) and benzodiazepines (40.7%). In non-secluded patients, olanzapine (22.2%), lorazepam (21.3%) and clotiapine (19.4%) were most frequently picked as number 1 choice drug. In secluded patients, clotiapine (21.3%), olanzapine (21.3%) and droperidol (14.8%) were the three most frequently chosen number 1 preferred drugs. Between-group comparisons show that emergency physicians prefer benzodiazepines significantly more than psychiatrists do. Zuclopenthixol and olanzapine show a particular profile in both groups of physicians. Polypharmacy is more frequently used in secluded patients. Published guidelines and safety or outcome monitoring are rarely used.

Conclusion: Our results show that prescription practice in Flanders (Belgium) in acute agitation shows a complex relationship with published guidelines. Prescription preferences differ accordingly to medical specialty. These findings should be taken into account in future research.

Policy of full disclosure: None.

P-19-009 Cotard's syndrome in glioblastoma patient

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Objective: Brain tumors are often associated with neurological as well as with psychiatric symptoms. Cotard's syndrome is a rare condition characterized with monothematic nihilistic delusions concerning one's own body. It is not listed as a specific disorder in the DSM-IV or in ICD-X, as it is typically viewed as a part of other underlying disorders. Delusions are most commonly related to a loss of specific body part or a body as a whole. Syndrome was described for the first time by Jules Cotard in 1880.g as a new form of agitated melancholy. Although most commonly described as a part of schizophrenia, bipolar disorder or psychotic depression it is also associated with numerous neurological conditions such as encephalitis, Parkinson's disease, migraine, brain tumors, a-v malformations or traumas.

Methods: In this poster we describe 37 years old patient diagnosed with glioblastoma which developed Cotard's syndrome in postoperative care. Patient was operated twice, and treated in post-op care with chemo and radiotherapy.

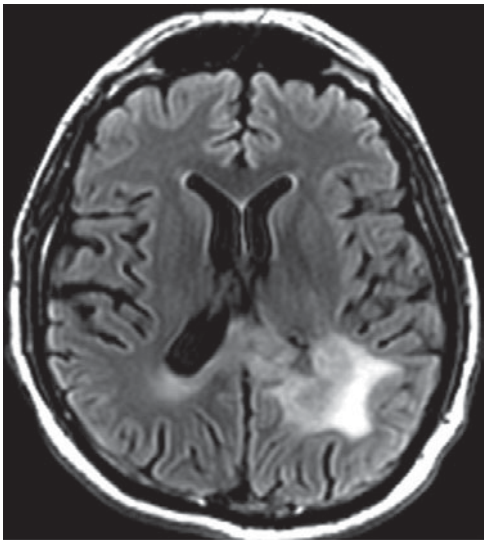
Results: Our patient manifested Cotard's syndrome as negative delusions, stating total absence of his heart and right arm. According to our data search we found Cotard's syndrome rarely associated to glioblastoma. His pharmacotherapy included fluvoxamine, promazine, diazepam, phenobarbital and dexamethasone. His discharge diagnoses (ICD-XI) were: F06.7; F91 because of C71.2 and 3; Brain tumor of right parietooccipital region (PHD glioblastoma multiforme); St. post op and reop; St post

radiotherapy; St post chemotherapy, Sensomotoric dysphasia; Right sided hemiparesis.

Conclusion: It remains important to recognize the syndrome because specific underlying mechanisms are present, and prognostic and therapeutic consequences have to be taken into account.

Policy of full disclosure: None.

Native, T1-weighted axial MRI of glioblastoma:



P-19-010 Similar American and Japanese venous endocrine changes after tobacco smoking

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Objective: Compared to Americans (~18%) there are far more mu opioid receptor (OPRM1) A118G variants in Japanese (~50%). Since this single nucleotide polymorphism (SNP) is important in tobacco smokers, a total of 19 Japanese and 23 American average tobacco cigarette smokers were recruited for a preliminary endocrine study.

Methods: Differences in venous blood nicotine, cortisol, prolactin and dehydroepiandrosterone sulfate (DHEAS) levels were determined before and after tobacco smoking in the overnight abstinent smokers. Adults aged 20 to 43 years of both sexes who smoked daily for many years were studied. The first venous blood sample was taken just before, 10 and 60 min after smoking their favorite cigarette.

Results: Significant increases in nicotine, but only slight increases in cortisol were observed 10 min after smoking. Marked increases in cortisol and prolactin levels were observed 60 min after smoking. Males had greater DHEAS levels than females. No DHEAS smoking differences were found. There were no significant differences in blood nicotine, prolactin, and cortisol at the 60 min measurement between the Americans and Japanese. At 10 min after smoking, the cortisol levels of the Japanese were slightly, but significantly, greater than the Americans ($p=0.05$). In addition, tobacco smoking craving scores were studied in the American smokers in relationship to their genotype of OPRM1 A118G SNPs. Not only smoking average nicotine (avnic) cigarettes but also smoking deniconized (denic) cigarettes significantly decreased craving. The craving scores of GG and GA (*G) carriers after avnic cigarette smoking were more reduced than in the AA allele SNP carriers ($p=0.06$).

Conclusion: This preliminary study indicates no really significant endocrine differences were found between American and Japanese smokers. The OPRM1 genotype SNP differences after favorite tobacco cigarette smoking and craving reduction should be pursued comparing American and Japanese smokers.

Policy of full disclosure: None.

P-19-011 Prevalence of vascular dementia in Upper Egypt

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Objective: The aim of this work was to study the prevalence of vascular dementia and possible risk factors in Upper Egypt.

Methods: All inhabitants of Al Khargah district; New Valley Governorate (n=62,583) and Al Quseir city; Red sea Governorate (n=33,285) were screened in a door to door manner by 6 specialists of neuropsychiatry and 15 female social workers. All subjects at the age of 50 years and more (n=12,508) who have been living in the screened area, for at least 6 months at the time of interview, were included in this study. Screening was carried out using a short standardized Arabic screening questionnaire (sensitivity 93.2% and specificity 96% respectively) and modified MMSE. Suspected cases were subjected to case ascertainment according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision, diagnostic criteria for dementia; full clinical assessment; psychometric assessment using Cognitive Abilities Screening Instruments, Hachinski Ischaemic Score, Instrumental Activities of Daily Living Scale and the Geriatric Depression Scale; neuroimaging (computed tomography and/or mag-netic resonance imaging); and laboratory investigations.

Results: Out of 12,508 inhabitants who aged 50 years and more 78 patients had vascular dementia with a prevalence rate of 0.62%. Prevalence of vascular dementia increases directly with age to reach its highest rate of 2.99% among those aged >85 years. Risk factors for vascular dementia in order of frequency were; past history of CVS (98.7%), hypercholesterolemia (56.4%), hypertension (51.3%), diabetes mellitus (51.3%), smoking (25.6%), hypertriglycridemia (24.4%), and hyperuricemia (12.8%).

Conclusion: Vascular dementia is the second cause of dementia in Egypt with a prevalence rate of 0.62%.

Policy of full disclosure: None.

Tuesday 24 June 2014

P-20. Addictive disorders B

P-20-001 Effects of pseudoginsenoside-F11 on methamphetamine-induced behaviors related to the dopaminergic and GABAergic neuronal system in the nucleus accumbens

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Objective: Addiction of methamphetamine (METH) is worldwide health and social problems to relate serious psychiatric symptoms. Since there is currently no effective pharmacological treatment for METH-induced addiction, we investigated the effects of pseudoginsenoside-F11 (PF11), which is isolated from Panaxquinquefolium (American ginseng), on the methamphetamine induced-behaviors.

Methods: We carried out the locomotor sensitization, conditioned place preference (CPP) test and in vivo microdialysis to investigate the effects of PF11.

Results: Repeated pretreatment with PF11 attenuated METH-induced locomotor sensitization. In the CPP test, the pretreatment with PF11 inhibited METH-induced place preference. In vivo microdialysis analysis indicated repeated pretreatment with PF11 prior to continuous METH administration-prevented METH-induced increase of extracellular dopamine (DA) level in the nucleus accumbens (NAc). Furthermore, microdialysis analysis also revealed that repeated administration with PF11 increases extracellular GABA level in the NAc, however, single administration would not.

Conclusion: These findings suggest that, PF11 possesses the inhibitive effect on METH-induced increased extracellular DA level via regulating the GABAergic neuronal system in the NAc.

Policy of full disclosure: None.

P-20-002 PCLO SNP rs13438494 regulates DA and 5-HT uptake, accompanied with splicing efficiency and dependence-like behaviors in genomic association studies

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Objective: Piccolo (PCLO) regulates the transport of synaptic vesicles in neuronal cells. A single nucleotide polymorphism (SNP) rs13438494 in the intron 24 of the PCLO was reported to be associated with bipolar disorder in the meta-analysis of GWAS and affected PCLO gene expression in the prefronral cortex. In this study, therefore, we have attempted to evaluate the possible functionality of the PCLO SNP in mechanisms

associated with uptake of neuronal transmitters of monoamines and, genome association study of dependence-like behaviors.

Methods: To characterize the intronic SNP rs13438494 in the PCLO gene, we constructed the C allele or the A allele of the SNP plasmids containing exon 24, intron 24 and exon 25. Plasmid constructs were transiently transfected in SH-SY5Y cells, followed by RT-PCR analysis was done to assess the genetic effect on splicing.

Results: The C allele and the A allele constructs displayed a different ratio between the transcripts, indicating that the intronic SNP affect the splicing pattern. We also generated the the C allele and the A allele plasmids containing C2A domain, which was reported to be one of the functional parts on the DA uptake, and then transfected into HEK293 cells with dopamine and serotonin transporters followed by DA and 5-HT uptake analysis. In the C allele plasmid transfected cells, both DA and 5-HT uptakes were altered compared with the A allele plasmids transfected cells. PCLO rs13438494 has also relationship with to the symptoms of drug dependence or related personality traits, such as the age of first exposure to methamphetamine, eating disorder, tobacco dependence and fentanyl requirement.

Conclusion: These results suggest that PCLO SNP rs13438498 regulates DA and 5-HT uptakes and involves psychiatric disorders.

Policy of full disclosure: None.

P-20-003 Dysfunction of GABAergic system in the insular cortex is associated with impaired decision-making in methamphetamine-treated rats

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Objective: Patients with neuropsychiatric disorders such as addictive disorders have impairments of decision making, which may be associated with their behavioral abnormalities. The underlying neuronal mechanism, however, remains obscure. In the present study, we examined the performance of methamphetamine (METH)-treated rats in a gambling test for rodents, and investigated the neural mechanism of impaired decision-making.

Methods: Rats were treated with METH at 4 mg/kg for 30 days and used as METH-treated animals. The animals were subjected to the gambling test for consecutive 14 days, in which the animals received 16 trials per day. In each trial the animals chose one of four choice arms [one low risk/low return (L-L) arm, one high risk/high return (H-H) arm and two empty arms]. Under a standard condition, choice of the L-L arm resulted in frequent (14/16 trials, 87.5%) small reward (1 food pellet) with infrequent (2/16 trials, 12.5%) punishment (1 quinine-coated food pellet). Choice of the H-H arm resulted in infrequent (2/16) big reward (7 food pellets) with frequent (14/16) punishment.

Results: METH-treated rats chose H-H arm more frequently than did control animals in the gambling test, suggesting impairment of decision-making. c-Fos immunohistochemistry revealed aberrant activation of the insular cortex (INS) as well as nucleus accumbens in METH-treated rats. Microinjections of GABA receptor agonists into the INS decreased the ratio of H-H arm choice in METH-treated rats while GABA receptor antagonists increased it in control animals. Brain microdialysis study indicated the decrease of depolarization-evoked GABA release in the INS of METH-treated rats.

Conclusion: These results suggest that INS is one of critical regions for decision-making in normal and METH-dependent animals, in which GABAergic dysfunction results in poor decision-making.

Policy of full disclosure: None.

P-20-004 Magnetic resonance imaging of changes in resting state brain connectivity during recovery from alcohol use disorder

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Objective: Alcohol use disorder is a global health problem affecting over 140 million people worldwide. The dynamic brain changes associated with alcohol dependence, recovery, and different treatments are only partially understood. We compared changes in functional connectivity of resting state networks in patients undergoing residential treatment for alcohol use disorder. This project's objectives were to identify changes in the resting state networks caused by chronic alcohol abuse and to compare how different treatments modulated these changes.

Methods: 20 male patients (age 24–63) with alcohol use disorder (DSM-IV) were recruited 5–10 days after detoxification and scanned before and after a 21-day residential treatment. 10 healthy volunteers matched for age, handedness, and education level were scanned for comparison. The subjects were scanned using 4.7 Tesla magnetic resonance imaging (MRI). Both scanning sessions included an anatomical scan, a resting-state functional MRI scan, and a diffusion tensor imaging scan. The functional data was analyzed using an independent component analysis with SPM8, GIFT, and a custom Matlab code.

Results: Our preliminary findings revealed significant changes in several resting state networks including the core and frontal networks. In comparison to controls, patients had significant differences in functional connectivity between anterior cingulate cortex and different somatosensory, motor, visual, and association regions.

Conclusion: These findings suggest changes in functional connections of anterior cingulate cortex in patients before and after undergoing treatment for alcohol dependence. Due to the role of anterior cingulate cortex in modulating execution of appropriate and suppression of inappropriate responses, not only in higher order motor control and signal processing but also in reward anticipation and impulse control, these results could help us better understand dynamic changes in functional connectivity which are closely associated with addiction, craving, and internal conflict resolution.

Policy of full disclosure: None.

P-20-005 Neurocognitive function in internet addiction: A comparison with alcohol dependence and healthy control

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Objective: This study aimed to assess neurocognitive functions in individuals with Internet addiction, and compared those with patients with alcohol dependence and healthy controls.

Methods: Three groups were as following: two addiction groups (Alcohol: n=15, 28.47±5.66 years; Internet: n=15, 20.80±5.09 years) which consist of outpatients of Boramae Medical Center and one healthy control group (n=15, 25.33±5.30 years). All subjects were male and young adults. We administered traditional neuropsychological tests including the Stroop test, trail making test (TMT), verbal fluency and also computerized neuropsychological tests using the Cambridge Neuropsychological Test Automated Battery (CANTAB).

Results: There were significant group differences in the stop signal task, spatial span and, TMT-B among three groups. Both the Internet addiction and alcohol dependence group showed decreased portion of successful stop on the stop signal task compared to the healthy control group, and that in the Internet addiction group was comparable to that in the alcohol dependence group. With regard to spatial span, Internet addiction group showed significantly higher scores than those in the alcohol dependence group, although both clinical groups showed no differences of spatial span with the healthy control group. Patients with alcohol dependence showed poorer performances on TMT-B than those in patients with Internet addiction and healthy controls. Furthermore, patients with Internet addiction showed impaired visuo-spatial planning, indicated by longer initial thinking times on the Stockings of Cambridge compared to healthy controls. There were no significant differences in others neurocognitive domains among three groups.

Conclusion: Common deficit shared by Internet addiction and alcohol dependence was impaired response inhibition. Alcohol dependence was associated with deficits in motor planning and cognitive shifting, whereas Internet addiction was associated with deficits in visuo-spatial planning. These findings suggest similarity and disparity in neurocognitive functions of Internet addiction and alcohol dependence.

Policy of full disclosure: None.

P-20-006 Suicide attempters with alcohol intoxication had equivalent suicide intent as non-drunken status suicide attempters

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Objective: It has been known that many suicide attempts were performed by alcohol intoxication. By this reason, it is easy to minimize sincere suicide intent of suicide attempters with drunken status by impulsive behavior. We aim to explore suicide intent of suicide attempters with alcohol intoxication by comparing to non-drunken attempters.

Methods: 2,080 subjects are included from preliminary Korea national suicide survey in 2010 and 2012. Ten medical centers joined that study

and all subjects were interviewed by psychiatric residents in the Emergency room and asked suicide intent by three questions, 'just crying for help', 'sincere but not-lethal' and 'sincere and lethal'. All demographic data between two groups, first and multiple suicide attempters were compared by student t-test and chi-square test. Multiple logistic regression was performed to analyze differences of suicide intent between two groups.

Results: There were more male subjects and multiple attempters in suicide attempters with alcohol intoxication. Drunken status attempters used suicide method stab wound and pesticide intoxication comparing to non-drunken status attempters. Seriousness of suicide intent was not significant different from two groups by performing multiple logistic regression to compensate other variables, sex, physical illness, psychiatric history, living status.

Conclusion: Seriousness of suicide intent of suicide attempters with alcohol intoxication was not significantly different from non-drunken status attempters. This result implies that attempts with alcohol intoxication should be managed closely.

Policy of full disclosure: None.

P-20-007 Sugar addiction: Positron emission tomography of dopamine and opioid receptor binding in minipig brain

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Objective: Obesity causes serious health problems worldwide. Our working hypothesis is that obesity, in addition to being a metabolic disorder, also consists of critical disturbances in the balance of the reward systems in the brain, which may override the physiological controls of appetite. Here we investigate the effects of subchronic sugar addiction on the dopamine and opioid reward system in healthy Göttingen minipigs of average weight.

Methods: Six adult female minipigs (26 kg) were anesthetized and scanned at baseline with C-11 labeled raclopride (an antagonist to dopamine D2/3 receptors) and C-11 labeled carfentanil (μ-opioid agonist) in a Siemens PET/CT scanner. Pigs were then given access to sugar water for one hour each morning for 12 consecutive days and were PET scanned with carfentanil after the first sugar exposure and with both tracers after the 12th day. Two of the minipigs were scanned again 2 weeks later, after cessation of the sugar treatment. PET data were registered to an average minipig MRI atlas and processed using MINC tools. The binding potentials (BPND) were obtained using the Logan graphical analysis, with cerebellum as a region of non-displaceable binding.

Results: On average in the six pigs, raclopride BPND was significantly reduced in the caudate, total striatum and thalamus after 12 days of sugar access. Carfentanil BPND was significantly reduced in the hippocampus after the first exposure to sugar and in the hippocampus, putamen, amygdala and frontal cortex after 12 days of sugar. Two weeks after the cessation of sugar treatment, the BPND of raclopride returned toward baseline values, whereas the reduced BPND of carfentanil persisted.

Conclusion: These data reinforce the importance of dopamine and opioids in wanting and liking food, respectively, and their role in the perpetuation of sugar addiction and obesity. Further insight into these systems in response to palatable food could provide new approaches for preventing addiction/obesity.

Policy of full disclosure: None.

P-20-008 Differential roles for Dopamine D1 and D2 receptors in the basolateral amygdala in modulating risk/reward decision making

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Objective: Different aspects of cost/benefit decision making involving uncertain rewards are facilitated by corticolimbic circuits linking regions of the prefrontal cortex, ventral striatum and basolateral amygdala (BLA). Dopamine (DA) also plays an integral role in promoting choice of larger, uncertain rewards; manipulations of DA transmission in the PFC or nucleus accumbens alters risky choice. Considerably less is known about how BLA DA regulates risk-based decision making. The present study assessed the effects of DA receptor antagonism within the BLA on risk-based decision making, assessed with a probabilistic discounting task.

Methods: Rats were trained to choose between a small/certain lever (1 reward pellet) and a large/risky lever (4 pellets) delivered in a probabilistic manner. The odds of obtaining the larger reward decreased or increased in a systematic manner across 4 blocks of discrete-choice trials (100-12.5% or 12.5-100%) during a daily session.

Results: In well-trained rats, blockade of BLA D1 receptors via infusions of SCH23390 increased discounting of the larger/uncertain reward and reduced risky choice, in a manner similar to D1 receptor antagonism within the medial prefrontal cortex or nucleus accumbens. In contrast, intra-BLA D2 blockade with eticlopride did not affect overall choice, but did reduce reward sensitivity, as reflected by a decrease in win-stay behavior.

Conclusion: These findings, in combination with previous data suggest that D1 receptors in multiple DA terminal regions, including the BLA have an important role in facilitating optimal decision making and promoting choice of larger/uncertain rewards. More generally, these findings highlight a key contribution by mesoamygdala DA in regulating certain aspects of cost/benefit decision making, with D1 activation promoting bias towards risky choices, and D2 receptors providing short-term feedback about recently rewarded actions. These findings may have important implications for understanding mechanisms underlying alterations in decision making and reward processes in psychiatric disorders linked to dysfunction of the amygdala and DA system.

Policy of full disclosure: None.

P-20-009 MTHFR and COMP polymorphisms and serum homocysteine levels in Korean patients with alcohol dependence

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Objective: Increase of homocysteine has neurotoxic effects on dopaminergic neurons, which occurs in alcohol intoxication or alcohol dependence. The level of homocyseine is regulated by several factors including functional polymorphisms within methylenetetrahydrofolate reductase (MTHFR) and catechol-O-methyltransferase (COMT) genes. We investigated single nucleotide polymorphisms (SNPs) in MTHFR and COMPT gene and serum homocysteine levels in Korean patients with alcohol dependence (AD).

Methods: Genotypes of 677C/T, 1793G/A and -393C/A in MTHFR gene and Val108Met in COMT were determined in 243 AD patients and 130 healthy controls. Serum homocysteine levels were examined at admission (non-abstinence state) and after 14 days of abstinence.

Results: Significant differences in genotype and allele frequencies of MTHFR 677C/T were found between AD patients and controls. A frequency of T/T genotype was significantly lower in AD patients than in controls. However, there were no significant differences in genotype frequencies of COMPT val108Met between AD patients and controls. Serum homocysteine levels in AD patients were 24.5±15.8 #mol/l at admission and 12.2±6.7 #mol/l at 14-day abstinence, which was significant alteration. There were no significant differences in homocysteine levels between genotypes of MTHFR and COMPT genes among AD patients.

Conclusion: This study suggests that AD patients had a lower frequency of T/T genotype in MTHFR 677C/T. However, alteration of homocysteine was not associated to MTHFT and COMPT gene polymorphisms in AD patients.

Policy of full disclosure: None.

P-20-010 Predictive factors for online game addiction

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Objective: Online game addiction has been increasingly recognized as a mental disorder that seriously affects the social, academic, and/or daily functionality of individuals. However, the predictive or causal factors that lead to online game addiction are not well established. The aim of this study is to identify factors which may influence the development of online game addiction.

Methods: A total of 263 patients with problematic online gaming habits and 153 healthy comparison subjects were recruited for participation in the current study. All subjects were asked to fill out questionnaires regarding the severity of their internet addiction, individual factors, family environment, social interaction, and comorbidities. The cognitive functioning of subjects was measured using the Wisconsin Card Sorting Test (WCST) and the Korean-Wechsler Adult Intelligent Scale (K-WAIS). Hierarchical logistic regression analyses among each set of variables were conducted. Individual factors (sex and age), cognitive factors (IQ levels and perseverative errors), psychopathological conditions (ADHD, depression, anxiety, and impulsivity), and social interaction factors

(family environment, social anxiety, and self-esteem) were evaluated in a stepwise fashion.

Results: All four factors (individual characteristics, cognitive factors, psychopathological conditions, and social interaction factors) predicted online game addiction, with psychopathological conditions being the strongest set of factors predicting online game addiction. In patients with pure online game addiction (i.e., patients with online game addiction only, with no psychiatric comorbidities), individual factors, psychological factor (attention, mood, and anxiety), and social interactions were predictive factors for the development of pure online game addiction.

Conclusion: The current study assessed risk factors for predicting online game addiction in light of the interaction of four sets of factors, including individual factors, cognitive functions, psychopathologies, and social interactions. Psychopathologies, including ADHD and depression, were the strongest factors associated with the development of online game addiction in individuals.

Policy of full disclosure: None.

P-20-011 Characteristics of suicide attempters affected by co-occurring serious mental illness and substance abuse

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Objective: To study the clinical characteristics of patients with Substance Use Disorders (SUD) comorbid with non-substance related Axis I or II disorder, admitted to a brief dual diagnosis unit for suicidal ideation.

Methods: Data on demographic, family, and clinical factors were gathered. A total of 187 patients, consecutively admitted to our dual diagnosis unit for suicidal ideation between September 2007 and May 2013, were included. Psychiatric disorders, substance use (SUDs) and non-substance use disorders (non-SUDs) were diagnosed according to DSM-IV criteria. Statistical analysis of data was performed using SPSS program.

Results: 39.6% of the sample were women, with a mean age of 40.25+8.8 years. The main SUDs diagnoses were alcohol (59.9%) and cocaine (48.7%). The most frequent non-SUDs diagnoses were: Personality Disorder (58.3%), Adjustment Disorder (15%), Depressive Disorder (13.9%) and Psychosis (9.6%). 17.6% of the sample showed comorbid diagnoses in Axis I and Axis II, whereas 50.8% had no diagnosis on Axis I. The mean age of onset of psychiatric disorder non-related with substance use was 26.5 +11.4. The most frequent dual diagnosis, as for Axis I, were: Adjustment Disorder-Alcohol (7.5%), Depressive Disorder-Alcohol (9.1%). As for Axis II, Personality Disorder-Alcohol (50%) and Personality Disorder-Cocaine (29.8%). 63.6% had a previous history of suicide attempts. Only 28.3% of the subjects had been taking a drug treatment regularly and 33.2% were receiving psychiatric follow-up, during the 6 months previous to hospital admission. 40.6% lived with family and 27.6% lived with company or in an institution; 62% were married; 12.8% were occupationally active; 50.8% had secondary education or higher. 35.8% had a family history of non-SUD diagnoses and 43.9% had a family history of SUD diagnoses.

Conclusion: In a Dual Population, alcohol and cocaine are the most frequent SUD disorders in patients with suicidal ideation, and the most frequent non-SUD diagnoses are personality disorders, whether mood disorders are relatively less represented. Also, factors as sex, previous suicide attempts and not doing regular treatment could be associated with suicidal ideation in these patients.

Policy of full disclosure: None.

P-20-012 Age of onset of dual schizophrenia: Is there any relationship with severity of addiction?

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Objective: Describe differences between the patients who had the onset of a schizophrenia spectrum disorder to prior or equal to 25 years (EO<25) compared to those whose age of disease onset was later (EO>25) in a group patients with comorbid substance use disorders (SUD).

Methods: Sociodemographic, clinical and administrative data of all patients diagnosed with schizophrenic disorder or schizoaffective disorder admitted to a dual diagnosis during 3-year period were collected. The psychiatric diagnosis was made according to DSM-IV-R criteria.

Results: The total sample was comprised of 154 subjects (128 with schizophrenic disorder and 26 with schizoaffective disorder). Predominantly male (75.3%), mean age of 38.5±8.54 years. In the comparison (Table 1) can be seen as the EO<25 (N=98)were younger, male, unmarried and mostly had higher prevalence of secondary education. They had lower prevalence of HIV and HCV. With regard to substance use, in the EO<25 group the primary drug was alcohol while in the other group was cocaine. These patients had an earlier first contact with hypnotics, amphetamines, cocaine and nicotine as well as the age of problematic consumption of cocaine and nicotine. They also had a lower cumulative deprivation time for both cannabis and nicotine and a higher frequency of alcohol consumption over the past 30 days. Figure 1 shows a comparison of the main dual reasons for admittance in both groups (psychopathological main reason for admission income plus primary drug use), while various combinations resulting from the SUD is reflected in Figure 2. By GEP severity scale we observed that patients in the EO group <25 had a higher family dystocia (1,43+1,17 vs 0,81+1,07; p= 0,002) and worst laboral background (1,11+1,34 vs 0,60+1,19; p=0,024).

Conclusion: Presenting a spectrum disorder of schizophrenia before age 25 gives is associated with early consumption amb early SUD as well as greater severity of drug addiction.

Policy of full disclosure: None.

Please see Table 1 appearing on page 89.

P-20-013 Blockade of endocannabinoid hydrolysis inhibits cocaine-induced seizure and neurotoxicity

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Objective: To test the hypothesis that the facilitation of the endocannabinoid system may reduce seizures and neurotoxicity induced by cocaine.

Methods: Male mice Swiss (n=9/10 per group) received intraperitoneal injections (ip) of vehicle or inhibitor of anandamide hydrolysis (URB597), followed by cocaine 75 mg/kg. There was concomitant monitoring of behavioral and electroencephalographic seizures. In another experiment the animals were pretreated with AM251 (CB1 antagonist) in order to evaluate the involvement of this receptor in the effects of URB597. Moreover, we also investigated, through imunohistochemistry analyzes with c-Fos protein, the neural activation induced by cocaine in hippocampus of animals following seizures and effects induced by URB597 treatment. Protection against cell death induced by cocaine was evaluated in cultured hippocampal neurons and hippocampal slices by ethidium homodimer assay. Data were subjected to ANOVA analysis followed by Newman-Keuls multiple comparisons.

Results: Treatment with URB597 increased the latency and reduced duration of eletroencephalografic and behavioral seizure. Pre treatment with CB1 antagonist reversed the effect of URB597, suggesting an involvement of CB1 receptor on the seizure. Immunostaining with c-Fos antibody in hippocampus showed that URB597 administration reversed the increase in the number of positive cells for c-Fos induced by cocaine. Moreover, treatment with cocaine increased the death of hippocampal neurons and this effect was also inhibited by URB597 effect. Again, AM251 blocked the effects of URB597.

Conclusion: URB597 induced neuroprotective effects against cocaine-induced convulsive seizure and cell death, both effects being mediated by CB1 receptor. Financial support was provided by FAPEMIG (no conflict of interest to declare).

Policy of full disclosure: None.

P-20-014 The relationship between coping styles, stressful life events, and cannabis use in young adults

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Objective: The latest national survey on drug use in the U.S. estimated that one third of young adults used cannabis in 2011. The high prevalence of cannabis use is of public health concern given the recent findings linking cannabis use to the development of psychosis. The objectives are: (1) To test if stressful life events (SLEs) in the past year are associated with greater frequency of cannabis use. (2) To test if coping styles (i.e., emotion-, task-, and avoidance-oriented) modify this association.

Methods: Data were drawn from the Nicotine Dependence in Teens Study, a longitudinal study of a school-based cohort in Montreal. The analytic sample consisted of 853 young adults (mean age=24.0 years) who completed self-report questionnaires regarding (1) SLEs in the past year using a modified List of Threatening Events, (2) cannabis use in the past year and (3) coping styles using the Coping Inventory for Stressful Situations-21. The associations between SLEs, cannabis use and coping styles were examined in multiple linear regressions and interaction testing.

Table reference P-20-012

Table 1. Significant differences between both groups on sociodemographic and clinical variables.

		EO≤25 N=98	EO>25 N=56	p
Sociodemographical				
Age (years) [mean, s.d]		36,8+8,8	41,5+7,2	p=0,001
Genre (males)		69,4%	75,7%	p=0,032
Marital status (single)		76,5%	50,9%	p=0,001
Educational level (high school)		54,0%	31,5%	p=0,01
Clinical data				
HIV infection		7,1%	26,8%	p=0,002
HCV infection		17,3%	37,5%	p=0,014
HIV-HCV coinfection		6,1%	26,8%	p=0,001
Age first psychiatric admission unrelated to SUD (years) [mean, s.d]		21,9±6,0	30,6±5,7	p<0,001
Reason for admission				
	Hallucinations/delusions	52,6%	57,1%	p=0,063
	Suicide temptatives	9,3%	0,0%	
	Other	38,1%	42,9%	
Primary drug of abuse				
	Cocaine	33,0%	48,2%	p=0,002
	Alcohol	45,4%	21,4%	
	Heroine	4,1%	3,6%	
	Methadone	1,0%	3,6%	
	Sedatives	0,0%	10,7%	
	Stimulants	2,1%	0,0%	
	Cannabis	14,4%	12,5%	
Age first use of sedatives (years) [mean, s.d]		22,38±5,9	25,6±6,7	p=0,022
Age first use of amphetamines (years) [mean, s.d]		17,63±4,1	20,06±4,7	p=0,043
Age onset of nicotine use (years) [mean, s.d]		13,7±3,3	16,6±3,7	p<0,001
Age onset of cocaine use (years) [mean, s.d]		19,4±5,4	25,8±8	p=0,001
Age onset of problem cocaine use (years) [mean, s.d]		22±7,39	28,34±6,35	p=0,037
Age onset of problem drug nicotine (years) [mean, s.d]		14,96±3,6	16,82±3,7	p=0,007
Período abstinencial acumulado de cánnabis (meses) [media, d.s]		27,3±55	60,43±96,44	p<0,001
Abstinencial nicotine accumulated period (months) [mean, s.d]		1,53±6,67	6,29±10,38	p<0,001
Alcohol consumption (days) in the last month [mean s.d]		19±12,94	12,39+12,8	p=0,001

Results: The number of SLEs was significantly associated with frequency of cannabis use (unstandardized B=0.101, p=0.000). In the presence of SLEs, task-oriented coping was associated with decreased frequency of cannabis use (unstandardized B=−0.113, p=0.044) whereas emotion-oriented coping was associated with increased frequency of cannabis use (B=0.125, p=0.029). There were no significant interactions between SLEs and avoidance-oriented coping.

Conclusion: Focusing on task-oriented coping and preventing emotion-oriented coping may help reduce the prevalence of cannabis use in this population.

Policy of full disclosure: None.

P-21. Anxiety disorders B

P-21-001 Effect of curcumin on benzodiazepine related drugs-induced anxiety-related behaviors in mice

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Objective: Stress manifests itself in various characteristic responses including emotions such as fear, anxiety and impulsivity. Animals under stress take adaptive actions that may lead to various types of behavioral disinhibition. Such behavioral disinhibition, when expressed excessively and impulsively, can result in harm in individuals and cause a problem in our society.

Methods: In the present study, we examined the effect of curcumin on benzodiazepine receptor-induced anxiety-related behaviors to clarify the anti-anxiety activity of curcumin. Mice had free access to vehicle or curcumin. After four weeks, we treated with vehicle, FG7142 or diazepam intraperitoneally, and more thirty minutes later, we investigated the effect of curcumin on FG7142- or diazepam-induced anxiety-related behaviors by several behavioral tests.

Results: FG7142 shortened open area spent time in the cliff avoidance test. However, curcumin, especially 30 mg/kg/day, significantly competed with the reduction of FG7142-induced open area spent time. In addition, curcumin (30 mg/kg/day) significantly reduced the enhancement of FG7142-induced glutathione in the mouse hippocampus. On the other hand, diazepam significantly prolonged open area spent time in the cliff avoidance test. However, curcumin, especially 30 mg/kg/day, significantly competed with the prolongation of diazepam-induced open area spent time. In addition, curcumin (30 mg/kg/day) significantly reduced hippocampal glutathione content of diazepam-treated mice.

Conclusion: Therefore, it is probably that curcumin may have anti-anxiety activity.

Policy of full disclosure: None.

P-21-002 Personality traits in patients with panic disorder

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Objective: Using models developed by Cloninger as predictors of response to treatment and observing the changes of the scores before and after treatment, the objective of this study was to evaluate the prevalence of personality dimensions in patients with panic disorder and compare the results with those found in the literature.

Methods: Were subjected to these study 42 patients, (25 women). The Temperament and Character Inventory Cloninger was administered to all participants.

Results: It was found compared the scores of personality dimensions of patients with panic disorder with healthy subjects, which were statistically higher scores of Harm Avoidance and lower scores in Self-Direction no differences between our results and those described in the literature.

Conclusion: The study of personality dimensions associated with psychiatric disorders has grown tremendously and been shown to be useful, both in understanding the different responses to therapy and for improvement of therapeutics approach to these patients. Therefore, we believe that outcomes of this project will help us to identify patients with the highest potential of reply to therapy instituted, and aid the development of more effective treatment for patients with less potential response.

Policy of full disclosure: None.

P-21-003 High baseline 'anxiety' in male wistar rats predicts an 'anxiogenic' effect of an SSRI which is dampened by subchronic SSRI treatment

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Objective: Behavioural responses to serotonin reuptake inhibitors (SRIs) in man depend on baseline anxiety; the anxiety-reducing effect of long-term administration of SRIs is hence not a non-specific sedative effect, but unique for subjects with enhanced anxiety, who are also more inclined than others to experience anxiety-enhancing effects of acute SRI administration. In this study, we explored if inter-individual variation within a batch of male Wistar rats with respect to 'anxiety' as assessed using the elevated plus maze (EPM) influences the response to SRIs (experiment I), and also to what extent these inter-individual differences are influenced by a drug arresting serotonergic transmission (experiment II).

Methods: In experiment I, 120 animals were pre-tested in the EPM. Animals were then subjected to treatment with the SRI escitalopram admixed to food pellets. After five weeks of treatment, animals were given one injection of another SRI, paroxetine, and then re-tested in the EPM. In experiment II, 65 animals were pre-tested in the EPM and re-tested three weeks later after three days of treatment with the TPH2 inhibitor p-chloro-phenyl-alanine (p-CPA). In both experiments the 1/3 of the animals displaying the highest level of baseline 'anxiety' were defined as high 'anxiety' (HA) rats and the remaining 2/3 as low 'anxiety' (LA) rats.

Results: Acute administration of paroxetine, exerted an 'anxiety'-enhancing effect in HA but not LA rats, which was eliminated by long-term pretreatment with escitalopram. Serotonin depletion obtained by administration of p-CPA eliminated the behavioural difference between the groups by reducing 'anxiety' in HA but not LA rats.

Conclusion: It is suggested that differences with respect to an 'anxiogenic' impact of serotonin partly explains differences in anxiety-like behaviour amongst Wistar rats, and that this influence is enhanced by acute and dampened by subchronic SRI administration.

Policy of full disclosure: None.

P-21-004 Ultra-long-term outcome of panic disorder with clonazepam or paroxetine: A randomized, open, systematic treatment for 3 years and a follow-up for 6 years after

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Objective: We aim to investigate relapse cumulative over time and remission and the efficacy and safety of clonazepam or paroxetine for treating PD in a ultra-long-term follow-up.

Methods: 120 PD patients were randomized in a prospective open study to get 2 mg/day clonazepam or 40 mg/day paroxetine. Patients with an insufficient primary outcome after 8 weeks were switched to combined treatment. A total of 94 patients finished long-term treatment and underwent drug discontinuation by decreasing slowly paroxetine and clonazepam.

Results: After two months of tapering out the drug 80% patients in the clonazepam group, 55% on the paroxetine but by no patient in the combination group were drug free. After six months 89%/64%/44% patients from the clonazepam/paroxetine/combination group were free of drug. Panic attacks (PA)/mth, CGI-S, and mainly HAMA worsened slightly during the withdrawal period and adverse events increased as compared to the treatment period. After the withdrawal phase 66 patients were followed annually during 6 years. 90% of patients are in average in remission during the six-year period after drug withdrawal. 73% of patients were in average free of PAs during the six-year follow up, 91.1% had a GCI-S score of 1, and 38.8% had a HAMA between 5 and 10 points. 33.3% of the patients needed drug treatment during each follow up year. The patients not followed every year had at the end of the observation period similar, but somewhat less favourable results, as could be expected: 88% were in remission, 72% had no PA, 62% had a CGI-S of 1 and 30% had a HAMA between 5 and 10 and 38.9% whereby 39% were under antipanic treatment.

Conclusion: The relapse rate was very high. Both paroxetine or clonazepam had the same long-term prognosis but the clonazepam group had a better profile of adverse events in the long-term treatment.

Policy of full disclosure: None.

P-21-005 The "anxiogenic" effect of acute escitalopram on startle behaviour, but not that of contextual conditioning, is more pronounced in wistar rats with high baseline reactivity

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Objective: The acoustic startle reflex is a common measure of contextual conditioned fear that often serves as an experimental model of anxiety.

Methods: In the present study, repeated testing was used to explore if acute administration of a selective serotonin reuptake inhibitor (SSRI), escitalopram (10 mg/kg), influences startle in the absence or presence of contextual conditioning in the form of foot shocks, and to what extent the baseline startle of the animal predicts drug response.

Results: Escitalopram and contextual conditioning both increased startle in male Wistar rats but did not display any synergistic effect. While animals displaying high startle at baseline showed higher susceptibility to the influence of escitalopram in the startle paradigm, the effect of contextual conditioning was more pronounced in those with low baseline startle.

Conclusion: We suggest that further studies using this model may shed light on why acute administration of SSRIs may exert anxiogenic effects in man and why subjects with anxiety disorders are considerably more susceptible to this effect than others.

Policy of full disclosure: None.

P-21-006 Randomized, placebo-controlled effectiveness study of Quetiapine XR in co-morbid depressive and anxiety disorders

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Objective: Atypical antipsychotics (AAPs) are among the first-line agents used to treat depressive and anxiety disorders. Co-morbidity of depression and anxiety is highly common, but few studies have explored the benefit of AAPs as augmentation for this group of patients. Quetiapine is an AAP with proven efficacy, as monotherapy or augmentation, for both conditions. The aim of this multi-centre, double-blind, placebo-controlled study was to examine the efficacy, tolerability and safety of quetiapine as augmentation in patients with depression and co-morbid anxiety.

Methods: Seventy-four adults (18–65 years), with a primary diagnosis of unipolar depression co-morbid with one or more anxiety disorders, were randomly assigned to receive flexible-dose quetiapine XR 50–300 mg/day or placebo for 12 weeks, in a 2:1 ratio. Pre/post measures included the Hamilton Depression Rating Scale (HAM-D), the Hamilton Anxiety Scale (HAM-A), the Clinical Global Impression Scale (CGI), the Penn State Worry Questionnaire (PSWQ), the Leibowitz Social Anxiety Scale (LSAS), the Panic Disorder Severity Scale (PDSS), the Post-traumatic Disorder Scale (PDS) and the Quality of Life Enjoyment and Satisfaction Scale (QLESQ). Adverse event data was collected at each study visit.

Results: Both groups showed comparable improvement on the HAMD, QLESQ and PSWQ, but no change on the PDSS and PDS ($p>0.05$). However, quetiapine was significantly superior to placebo in improving scores on the HAMA ($p=0.048$), CGI ($p=0.019$) and LSAS ($p<0.04$). The mean dose of quetiapine was 138.5 mg/day and the mean dose of placebo was 155.5 mg/day. Side effects were generally mild, with drop out mainly due to lack of efficacy, and drop-out rates were similar for both groups ($p=0.066$).

Conclusion: While the benefit of quetiapine augmentation was not better for depression itself, it was significantly superior in improving anxiety symptoms in patients with depression and co-morbid anxiety. Quetiapine was also reasonably well tolerated.

Policy of full disclosure:

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P-21-007 Afobazole increases binding of sigma-1 receptor selective agonist in P2 fraction of CD-1 mice brain homogenate ex vivo

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Objective: Anxiolytic afobazole (5-ethoxy-2-[2-(morpholino)-ethylthio] benzimidazole dihydrochloride) possesses ligand properties towards sigma-1 receptor (Sigma1R) in vitro (IC50 human T-cells=7,1*10-6M, IC50 mice brain=1,37*10-5M) (Ryaskina et al., 2012). Afobazole and Sigma1R agonists induce receptor's translocation to the extracellular space in vitro which correlates with the increase of Sigma1R in P1, P2 and P3 heavy-density fractions (Hayashi et al., 2003; Seredenin et al., 2009). The aim of our research is to study ex vivo the influence of intraperitoneal injection of afobazole on Sigma1R selective agonist binding in P2 and P3 fractions of CD-1 mice brain homogenates.

Methods: In the experiments were used male CD-1 mice. Afobazole in anxiolytic dosage 5 mg/kg and vehicle saline were injected intraperitoneally in 30 minutes before decapitation. Differential centrifugation was used to obtain P2 and P3 fractions of brain homogenates. Sigma1R activity was measured by radioligand binding assay using [Ring-1,3-3H]-(+)-Pentazocine.

Results: Specific [Ring-1,3-3H]-(+)-Pentazocine binding to Sigma1R (mean±S.D., DPM/mg of protein) in P3 fractions of mice brain homogenates in control group (8799±1696) and group with afobazole pretreatment (8697±1553) was significantly higher ($p<0.0001$, t-test) then in P2 fractions of the same groups (3976±517,9 and 4525±610,5) correspondingly. These data conform to previously obtained results (McCann et al., 1994). Afobazole (5 mg/kg i.p.) caused significant increase of [Ring-1,3-3H]-(+)-Pentazocine binding in P2 fractions ($p=0,0246$, t-test) and absence of differences between binding of the selective agonist to Sigma1R in P3 fractions ($p=0,88$, t-test).

Conclusion: Afobazole pretreatment increases (+)-Pentazocine binding to Sigma1Rs in P2 fractions of mice brain homogenates ex vivo which corresponds to afobazole induced intacellular dynamics of Sigma1Rs in vitro and agonistic activity determined for prototype ligands.

Policy of full disclosure: None.

P-22. Bipolar disorders B

P-22-001 Prescription of antidepressants for bipolar disorder: A retrospective study at Tokyo Women's Medical University Hospital

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Objective: In patients with bipolar disorder, it is necessary to treat and prevent the depression and manic phases. Antiepileptic, lithium, or antipsychotic drugs are typically used for this. The use of antidepressants during the acute depressive state of bipolar disorder is suggested to be associated with a risk of inducing changing manic phase, or causing rapid cycling; however, no conclusive evidence has been found. We performed this retrospective study to determine the clinical effects related to the use of antidepressants to treat patients with bipolar disorder.

Methods: Patients with bipolar disorder, who were treated in the outpatient section of the Tokyo Women's Medical University Hospital psychiatry and the department of psychosomatic medicine between January 1, 2011 and December 31, 2011, were included in this study. From these patients' medical records, the antidepressant prescription and the related effects were investigated. This protocol was approved by the ethical committee of TWMU.

Results: Of the 358 patients with bipolar disorder who were included in the study, 228 had been prescribed antidepressants. Of these, 24 showed rapid cycling. Of the patients who did not receive antidepressants, 3 showed rapid cycling. Thus, more patients who were prescribed antidepressants showed rapid cycling.

Conclusion: Antidepressants are prescribed frequently to patients with bipolar disorder. Our results suggest that using antidepressants to treat bipolar disorder could induce rapid cycling. However, the reasons for using antidepressants, such as the severity of bipolar disorder and unipolar disorder obstacle discriminating should be considered to draw an accurate conclusion.

Policy of full disclosure: None.

P-22-002 Patients' preference for treatment of bipolar disorder: An internet survey

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Objective: Though various clinical guidelines for bipolar disorder (BP) have recommended monotherapy or combination of mood stabilizers and second generation antipsychotics, it is unclear that patients' preference for treatment of BP which could affect adherence of those drugs. Therefore we conducted an internet survey to elucidate the preference.

Methods: From registrants of web research monitor, 1,050 subjects who had been diagnosed with BP and currently treated were randomly chosen. Through screening procedures, we identified 457 participants who had experienced manic episode(s) which was evaluated by using Manic Episode Screening Questionnaire#Kameyama, 2013). Participants were asked as to which the current prescription they took, what bothered them in the course of treatment, and what kind of treatment they needed in future.

Results: Majority of participants were in their 40s or 30s (41.1%, 33.5%, respectively) and prescription which they currently took were mood stabilizers (77.0%), SSRIs/SNRIs (45.1%), second generation antipsychotics (40.3%) and first generation antipsychotics (14.7%). Things which bothered them in the current treatment were "Long-term therapy with taking prescription" (65.6%), "Difficult stabilization of manic/depressive

symptoms" (61.1%), and "Unpredictable mood switch of symptoms" (60.2%). Their wishes for future direction of BP treatments were "Prescription to improve symptoms rapidly" (53.0%), "Prescription which can prevent relapse or recurrence of symptoms" (27.4%), and "Test to diagnose BP accurately" (24.5%).

Conclusion: We clarified that preferred treatments for BP were those with rapid improvement as well as with stabilization of symptoms. We also elucidate that many subjects were prescribed SSRIs/SNRIs despite the recommendation of clinical guidelines.

Policy of full disclosure: None.

P-22-003 Affective switch under antidepressants: Reality or fiction?

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Objective: Since decades, an association between antidepressant drug treatment/prophylaxis and mood conversion into (hypo-)manic states in patients with bipolar disorders is discussed. Aim of this paper is to find methodologically sound controlled clinical studies addressing antidepressant induced affective switching and to formulate corresponding recommendations for clinicians.

Methods: Literature retrieval on the basis of preexisting researches by the British NICE and the German DGPPN/DGBS.

Results: Regarding antidepressant monotherapy in acutely depressed bipolar patients (5 studies), significantly more switches under imipramine vs. fluoxetine were reported; other investigations found no switch rate differences under paroxetine vs. placebo and under venlafaxine vs. lithium, respectively. As to psychotropic drug combinations (antidepressant plus mood stabilizer and/or antipsychotic; 6 studies), affective switches were more frequent under venlafaxine vs. bupropione and sertraline while between bupropione and paroxetine no differences were detected. Furthermore, paroxetine plus mood stabilizer produced no more switches than a combination of 2 mood stabilizers; a fluoxetine-olanzapine combination was not more frequently associated with switches than olanzapine alone/lamotrigine/placebo. Regarding long term prophylaxis, only 2 studies were found: no different conversion rates were reported between mood stabilizer/antipsychotic with vs. without additional antidepressant on the one hand and fluoxetine vs. lithium on the other.

Conclusion: In acute treatment of bipolar depression, SSRI and bupropione should be favoured over venlafaxine and tricyclic antidepressants. Due to scarce data, no clear recommendations can be made with regard to both psychotropic drug combinations including antidepressants and long term antidepressant treatment. Regarding the lack of unambiguous proof of efficacy of antidepressants in bipolar depression, antidepressants should regularly be combined with mood stabilizer(s) and/or antipsychotic(s) and be used with caution, especially in milder bipolar depression, rapid cycling/mixed/bipolar I disorders and patients reporting anamnestic switch(es). Future research should focus on the identification of predictors for affective switching under antidepressant drug regimen.

Policy of full disclosure: None.

P-22-004 Korean medication algorithm project for bipolar disorder 2014: Rapid cycling

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Objective: Bipolar disorder is an illness with significant morbidity and mortality that contributes to disturb social function. Our objective for this study is to revise Korean Medication Algorithm Project for Bipolar Disorder 2010 for rapid cycling.

Methods: The questionnaires to survey the expert opinion of medication for rapid cycling were completed by the review committee consisting of 64 Korean expert psychiatrists. We classified the experts' opinion to 3 categories based on the lowest category in which the confidence interval fall (6.5# for first-line and 3.5# for second-line treatment).

Results: The first-line treatment was the combination of a mood stabilizer and an atypical antipsychotic. And also, monotherapy of atypical antipsychotics was included in the first-line treatment. Additionally, a mood stabilizer with lamotirgine therapy and an atypical antipsychotic with lamotrigine combinations were the first-line treatment in depressive phase. Mood stabilizer monotherapy, combination of two mood stabilizers, combination of mood stabilizer, atypical antipsychotics and antidepressants were preferred as next strategy. The first-line medications in all cases are valproic acid, lithium, quetiapine, olanzapine and aripiprazole. For the treatment of depressive phase, lamotrigine is the first-line medication.

Conclusion: Compared to the surveys in 2010, the preference for atypical antipsychotics and lamotrigine were increased, and modalities as a second-line treatment were diverse.

Policy of full disclosure: None.

P-22-005 Effects of mood-stabilizing drugs on dendritic outgrowth and synaptic proteins levels in the primary hippocampal neurons

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Objective: Mood-stabilizing drugs, such as lithium (Li) and valprate (VPA), are widely used for the treatment of bipolar disorder, a disease marked by recurrent episodes of mania and depression. Growing evidence suggests that Li exerts neurotrophic and neuroprotective effects, leading to an increase in neural plasticity. The present study investigated whether other mood-stabilizing drugs produce similar effects in primary hippocampal neurons.

Methods: Mood-stabilizing drugs, such as lithium (Li) and valprate (VPA), are widely used for the treatment of bipolar disorder, a disease marked by recurrent episodes of mania and depression. Growing evidence suggests that Li exerts neurotrophic and neuroprotective effects, leading to an increase in neural plasticity. The present study investigated whether other mood-stabilizing drugs produce similar effects in primary hippocampal neurons.

Results: (0.5–2 mM), VPA (0.5–2 mM), CBZ (0.01–0.1 mM), and LTG (0.01–0.1 mM) significantly increased dendritic outgrowth ($p<0.05$ or $p<0.01$). The neurotrophic effect of Li and VPA was blocked by inhibition of phosphatidylinositol3-kinase (PI3 K), extracellular signal-regulated kinase (ERK), and protein kinase A (PKA) signaling ($p<0.05$ or $p<0.01$); the effects of CBZ and LTG were not affected by inhibition of these signaling pathways. Li, VPA, and CBZ significantly prevented B27 deprivation-induced decreases in BDNF, PSD-95, NLG1, Beta-neurexin, and SYP levels ($p<0.05$ or $p<0.01$), whereas LTG did not.

Conclusion: Taken together, these results suggest that Li, VPA, CBZ, and LTG exert neurotrophic effects by promoting dendritic outgrowth; however, the mechanism of action differs. Furthermore, certain mood-stabilizing drugs may exert neuroprotective effects by enhancing synaptic protein levels against cytotoxicity in hippocampal cultures.

Policy of full disclosure: None.

P-22-006 Efficacy of long-acting injectable antipsychotics in the treatment of bipolar disorder

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Objective: Long-acting injectable antipsychotics (LAI) have been used to treat bipolar disorder, especially for patient with poor medication adherence. This study compared the first (FLAI) and second generation LAI (SLAI) regarding the efficacy and side effects in a psychiatric hospital.

Methods: Nineteen patients with bipolar disorder receiving FLAI (1 fluphenazine, 7 haloperidol, 10 flupenthixol and 1 clopenthixol) and ten receiving SLAI (risperidone) from outpatient department of Taipei City Psychiatric Center were surveyed by chart review regarding their onset of age, latency to treatment, number of mood episode and hospitalization. Also patients were administered with questionnaire of quality of life (WHO), drug induced extrapyramidal syndrome scale, antipsychotic side-effect checklist, personal and social performance scale, clinical global impression, lack of judgment and insight, and visual analogue of pain on injection site.

Results: The mean age of study subjects was 46.4±10.3 years, with an illness course of 22.3±9.2 years, and LAI treatment for 7.2±8.1 years. The frequencies (times per year) of mood episodes before and after LAI antipsychotic were 0.78±0.70 and 0.33±0.8, respectively ($p<0.05$); while the frequencies of hospitalization were 0.64±0.80 and 0.06±0.20, respectively ($p<0.001$). There is no difference between FLAI and SLAI groups in terms of the above mentioned efficacy, quality of life, side effects, judgment of insight, and pain on injection site.

Conclusion: The use of LAI, both first and second generation, can improve the medication adherence and significantly ameliorate the course of bipolar disorder. Due to the small number of study subjects, no difference was found between FLAI and SLAI in terms of efficacy and side effects.

Policy of full disclosure: None.

P-22-007 Impact on biomarkers of a comprehensive rehabilitation program in bipolar disorder (PRISMA): A multimodal approach

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Objective: Characterize actual situation of BD, and then apply a multimodal approach to analize the clinical, neurocognitive, neurofunctional, psychlogic, ocupational, social effect in short-mid-long term of a multimodal approach in patients with BD and to determine if it affects clinical functionality, brain activation and its effect on specific biomarkers.

Methods: 200 BD, aged 18 to 65, were randomized to control or intervention group, all subjects were assesed using psychiatric (DIGS, HRSD, YMRS), psychologic (AQ-12, TEMPS-A, FAST, BIS-11, SAI-E), neuropsychlogic (WCST, CVLT-II, WAIS III, TMT, WMS III, Rey-Osterrieth complex figure), ocupational (SSI, EMES-M, EMES-C, assertiveness test, SAD scale), familiar (FEICS, FACES-III, ECF) and general practitioner (BRIAN, MMSE) evaluations; samples for biomarkers (NT-3, IL6, 10, 17, BDNF, NT-3, TNF-alpha, Carbonylation of proteins, Nitration of proteins and TBARS) were obtained and fMRI studies (3 tesla scanner) were made in 90 patients defined randomly. Intervention comprises 12–18 specific interventions and 10 psychoeducation sessions compared to control group, evaluated only by psychiatry and general practitioner. All instruments will be applied twice to compare data before and after intervention.

Results: Preliminary data: Evaluated to date: 172. Mean age(years): 40,22(SD: 11,742). Females: 121(70,3%). Males: 51(29,7%). FAST: 118 (68%) patients showed functional impair vs. 54(31,4%) with normal results (Mean score: 26,71, SD: 14,097). Data will be compared after intervention.

Conclusion: Our final results will show if comprehensive rehabilitation programs affect biomarker levels and functional and structural MRI as it influences functional outcomes in patients with bipolar I disorder as compared with standard intervention.

Policy of full disclosure: None.

P-22-008 A preclinical model and human genetic studies implicate abnormal development of monoaminergic neurons in bipolar disorder

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Objective: Subtle mood fluctuations are normal emotional experiences. However, when very drastic, mood swings can be a clinical manifestation of bipolar disorder. Despite the importance for normal and pathological behavior, the mechanisms underlying endogenous mood instability are largely unknown. A major obstacle preventing progress of our understanding of this behavior has been the lack of appropriate animal models. Previously, we demonstrated that the suggested susceptibility genes for bipolar disorder Otx2 together with Wnt pathway members are upstream regulators of genes specifying monoaminergic neurons. Here we behaviorally phenotyped mouse mutants overexpressing Otx2 in the hindbrain, resulting in an increased number of dopaminergic neurons and decreased numbers of serotonergic neurons. Combining these preclinical experiments with human genetic studies we further investigate the significance of the development of monoaminergic neurons for bipolar disorder.

Methods: Using a translational approach we combine behavioral experiments in mouse mutants with a pathway analysis tool for genome-wide association studies.

Results: During one month of monitoring home cage activity, control animals showed stable locomotor activity levels, while mutants showed extended periods of elevated or decreased activity relative to their individual average. Repeated measurements in the open field demonstrated for mutants increased intra-individual fluctuations in locomotor activity, habituation, risk-taking behavioral parameters and social interaction. In the sugar preference test, mutants showed increased intra-individual changes in hedonic-like behavior. Olanzapine, lithium, carbamazepine and the serotonin receptor agonists quipazine and CP-809101 improved behavioral alterations of mutants. Testing the relevance of our findings for bipolar disorder in humans, we used an interval-based enrichment analysis tool for genome-wide association studies. We found that genes specifying dopaminergic and serotonergic neurons exhibit a significant level of aggregated association with bipolar disorder.

Conclusion: Our results suggest that an abnormal development of monoaminergic neurons leads to affective instability and is implicated in bipolar disorder.

Policy of full disclosure: The authors declare no competing financial interests.

P-22-009 Short- and longer-term treatment with lurasidone in patients with bipolar I depression: Effect on metabolic syndrome

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Objective: To evaluate the effect of lurasidone on the prevalence of metabolic syndrome in bipolar I depression.

Methods: Data were pooled from 3 short-term studies in patients with bipolar I depression were randomized to 6 weeks of once-daily, double-blind, placebo-controlled treatment with lurasidone (20–120 mg/d), either as monotherapy (one study, N=499), or adjunctive therapy with lithium (Li) or valproate (VPA; two studies, combined N=694). Patients completing the three 6-week studies continued to receive 6 months of additional treatment with lurasidone 20–120 mg/d in an open-label extension study (N=494). NCEP criteria (JAMA 2001;285:2486–2497) for metabolic syndrome were used. Change at 6 months (for completers) was calculated from double-blind baseline of the 6-week acute study.

Results: At baseline, the prevalence of metabolic syndrome was similar in the adjunctive studies (lurasidone, 14.8%; placebo, 13.5%) and in the monotherapy study (lurasidone, 14.3%; placebo, 15.5%). After 6 weeks of adjunctive therapy, the prevalence of metabolic syndrome in the lurasidone vs. placebo groups was 17.0% vs. 12.4% (LOCF); after 6 weeks of monotherapy, the prevalence was 15.8% vs. 17.7% (LOCF). For patients who completed 6 months of extension phase treatment, the prevalence of metabolic syndrome was 23.8% (adjunctive therapy) and 17.9% (monotherapy). For the subgroup with metabolic syndrome at baseline in the adjunctive therapy studies (n=31), the following median changes were observed (completer analysis): weight (0.0 kg), cholesterol (−6.0 mg/dL), triglycerides (+11.0 mg/dL), and glucose (+2.0 mg/dL). For the subgroup with metabolic syndrome at baseline in the monotherapy study (n=30), the following median changes were observed: weight (−0.3 kg), cholesterol (−4.0 mg/dL), triglycerides (−22.0 mg/dL), and glucose (−2.0 mg/dL).

Conclusion: In patients with bipolar depression, 7 months of treatment with lurasidone was associated with minimal metabolic changes. In at-risk patients with metabolic syndrome at baseline, treatment with lurasidone was not associated with worsening of metabolic parameters.

Policy of full disclosure: Dr. McElroy is a consultant to, or member of the scientific advisory boards of Alkermes, Shire, and Sunovion; she is (or has been) a principal or co-investigator on research studies sponsored by the Agency for Healthcare Research & Quality (AHRQ); Alkermes, AstraZeneca, Brackett, Cephalon, Corcept, Eli Lilly and Company, Marriott Foundation, NIMH, Orexigen Therapeutics, Inc., Pfizer, Shire, Takeda Pharmaceutical Company Ltd, and Transcept Pharmaceutical, Inc.; she also holds a patent for the use of sulfamate derivatives for treating impulse control disorders and has received payments from Johnson & Johnson Pharmaceutical Research & Development, L.L.C., which has exclusive rights under the patent. Drs. Pikalov, Cucchiaro, Hsu, Kroger, Loebel, and Ms. Phillips are full-time employees of Sunovion Pharmaceuticals Inc.

P-22-010 The effect of childhood abuse and neglect on clinical severity in mood disorders

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Objective: Mood disorders are common psychiatric disorders which affect 20% of the population during their lifetime. They are characterized by early onset, chronic nature, and severe consequences, including suicide attempts. Childhood adversity (CA) has been investigated as a major risk factor for the development of mood disorders, increasing the risk by 2–3-fold. However, significant knowledge gaps remain in the association between CA and mood disorders, especially regarding the impact of specific types of CA on specific indicators of mood disorder severity. Therefore, this study tests whether different types of childhood adversity are associated with worse disease severity in mood disorder patients as indicated by age of first psychiatric treatment and first psychiatric hospitalization, number of psychiatric hospitalizations, and suicidal behavior.

Methods: Data were drawn from the Mood Disorders Program of McGill University Health Centre. The analytic sample includes 77 adults with a DSM-IV diagnosis of a mood disorder (Bipolar Disorder or Major Depression). Participants filled out self-report questionnaires, including the Childhood Experience of Care and Abuse questionnaire

(CECA-Q) which assesses childhood adversity, and underwent the Structured Clinical Interview for DSM-IV (SCID).

Results: Individuals who had experienced at least one form of childhood sexual abuse had a 13-fold increased likelihood of being hospitalized for psychiatric reasons during their lives. Parental loss or separation during childhood was associated with an earlier age of first psychiatric admission. Furthermore, severity and frequency of maternal psychological abuse, as well as physical abuse during childhood, was associated with a later age of first psychiatric admission.

Conclusion: Physical, sexual, and psychological abuse, as well as separation from parents, all appear to have longstanding negative effects in those with mood disorders. It is very important that the presence and types of childhood adversity be systematically reviewed in initial psychiatric assessments as this may help prognosticate the treatment and severity of illness.

Policy of full disclosure: None.

P-23. Depression B

P-23-001 Spatiotemporal activation during verbal fluency task in remitted patients with major depression: An MEG study

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Objective: The thought symptoms of major depression could be classified into two categories: decrement in the amount or speed of thought (e.g. psychomotor retardation), and altered contents of thought (e.g. pessimistic thought or suicidal ideation). In previous study using fMRI, we have demonstrated that patients with major depression show limited amount of elevation in cerebral perfusion during verbal fluency task, even in the remitted state. However, using hemodynamic methods, it is difficult to estimate the altered pattern of activation during verbal task in depression with a high temporal resolution. In the present study, we aimed to compare the neural activity during the performance of verbal fluency task, using magnetoencephalography (MEG).

Methods: Twelve remitted patients with major depression and twelve age- and sex-matched healthy volunteers participated. The task consisted of three conditions namely verbal generation, verbal repetition and rest condition, presented alternately (at least 30 epochs for each condition). In verbal generation condition, one of three Japanese syllabaries was randomly presented for 7 sec and subjects were required to covertly generate words which begin with those letters. In verbal repetition condition, subjects were required to articulate a Japanese word covertly. Magnetic field was recorded with whole-head 306ch neuromagnetometer. Within each subject#s MRI, source current was estimated using spatial filter technique, and event-related spectral perturbation of beta band (18~24 Hz) activities were calculated with bandpass filter. The processed data was spatially normalized, and statistically compared in the two subject groups.

Results: In verbal generation condition, both groups showed similar activation pattern, first in the occipital area around 200 ms after stimulus presentation, followed by left lateral prefrontal and somatosensory area occurring around 300 ms. However, the depression group showed greater activation in somatosensory area and in right occipital area.

Conclusion: Patients with major depression might recruit different strategy to conduct a verbal task.

Policy of full disclosure: None.

P-23-002 How often have depressed patients received psychoeducation about antidepressants treatment? The survey of 424 outpatients in Japan

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Objective: Recently many studies have suggested that successful psychoeducation to depressed patients is associate with improvement of antidepressant adherence, a decrease in the symptom and an effectiveness in the relapse prevention of depression. However, there is little information how often depressed patients receive the adequate psychoeducation. Therefore, we surveyed outpatients in Japan about the subjective experience that received psychoeducation.

Methods: The subjects were 424 outpatients recruited according to the following inclusion criteria: (a) outpatient; (b) who have been a depressive, or depressive now; (c) who have taken antidepressant, or taking now. We use self-administered questionnaires. Questionnaires is formed in 8-items from A to H: (A) Depressive symptoms, (B) The course of the depression, (C) The onset mechanism of the depression, (D) Treatment plan, (E) Duration of taking antidepressants, (F) How to discontinue antidepressants, (G) Side effect of antidepressants and (H) Psychotherapy. For each item, we questioned "Have you received an explanation by doctor in charge?" and "How much do you understand about it?" Understanding for each item is rated 11 anchor points (0 through 10).

Results: Ratios of person receiving explanations were 62% for (A), 49% for (B), 51% for (C), 57% for (D), 46% for (E), 29% for (F), 51% for (G) and 37% for (E). Understanding scores in patients with receiving explanations were significantly higher than those without receiving explanations in all items. Average understanding scores were relative low around 5.5 to 6.4 even in patients with receiving explanations, while those without receiving explanations were 2.0 to 3.7. Significant negative correlations were found between understanding scores and age or onset age.

Conclusion: We concluded that adequate psychoeducation is not sufficiently performed. It is required to provide an effective, quick, and easy psychoeducational method for depressed patients to general physician and psychiatrist.

Policy of full disclosure: None.

P-23-003 Baseline difference between patients' and clinicians' rated illness severity scores and subsequent outcomes in major depressive disorder: Analysis of the STAR*D Data

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Objective: Data have been scarce on the association of the difference between subjective and objective severity of the illness with the subsequent response to antidepressant treatment in Major Depressive Disorder (MDD), which was addressed in this study.

Methods: This was a post hoc analysis of the data from level 1 of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, in which non-psychotic MDD patients were treated with 10–60 mg/day of citalopram for 12–14 weeks and evaluated with the 16-item Quick Inventory of Depressive Symptomatology, Clinician Rating (QIDS-C16) and the 16-item Quick Inventory of Depressive Symptomatology, Self-Report (QIDS-SR16). A baseline QIDS difference score was defined as a value of a baseline QIDS-SR16 score minus a baseline QIDS-C16 score. Remission was defined as both QIDS-SR16 and QIDS-C16 scores of #5 at the treatment exit. Logistic regression analysis was performed to examine correlation between the baseline QIDS difference score and the subsequent remission.

Results: Of the evaluable 2872 participants, 28.0% (n=803) remitted. A baseline QIDS difference score ranged from −16 to +10 (mean±SD, −0.7±3.1). A higher QIDS difference score at baseline was significantly associated with a lower remission rate after controlling demographic and clinical variables (odds ratio=0.953, 95% confidence interval=0.925–0.982, p=0.002).

Conclusion: Patients who perceived their illness to be more severe than assessed by clinicians were less likely to achieve remission. These findings suggest the importance of taking caution for such patients who regard the symptomatology as more negative before starting antidepressant therapy in an effort to improve treatment outcomes for MDD.

Policy of full disclosure: None.

P-23-004 The evolution of antidepressant switch and augmentation therapy in the treatment of depression: A chart review

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Objective: The objective of this study was to examine the evolution of antidepressant switch and augmentation therapy (i.e. concomitant use of a mood stabilizer or an antipsychotic) in the real-world from a longitudinal perspective.

Methods: A systematic chart review of longitudinal prescriptions was conducted regarding 633 patients with major depressive disorder for up to two years after their first visit to one of six psychiatric clinics in Japan between July, 2010 and June, 2011. Patients who had already received antidepressants for the current episode were excluded. Reasons for prescription changes were examined.

Results: 22.6% (N=143) of the patients completed or continued the outpatient treatment over the two years while 27 (4.3%), 23 (3.6%), and 439 (69.4%) patients discontinued it due to hospitalization, referral to another clinic, and loss to follow-up, respectively. A total of 324 episodes of antidepressant switch or discontinuation were identified; the most frequent reason for the regimen change was 'symptomatic improvement' (35.8%, N=116) followed by 'ineffectiveness' (32.7%, N=106) and 'side effects' (26.5%, N=86). In the 106 episodes of antidepressant switch or discontinuation due to ineffectiveness, 84.0% (N=89) of the regimen change were commenced even before the maximum dosages in package inserts were tried. Fifty patients (7.9%) received augmentation therapy; it was employed after a median of only one antidepressant had been tried.

Conclusion: These preliminary findings raise a concern that psychiatrists may be hasty in performing an antidepressant switch or augmentation therapy in the treatment of depression.

Policy of full disclosure: None.

P-23-005 The study of treatment response in depressive patients with alcohol use disorders by using HAM-D

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Objective: It is known that high rate of comorbidity exists between mood disorders and alcohol use disorders. We have previously reported that depressive patients with comorbid alcohol use disorders showed poorer response to antidepressant treatment. In this study, we assessed the change of the HAM-D 17-items from baseline to study endpoint (week12) to evaluate treatment-resistant depression symptoms in those patients with alcohol use disorders.

Methods: Fifty-eight participants with depression were divided into 2 groups: non-alcohol use disorder (NAUD) group (n=36) and alcohol use disorder (AUD) group (n=22) according to Alcohol Use Disorder Identification Test (AUDIT) score (NAUD<12, AUD#12). Depression was assessed by the Mini-International Neuropsychiatric Interview (M.I.N.I). The effect of medication on depressive symptoms was monitored at 2, 4, 8 and 12 weeks using the HAM-D.

Results: The baseline score of HAM-D sleep item was higher in AUD group than in NAUD group. AUD group showed significantly less improvement in the HAM-D sleep items from baseline to endpoint compared to NAUD group. Benzodiazepine medications (dose of benzodiazepines used was equivalent to greater than 10 mg of diazepam) resulted in significant baseline to endpoint improvement in insomnia early item of HAM-D in NAUD group. On the other hand, there was no significant improvement in HAM-D sleep items after treatment in AUD group. The overall response rate was greater in NAUD group than in AUD group.

Conclusion: These results suggest that alcohol use disorder may negatively affect depression treatment outcomes not only in the overall response rate but also in the efficacy of benzodiazepines for sleep disturbance.

Policy of full disclosure: None.

P-23-006 The influence of 5- HTTLPR genotypes on the association between paroxetine plasma concentrations and their therapeutic effects in patients with major depressive disorder

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Objective: The efficacy of treatment with selective serotonin reuptake inhibitors in patients with major depressive disorder (MDD) can differ depending on serotonin transporter-linked polymorphic region (5-HTTLPR) genotype, and the efficacies of plasma concentration measurements can also differ. We aimed to investigate the differences in the associations between paroxetine plasma concentrations and clinical responses in patients with different 5-HTTLPR genotypes.

Methods: Fifty-one patients were enrolled in this study. The Montgomery-Asberg Depression Rating Scale (MADRS) was used to evaluate patients at 0, 1, 2, 4, and 6 weeks. The patients# paroxetine plasma concentrations at week 6 were measured using high-performance liquid chromatography. And their 5-HTTLPR polymorphisms (alleles S and L) were analyzed using polymerase chain reaction with specific primers. We divided the participants into two groups based on their L haplotype: the SS group and the SL and LL group. We used single and multiple regression analyses to investigate the associations between MADRS improvement and paroxetine plasma concentrations or other covariates for each group.

Results: There were no significant differences between the two groups with regard to demographic or clinical data. In the SS group, the paroxetine plasma concentrations were significantly negatively correlated with improvement in MADRS at week 6. In the SL and LL group, the paroxetine plasma concentration was significantly positively correlated with improvement in MADRS at week 6 according to the results of single regression analysis, but it was not significantly correlated with improvement in MADRS at week 6 according to the results of multiple regression analysis.

Conclusion: For the patients with MDD who does not respond to paroxetine, a lower plasma concentration or an oral dose of paroxetine might be more effective in patients with the SS genotype, and a higher that might be more effective in patients with the SL or LL genotype.

Policy of full disclosure: None.

P-23-007 Decreased serum levels of polyunsaturated fatty acids and folate, but not brain-derived neurotrophic factor, in adolescent depression

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Objective: Evidence from observational studies suggests that there is an association between depression and brain-derived neurotrophic factor (BDNF), polyunsaturated fatty acids (PUFAs), and folate; however, this association has yet to be examined in adolescent depression. The objective was to determine whether the BDNF, PUFAs, and folate in serum differ between first-episode adolescent depressed patients and healthy controls.

Methods: We measured the serum levels of BDNF, PUFAs, and folate of cases admitted to the hospital for depression (n=28) and compared it to that of controls (n=24). Subjects and their parents were informed about the nature and the purpose of this study, and a consent form was signed by parents. The ethics committee of Hirosaki University Graduate School of Medicine approved the study protocol.

Results: There were significant differences in the docosahexanoic acid (DHA), arachidonic acid (AA), and folate levels between cases and cintrols. Serum levels of DHA, AA, and folate levels in the patients group were statistically lower than those in the control group ($p<0.001$, $p=0.001$, and $p=0.01$, respectively), while serum levels of BDNF were not different between cases and controls.

Conclusion: These results are in line with findings of previous studies involving adult and elderly subjects, demonstrating lower levels of PUFAs and folate in depressed patients than healthy controls. However, further studies using larger sample size are warranted.

Policy of full disclosure: None.

P-23-008 Antidepressant dose increase or stay in early non-responders with depression

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Objective: The primary objective of this study is to compare 6-week outcomes between increasing the dose of mirtazapine versus maintaining the same dose in patients with depression who failed to show initial treatment response.

Methods: Data from a 6-week double-blind placebo-controlled randomized trial of mirtazapine in subjects with major depression were used for this post-hoc analysis. Percentages of subjects who achieved remission (i.e. a HAMD-score of#7) and changes in the 17-item Hamilton Rating Scale for Depression (HAM-D) scores from baseline at week 6 were compared between the following two groups, respectively: (1) subjects who failed to show a #20% decrease in the HAM-D total scores at week 1 but were assigned to continue 15 mg (N=21), and (2) those who failed to show a #20% decrease in the HAM-D total scores at week 1 and were assigned to increase the dose to 30 mg for another 5 weeks (N-23). Differences between groups were tested using a Student t-test or Fisher's exact test for categorical variables.

Results: The remission rate in subjects who experienced a dose increment to 30 mg was numerically higher than those who continue the initial dose (15 mg) although the difference did not reach any statistical significance (14.3% [3/21] vs. 34.7% [8/23], $p=0.17$). The 30 mg group showed a greater decrease in the HAM-D total score than the 15 mg group (mean±SD, 12.4±8.7 vs. 10.0±5.8); however, again, no statistically significant difference was observed ($p=0.31$).

Conclusion: No significant dose-response relationship was observed in mirtazapoine, possibly due to the small sample size. However, although not statistically significant, these wide differences may suggest the

possible clinical utility of antidepressant dose increase in patients with depression who failed to respond to an initial dosage.

Policy of full disclosure: None.

P-23-009 Leukocyte gene expression-based diagnostic test for major depressive disorder: A pilot and replication study

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Objective: To establish biological and easy-to-use diagnostic test for MDD can help to make early diagnosis and provide adequate treatment. In the present study, we examined the biological diagnostic test for MDD based on the leukocytes gene expression.

Methods: 25 drug-naive MDD subjects and 25 age-and-sex matched healthy subjects participated in the pilot study. The replication study involved 19 MDD subjects and 18 healthy subjects. We selected 40 candidate genes under the following criteria. 1) Genes whose expression levels were reported to be altered in the leukocytes of MDD, 2) Genes whose expression levels were found to be altered after lithium administration. 3) Candidate genes for neurobiology of MDD expressed enough in human leukocytes. We examined the level of these gene expressions using custom-made PCR array plates to differentiate MDD subjects from healthy subjects based on the gene expression profiles.

Results: Among 40 candidate genes, we identified a set of 13 significantly changed genes in MDD subjects in the pilot study. In the pilot study, the discrimination analysis based on these 13 gene expression levels demonstrated a sensitivity and specificity of 80% and 92%, respectively, in differentiating between the two groups. The replication study yielded nearly identical sensitivity and specificity (85% and 83%, respectively). We also found that the most significant 6 genes among 13 genes could yield the identical results.

Conclusion: Using leukocyte gene expression profiles, we could differentiate MDD subjects from healthy subjects with adequate sensitivity and specificity. Further research is needed to confirm the performance of the test across various psychiatric diseases. Additional markers not yet identified can further improve the performance of this test.

Policy of full disclosure: None.

P-23-010 Effect of repeated restraint stress on glucocorticoid receptor function in the rat brain

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Objective: The objective of this study was to investigate the effect of repeated restraint stress on depression- and anxiety-like behaviors in male rats and the impact of this stress on HPA axis system.

Methods: Rats were subjected to restraint stress for seven consecutive days (3 h/day) (RS7) or once as acute restraint stress (RS1). Two weeks after the last restraint stress, elevated plus maze (EPM) and forced swim tests (FST) as well as protein assay were conducted. Plasma corticosterone was also measured to assess HPA axis function.

Results: The expression of glucocorticoid receptors (GR) and FK 506 binding protein 51 (FKBP5), a co-chaperone of GR, in medial prefrontal cortex (mPFC), amygdala and hippocampus were analyzed by western blot. RS7 rats but not RS1 showed decreased time spent in open arms of EPM. Both RS7 and RS1 increased immobility time in FST. Plasma level of corticosterone in RS7 group was still increased two weeks after the last restraint stress but not altered by acute restraint stress. RS7 had no effect on GR in any brain regions analyzed, but increased FKBP5 expression in amygdala.

Conclusion: These results suggest the alteration of GR function induced by increment of FKBP5 in amygdala may mediate repeated restraint stress-induced depressive-like and anxiety-like behaviors.

Policy of full disclosure: None.

P-23-011 Efficacy and safety of vilazodone 20 mg and 40 mg in major depressive disorder: A randomized, double-blind, placebo- and active-controlled trial

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Objective: This study (NCT01473381) assessed the efficacy and safety of once-daily vilazodone (VLZ) 20 mg and 40 mg in adults with major depressive disorder (MDD).

Methods: This was a 10-week randomized, double-blind study in MDD patients comparing VLZ 20 mg/d and VLZ 40 mg/d with placebo (PBO); citalopram 40 mg/d (CIT) was included for assay sensitivity. Primary efficacy outcome was change in Montgomery-Åsberg Depression Rating Scale (MADRS) score; secondary outcomes were change in Clinical Global Impressions-Severity (CGI-S) and MADRS sustained response rate (score $\leqslant$12 for at least the last 2 consecutive visits). Safety assessments included adverse events, laboratory and vital signs, ECG, and Changes in Sexual Functioning Questionnaire (CSFQ).

Results: The safety population comprised 281 PBO, 288 VLZ 20 mg, 287 VLZ 40 mg, and 282 CIT patients; discontinuation rates were 25%, 31%, 34%, and 29%, respectively. MADRS scores improved significantly more than PBO for VLZ 20 mg (LSMD, −2.57; adjusted P=0.0073), VLZ 40 mg (LSMD, −2.82; adjusted P=0.0034), and CIT (LSMD, −2.74; P=0.0020). Reduction in CGI S scores were significantly greater than PBO for VLZ 20 mg (LSMD, −0.35; adjusted P=0.0073), VLZ 40 mg (LSMD, −0.33; adjusted P=0.0097), and CIT (LSMD, −0.35; P=0.0025). MADRS sustained response rates were higher in VLZ 20 mg (29.9%), VLZ 40 mg (33.5%), and CIT (31.1%) groups versus PBO (26.3%); differences were not statistically significant. Treatment-emergent AEs (TEAEs) were similar for VLZ 20 mg (72.2%), VLZ 40 mg (77.4%), and CIT (77.0%) and PBO (63.3%). TEAEs occurring in $\geqslant$5% of VLZ patients and twice PBO were diarrhea, nausea, vomiting, and insomnia. Most TEAEs were mild/moderate in severity. Serious AEs were reported in 2 PBO, 4 VLZ 20 mg, 4 VLZ 40 mg, and 6 CIT patients. VLZ groups improved more than CIT on the CSFQ; differences were not statistically significant.

Conclusion: These results support the efficacy, safety, and tolerability of VLZ 20 mg and 40 mg for the treatment of MDD in adults.

Policy of full disclosure: Supported by funding from Forest Laboratories, Inc. Carl Gommoll is an employee of Forest Research Institute.

P-23-012 Agomelatine's efficacy in positive and negative affects in depression

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Objective: Agomelatine is an antidepressant with a novel mechanism of action releasing dopamine and noradrenaline specifically in the limbic regions without affecting brain serotonin levels. Depressed patients given agomelatine have shown early improvement of interest and pleasure. The present study evaluated the effects of agomelatine on positive and negative emotions since their improvement in depression is important to obtain recovery.

Methods: 1565 adult outpatients with major depressive disorder receiving agomelatine were assessed using the QIDS-C, CGI, and MATHYS scales at inclusion, week 2 (W2) and week 6 (W6). The MATHYS is a self-rated visual analogue scale proposing five dimensions and 7 emotions rated according to their frequency.

Results: All negative emotions significantly decreased from inclusion to W2 and from W2 to W6. The emotional tone scores at inclusion, W2, and W6, respectively, were 2.77, 2.15, and 1.90 for sadness, 2.81, 2.20, and 1.97 for anxiety, 1.70, 1.35, and 1.15 for panic, 2.08, 1.85 and 1.70 for irritability, and 1.48, 1.37, and 1.27 for anger. Joy increased from 0.87 to 1.00 at W2 and 1.13at W6 and exaltation remained stable at around 0.65. All dimensions of the scale improved significantly ($p<0.001$) from inclusion to W2 and from W2 to W6 ($p<0.001$): emotional reactivity (from 5.36 to 5.58 and 5.60), cognitive speed (from 4.56 to 4.95 and 5.08), psychomotor function (from 2.86 to 3.86 and 4.24), motivation (from 2.36 to 3.65 and 4.09), and sensory perception (from 4.67 to 4.93 to 5.07). These changes were correlated with significant decreases of the QIDs-C and CGI scales after 2 and 6 weeks of treatment.

Conclusion: These results show an improvement of negative but also positive emotions with agomelatine that is significant as soon as the second week of treatment. This improvement may be an asset to obtain more complete functioning recovery.

Policy of full disclosure: Unrestricted grant from Servier.

P-23-013 Glutamate complex and BDNF concentration of depressive patients with cognitive dysfunction

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Objective: Decreased BDNF levels have been reported in Alzheimer's disease and regarded as a contributor to neurodegenerative change and cognitive impairment. Changes of BDNF levels in depressive patients also have been reported. So we aimed to find differences in biological markers like Glutamate and BDNF in MCI patient with and without depression, which may promote our understanding in the relationship between depression and cognitive impairment.

Methods: 163 patients diagnosed as MCI by subjective complaints and neurocognitive tests were divided into a depression group and a non-depression group. Serum BDNF levels were tested by blood sampling, and the level of glutamate in the anterior cingulate gyrus was tested by Magnetic resonance spectroscopy. A Students' T-test was performed to compare level of BDNF and glutamate between the depression group and the non-depression group.

Results: There were no significant differences in serum BDNF levels between depression and non-depression groups. Glutamate levels in the anterior cingulate gyrus were significantly lower in the depression group than in the non-depression group.

Conclusion: A decrease in glutamate levels was specific to depression in MCI patients. It suggest that depression may contribute to cognitive impairment and its progression independently, rather than just share same risk factor or being an early symptom of dementia, and that glutamate may play a role in cognitive decline. Future studies should confirm whether MCI with depression shows a higher conversion rate to dementia than MCI without depression, and longitudinally follow glutamate level and cognitive function under the treatment of depression.

Policy of full disclosure: None.

P-23-014 The alleged ineffectiveness of SSRIs in depression is an artefact caused by the use of an inappropriate measure of efficacy

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Objective: Many studies have questioned if summation of the scores of the 17 disparate items constituting the Hamilton Depression Rating Scale (HDRS-17) is a reliable index of severity in depression; yet the current questioning of the efficacy of antidepressant drugs is to a large extent based on the assumption that response to treatment is reliably reflected by this instrument. We aimed to investigate the possibility that the shortcomings of the HDRS may contribute to the failure of antidepressants to outperform placebo in many trials.

Methods: We analyzed thirteen industry-sponsored trials of selective serotonin reuptake inhibitors (SSRIs) comprising twenty-four drug-placebo comparisons and including patient-level data from 5381 subjects (administered paroxetine, citalopram, fluoxetine, or placebo), the aim being to assess what the outcome would have been if the single item depressed mood (rated 0–4) had been used as measure of efficacy.

Results: While 12 out of 24 comparisons (50%) revealed a significant difference between active drug and placebo at week 6 with respect to reduction in HDRS-17-sum, 23 out of 24 comparisons (96%) showed the active drug to be superior to placebo in reducing depressed mood. Correspondingly, a pooled analysis of all cases showed the effect size when assessed using the HDRS-17-sum to be 0.30, whereas it, when measured using the depressed mood item alone, was 0.42.

Conclusion: While not claiming that measuring one item only is the most appropriate way of recording symptom severity in depression, we do suggest that the inclusion of a number of varying symptoms in the assessment, some of which may be side-effects of treatment and/or are unrelated to the disorder, reduces the sensitivity to detect a difference between active drug and placebo. This lack of sensitivity of HDRS-17 might partly explain why a high fraction of antidepressant trials fail to reveal a significant difference between treatment groups.

Policy of full disclosure: None.

P-23-015 Abnormality of fractional amplitude of low frequency fluctuation (fALFF) in drug naive patients with major depressive disorder

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Objective: Recent resting-state fMRI studies on major depressive disorder (MDD) have found altered temporal correlation between low-frequency oscillations (LFOs). However, changes on the amplitudes of these LFOs remain largely unknown.

Methods: Male or female Han Chinese patients (18 to 45 years of age) with MDD and age, gender and education matched control subjects (n=26) were were recruited. Resting-state fMRI was obtained by using an echo-planar imaging sequence and the fractional amplitude of low-frequency fluctuations (fALFF) was calculated to investigate the amplitude of LFOs in the resting state.

Results: The depression group exhibited lower fALFF values in the left superior frontal gyrus, left middle frontal gyrus, left inferior frontal gyrus, bilateral superior parietal gyrus regions, left parahippocampal gyrus, right cerebrum, and left insula. Higher fALFF values in the depression group were observed in left inferior temporal gyrus, right caudate and right parahippocampal gyrus.

Conclusion: These findings indicated LFOs abnormalities in MDD and the fALFF analysis might be a potential approach in further exploration of this disorder.

Policy of full disclosure: None.

P-23-016 Brain serotonin transporter may predict patient with suicide attempts in drug-naïve major depressive disorder

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Objective: Much evidence suggests that the serotonergic system may play an important role in the pathophysiology of major depressive disorder (MDD) and suicide behaviors. The aim of this study was to examine whether the serotonin transporter (SERT) availability is associated with severity of MDD and a possible prediction of suicide attempt.

Methods: SERT availability was investigated in 17 drug-naïve MDD patients and 17 age-gender matched healthy controls using 4-[18F]-ADAM as a SERT radiotracer in PET brain imaging. Subjects underwent PET/CT after intravenous administration of 4-[18F]-ADAM. SERT availability was measured by PMOD software to demarcate the region-of-interest in the midbrain, thalamus, striatum, and prefrontal cortex (PFC). The 21-item Hamilton Depression Rating Scale (HDRS21) and Beck Scale for Suicide Ideation (BSS) were used to assess the severity of depression and intent of suicide idea prior to brain image.

Results: A significant differences of SERT availability were found between in drug-naïve MDD and controls in midbrain, thalamus, and striatum. SERT availability in midbrain had a linear correlation with HDRS21 in MDD group. The SERT ratio between serotonergic projection area (PFC) and raphe nuclei (midbrain) was significantly higher in suicide attempters, but no difference was noted between depressed non-suicide subjects and controls.

Conclusion: This study suggests regional SERT availability in the midbrain, thalamus, and striatum was significantly lower in drug naïve MDD than in healthy controls, and this effect was more pronounced in suicide attempters. Non-synchronous reduction of brain serotonin transporter may predict suicide attempts in drug-naïve patients with major depressive disorder.

Policy of full disclosure: None.

P-23-017 A phase 3, long-term, open-label extension study evaluating the safety and tolerability of 15 and 20 mg vortioxetine in subjects with major depressive disorder

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Objective: Vortioxetine is a recently approved antidepressant for adults with major depressive disorder (MDD). We evaluated its long-term safety, tolerability, and clinical effectiveness in MDD patients.

Methods: This 52-week flexible-dose open-label extension (OLE) trial (NCT01152996) enrolled subjects who completed 1 of 3 short-term studies (NCT01153009, NCT01163266, or NCT01179516). All subjects

switched to vortioxetine 10 mg/day for week 1, and increased to 15 or 20 mg/day based on investigator judgment. Safety and tolerability were assessed by treatment-emergent adverse events (TEAEs), laboratory values, and physical examination. Efficacy measures included the Montgomery-Åsberg Depression Rating Scale (MADRS), Hamilton Anxiety Scale (HAM-A), Clinical Global Impressions of Severity (CGI-S), and Sheehan Disability Scale (SDS).

Results: Of 1075 subjects enrolled, 538 (50.0%) completed the OLE study. Of 537 who withdrew, 115 (10.7%) discontinued due to TEAEs. TEAEs were reported by 854 subjects (79.6%), with 34 serious adverse events (SAEs) reported by 29 subjects (2.7%),11 (1.0%) of whom withdrew. SAEs reported by >1 subject included acute cholecystitis (n=2; unrelated), breast cancer (n=3; unrelated), and suicide attempt (n=2; 1 possibly related, 1 unrelated). No deaths occurred. Long-term treatment was well tolerated. TEAEs reported by ⩾5% of subjects included nausea (24.0%), headache (12.7%), diarrhea (7.5%), nasopharyngitis (6.3%), vomiting (6.3%), viral upper respiratory tract infection (URTI) (6.2%), constipation (6.1%), weight increase (6.1%), URTI (5.6%), and insomnia (5.2%). Laboratory values and physical examinations revealed no clinical trends. Mean MADRS total score and HAM-A score were 32.8 and 18.8 before the initial studies, 19.9 and 11.5 at the OLE start, and 11.9 and 7.8 after week 52 (observed cases), respectively. Maintenance of improvement was also seen in mean CGI-S and SDS scores.

Conclusion: After 52 weeks' OLE treatment, vortioxetine 15 and 20 mg were safe and well tolerated, with subjects continuing to improve on depression, anxiety, and disability symptoms.

Policy of full disclosure: This study was funded by the Takeda Pharmaceutical Company, Ltd and H. Lundbeck A/S. Paula L. Jacobsen is an employee of Takeda Development Center Americas, Inc.

P-23-018 Initial response to medication predicts early improvement after 2 weeks in patients with major depressive disorder

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Objective: A number of large-scale study and meta-analyses suggested that some current antidepressant treatments can exert some beneficial effect within the first week. Early improvement (more than 20% improvement of symptoms severity at 2 weeks) was a highly sensitive predictor of response or remission and so was a positive prognostic sign. With earlier prediction, we can avoid time wasting with unpromising medications and optimize medication for MDD patients. We investigated whether initial clinical change (ICC) and initial subjective response (ISR) can predict early improvement of antidepressant pharmacotherapy.

Methods: The symptoms of depression were assessed on the Hamilton Rating Scale for Depression (HAMD-17). ISR was checked by a Korean translation of the Modified Van Putten and May scale. CGI-I was used to assess ICC. Ratings were made at baseline, day 1, 2, 4, and 14 after treatment initiation. We employed Pearson's correlation analysis and multivariate logistic regression analyses. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and receiver operating characteristic (ROC) curves were calculated.

Results: Among 33 MDD patients, 72.7% of patients achieved early improvement on HAMD-17. Significant correlation between initial response (ICC or ISR on 2, 4 and 7 day) and early improvement were found. CGI-I score of # 3 (sensitivity 79.2%, specificity 77.8%) and change in Modified Van Putten and May scale score of # 9 (sensitivity 62.6%, specificity 77.8%) on day 7 predicted later HAMD-17 early improvement at 2 weeks.

Conclusion: The findings show that ICC and ISR might be significant predictors of early improvement in MDD pharmacotherapy. By using ICC and ISR as an indicator for the future treatment outcome, we can determine the optimal medication for MDD patient as early as within 7 days of treatment initiation.

Policy of full disclosure: None.

P-23-019 The relationship between low self-esteem and suicide attempt in patients with major depressive disorder: A pilot study

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Objective: Depression is a major risk factor for suicide, and several psychological factors such as low self-esteem are involved on suicide. The aim of this study was to investigate the difference in self-esteem between non-suicide attempters (NSA) and suicide attempters (SA) with major depressive disorder (MDD).

Methods: The study subjects consisted of 52 patients who received inpatient or outpatient treatments at the Hallym University Sacred Heart Hospital. All participants were diagnosed as MDD by Korean version of the Mini-international Neuropsychiatric Interview (K-MINI). Columbia Suicide Severity Rating Scale (C-SSRS) was used to evaluate patient's suicide attempt. They completed a questionnaire that included Rosenberg Self-Esteem Scale (RSES), Beck Depression Inventory (BDI) and Beck Scale for Suicide Ideation (BSI).

Results: A total of 52 subjects were evaluated by C-SSRS, and among them, 32 were NSA and 20 were SA. Compared to NSA, SA showed significantly lower levels of self-esteem ($t=3.49$, $p=0.001$) and higher levels of BSI ($t=-4.89$, $p<0.001$). Although there was no significant difference between two groups for severity of overall depressive symptoms, negative attitude subscale of BDI was higher in SA than NSA ($t=-2.596$, $p=0.014$). A stepwise multivariate logistic regression analysis showed that low self-esteem was significant association with suicide attempt after adjusted by negative attitude subscale of BDI and BSI (odds ratio=0.78, $p=0.04$).

Conclusion: The present study indicated that low self-esteem plays a significant role in SA with MDD. Assessment of suicide risk should include not only suicide ideation and severity of overall depressive symptoms but also low self-esteem.

Policy of full disclosure: None.

P-23-020 Modelling the cycling of mood in a preclinical model of depression

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Objective: Major depression is a recurrent condition. Almost without exception, animal models of depression have not addressed the sensitization that develops over the course of subsequent depressive episodes, and therefore, they do not provide means to understand the neurobiological mechanisms by which depression becomes autonomous of stress. In our recent work, we have attempted to recapitulate the cyclical course of human depression in a preclinical animal model of depression.

Methods: We assessed depression-like behavior in rats through 3 cycles of treatment with and recovery from the stress hormone corticosterone (CORT). Each cycle of treatment comprised 21 days of CORT injections (either 10 mg/kg, 20 mg/kg, or 40 mg/kg) followed by 21 days of stress-free recovery. Depression-like behavior was measured in the middle and end of each CORT treatment and at the end of each recovery period using the forced swim test. We also collected brain tissue at each behavioral time point so we could analyze the number and maturation rate of immature neurons within the granule cell layer of the dentate gyrus.

Results: CORT administration produced increasingly greater effects on depression-like behavior through each cycle of treatment. In the first cycle, CORT increased depression-like behavior after 21 days of treatment, which then normalized after the recovery period. In the second and third cycles however, CORT induced an early manifestation of depression-like behavior after only 10 days of treatment. In addition to these behavioral changes, CORT also produced physiological alterations indicative of depression: decreased body weight gain (1st cycle) and body weight loss (2nd and 3rd cycles) and accumulative decreases in the number and dendritic complexity of immature granule neurons.

Conclusion: These results present a promising model for better understanding the mechanisms of chronic and recurring depression.

Policy of full disclosure: None.

P-23-021 Serum mirtazapine monitoring in the Korean psychiatric patients

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Objective: Mirtazapine is a tetracyclic antidepressant that acts by enhancing serotonergic and noradrenergic neurotransmission. This study aimed to evaluate mirtazapine pharmacokinetic (PK) data from Korean psychiatric patients on long-term mirtazapine treatment, and to understand potential factors affecting its steady-state concentrations in a clinical setting.

Methods: Total 337 steady-state mirtazapine concentrations from 189 adult psychiatric outpatients were evaluated. Serum mirtazapine concentrations were measured by HPLC-MS/MS as a routine. We retrospectively collected data including patients' demographics, mirtazapine dosing history, and concurrent medications.

Results: Median mirtazapine concentration was 42.3 ug/L (range: 2.9~199.3) at the 7.5 to 60 mg daily dosage range. At steady state, mirtazapine dose had positive correlation with the drug concentration ($r=0.498$, $P<0.0001$). However, even at a constant dose, large intra- and inter-individual variations in the drug concentrations were observed; individual C/D ratio ranged from 0.06 to 5.52 and maximum to minimum

concentration ratio in an individual with a constant dose was shown up to 11 fold. In elderly patients, dose-adjusted serum concentrations were higher than those of the younger ones. Body weight, sex, and co-medications (eg. paroxetine, venlafaxine, diazepam, sertraline, fluoxetine) did not reach statistical significance in correlation with dose-adjusted drug concentrations. In addition, treatment responsiveness was not associated with initial mirtazapine concentration.

Conclusion: This study presented therapeutic drug monitoring data of mirtazapine and pharmacokinetic variations in a routine outpatient setting. Considering the large inter- and intra-individual variability and poor compliance in psychiatric patients, therapeutic drug monitoring of mirtazapine would be helpful to improve pharmacotherapy.

Policy of full disclosure: None.

P-23-022 Aripiprazole augmentation for major depressive disorder: Dosing patterns in a naturalistic treatment setting

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Objective: This study investigated the dosing patterns for aripiprazole augmentation for major depressive disorder (MDD) in a naturalistic treatment setting.

Methods: Between 1 January 2009 and 31 March 2012, patients with a diagnosis of MDD who were receiving aripiprazole augmentation in conjunction with an ongoing antidepressant were recruited for this study. The electronic medical records and clinical data for a total of 276 patients were reviewed up to a year.

Results: The mean duration of aripiprazole augmentation was 5 months; the mean time to the first increase of aripiprazole was about 3 weeks; and the mean initial, first up-titrated, maximal, and maintenance doses were 3.4, 4.2, 4.7, and 4.4 mg/day, respectively. The most frequent adverse events were insomnia, followed by anxiety and sedation.

Conclusion: The current results indicate that the actual doses of aripiprazole augmentation with ongoing antidepressant for MDD should be lower than the doses used in placebo-controlled clinical trials and those recommended by the US Food and Drug Administration. Adequately powered and well-controlled prospective studies are needed to better understand the exact role of low doses of aripiprazole augmentation in the treatment of MDD, particularly in routine practice.

Policy of full disclosure: None.

P-23-023 Decreased quality of life in elderly patients with subsyndromal depression

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Objective: Non-major depression with fewer symptoms than required for a DSM-IV diagnosis of major depressive disorder (MDD) has consistently been found to be associated with functional impairment. In this study, we aim to estimate the quality of life in elderly patients with subsyndromal depression (SSD) compared with non-depressive elderly (NDE).

Methods: The Korean version of Mini International Neuropsychiatric Interview was administered to 194 of outpatients with depression and 108 of normal control group. SSD is defined as having five or more current depressive symptoms with core depressive symptoms (depressive mood or loss of interest or pleasure) during more than half a day and more than seven days over two weeks. Depression was evaluated by the Korean form of Geriatric Depression Scale of a 15-item short version (KGDS-15). Global cognition was assessed by the Korean Version of Revised form of Hasegawa Dementia Scale (K-HDS) and Mini-Mental State Examination in the Korean version of CERAD assessment packet (MMSE-KC). Subjective cognitive impairment was assessed Subjective Memory Complain Questionnaire (SMCQ). Quality of life was evaluated by The Korean Version of Short-Form 36-Item Health Survey (SF-36).

Results: The scores of physical component summary (PCS)($F=9.274$, $p=0.003$, ANCOVA) and mental component summary (MCS) ($F=53.166$, $p<0.001$, ANCOVA) in the SSD group were lower than those in NDE group with adjustment for age, gender, and education.

Conclusion: Subjects with SSD, as well as those with MDD, were experienced low quality of life in both physical and mental aspects, compared to NDE group.

Policy of full disclosure: None.

P-23-024 Infanticide in psychiatry: Theoretical concepts and clinical practice

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Objective: Infanticide committed by women suffering from mental disorder is a serious medical, social and ethical issue. We present theoretical concepts of this topic as well as case reports of such incidents. We also deal with therapeutic implications and possibilities of re-entry into normal life. Transcultural socio-legal differences in terms of this issue is also investigated.

Methods: Our work analyze and sumarize theoretical concepts of infanticide committed by women suffering from mental disorder. Case reports from our practice are atteched.

Results: It is often very difficult, from forensic point of view, to determine the extent of distortion control and cognitive abilities at the time of committing the incriminating act. The result of this assessment has serious legal consequences and a tremendous influence on the fate of the patient. However, regardless of verdict of the court, many other factors are no less important for the woman: psychological support to cope with the event after resolving of psychotic symptoms; attitude of partner and close relatives; psychopharmacological treatment; social attitudes towards this issue and toward mental disorders per se etc. These factors together participate on the quality of next life and course of mental illness.

Conclusion: Psychotic symptoms give rise to the infanticide in many cases – Transcultural differences in the approach to the infanticide are evident – Postapartum psychosis as a risk factor of infanticide.

Policy of full disclosure: None.

P-23-025 Female transgenic mice with conditional glucocorticoid receptor deletion in noradrenergic system display depressive-like behavior reversed by desipramine and fluoxetine

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Objective: Hyperactivity of hypothalamic-pituitary-adrenal system (HPA) is believed to be one of the major contributors to depression pathology. The activity of HPA is controlled by glucocorticoid receptors (GR) which function may be impaired in depression, resulting in reduced GR-mediated negative feedback on the HPA axis. Animals carrying mutations of GR reveal alterations in the HPA comparable to those observed in depressed patients. The aim of this study was to investigate if conditional inactivation of GR narrowed to noradrenergic system (an important target for antidepressant therapy) may evoke depressive-like behavior in mice.

Methods: The experiments were carried out on male and female mice lacking GR selectively in noradrenergic neurons. Ablation of GR in noradrenergic system was achieved using the Cre/loxP approach by crossing transgenic mice hosting the Cre recombinase under the dopamine beta-hydroxylase promoter with animals harboring the floxed GR gene. Mice were screened for anxiety- and depressive-like behavior in Light/Dark Box Test and Tail Suspension Test (TST). Desipramine (20 mg/kg, i.p.) and fluoxetine (10 mg/kg, i.p.) were administered in single dose 30 minutes before test.

Results: Resulting GRDBHCre mice were born at expected rates, viable and showed no obvious physical impairment regarding life span, fertility, weight gain and locomotor activity. Interestingly, female GRDBHCre mice showed anxiety-like behavior (increased latency to enter light box compartment), and depressive-like behavior (increased immobility time in TST) while no changes were observed in male mutants. This depressive-like behavior was reversed after single dose of desipramine and fluoxetine. However, we observed that the effect of fluoxetine was more pronounced in female mutant mice than in their littermate controls, while the effect after desipramine treatment remained similar despite of genotype.

Conclusion: Female GRDBHCre mice may represent an interesting novel genetic model to study depression. Moreover, our results emphasize the gender variability in depression often neglected in experimental study.

Policy of full disclosure: None.

P-23-026 Molecular analysis of prefrontal cortex in mice exposed to chronic mild stress; the influence on lipid and carbohydrate metabolism under depressive state

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Objective: Major depressive disorder (MDD) is a common disorder and is responsible for considerable disability, anorexia, and physical comorbidity. Recently, there have been some researches regarding the relationship between MDD and metabolic disorders such as dyslipidemia. As a risk factor of developing MDD, additionally, the oral hypoglycemic agents such as sulfonylureas should be noted and certain causal relations between MDD and diabetes may exist. In this study, we generated depression-like behavior in mice animal models by chronic mild stress (CMS) according to the standardized procedure to investigate the relations between MDD and metabolic disorders focusing on molecular mechanism.

Methods: C57BL/6N mice that had been received CMS for four weeks showed several kinds of depression-like behavioral changes. We performed comparative analysis of the gene expression profile of the prefrontal cortex between CMS mice and the controls using microarray and Quantitative real-time PCR (qRT-PCR). For further analysis, we categorized the genes by using two web-based bioinformatics analysis tools. The 1st tool consisted of the Database for Annotation, Visualization and Integrated Discovery (DAVID), which looked for significantly enriched genes, and categorized them by Gene Ontology#(GO) terms. The 2nd one was network explorer of ingenuity pathway analysis (IPA), which looked for the functions, interactions, and diseases of these extracted genes particularly. We confirmed the expression level of mRNA and protein of some genes by qRT-PCR and Western blotting analysis, respectively.

Results: According to the microarray results, 494 genes were differentially expressed. The two kinds of web tools suggested that many differentially expressed genes were significantly related to dyslipidemia and to diabetes.

Conclusion: We found a number of isolated genes with significant differences and direct interactions between MDD and metabolic disorders. Further examinations focusing on the roles of these genes in the PFC should be needed for strengthening the possibility of novel drug development for MDD.

Policy of full disclosure: None.

P-24. Eating disorders

P-24-001 Exploring cognitive function in obesity: Assessment of 5-choice serial reaction time task performance in leptin-knockout rats

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Objective: Impulse control deficits may contribute to excessive food intake in some individuals with obesity. In addition to its role in regulating appetite and energy expenditure, leptin also directly modulates the activity of central dopaminergic circuits. While dopamine is involved in mediating impulsivity, the influence of leptin on this cognitive domain remains unclear. Here, we explored the performance of leptin-knockout (leptin-KO) rats in the 5 Choice Serial Reaction Time task (5CSRT), a rodent analogue of the Continuous Performance Test used clinically to assess impulse control and attention.

Methods: Male leptin-KO (n=7) and wild type (n=11) rats were food restricted under standard conditions and trained in the 5CSRT. Animals learned to respond to a brief light stimulus presented in one of five locations to earn a food reward. Responses made before stimulus presentation provided an index of motor impulsivity, while other variables measured attentional ability and motivation to perform the task. Performance was assessed at baseline, after 4-week's consumption of high-fat diet, and after acute amphetamine challenge.

Results: Leptin-KO rats showed a mild learning deficit compared to controls, yet there were no differences in baseline performance once the task was acquired. Prolonged consumption of a high-fat diet did not affect 5CSRT performance in either group. In contrast, leptin-KO rats showed enhanced impulsive responding following amphetamine treatment compared to controls, while other behavioural variables remained unchanged.

Conclusion: Leptin deficiency slowed the rate at which animals learned the 5CSRT but did not alter performance at baseline or after high-fat diet consumption. A genotype effect on motor impulsivity was prominently observed after amphetamine treatment, with leptin-KO rats showing potentiated premature responses; however, the caveat that both groups had been consuming high-fat diet limits our interpretation of these data. Molecular assays of dopaminergic markers are ongoing and may shed light on the mechanisms underlying these findings.

Policy of full disclosure: None.

P-24-002 Effects of high-fat diet and binge-like food intake on cognitive performance in the 5-choice serial reaction time task

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Objective: Compulsive overeating, as seen in binge-eating or obese individuals, may involve abnormalities in reward, motivation and impulse control circuits akin to those seen in drug addiction. While rats preferentially consume high-fat foods, the behavioural effects of chronically consuming a high-fat diet have yet to be thoroughly investigated. This study explored the effect of a high-fat diet on attention, motivation for food rewards and impulsivity in rats, in states of hunger and after binge feeding.

Methods: 31 male Long-Evans rats received restricted daily allotments of either a high-fat (n=15) or control (n=16) diet, and trained on the 5-Choice Serial Reaction Time task (5CSRT). In this task, animals must respond to a brief light stimulus to receive a food reward; accuracy (%correct responses) indexes attention, reward collection latencies and omitted trials index motivation, and premature responses index motor impulsivity. Once animals were trained, they were allowed to binge for 2 hours/week on control food (5 weeks), and then on high-fat food (5 weeks). The basal effects of high-fat diet consumption, as well as the influence of binge feeding, on task performance were assessed.

Results: Rats maintained on a high-fat diet omitted fewer trials at baseline, and showed a blunted increase in omissions in sessions after binge-feeding, than rats maintained on a control diet. High-fat diet animals also collected food rewards more quickly than controls. However, diet or bingeing did not affect other 5CSRT variables.

Conclusion: Our results indicate that long-term consumption of high-fat diets increases motivation for food rewards and attenuates the acute demotivating effects of bingeing. As such, these data suggest that individuals who chronically consume high-fat foods may continue to seek and eat food even when physically satiated. Molecular analyses of brain regions involved in motivation and reward may help clarify the neurobiological mechanisms underlying these behavioural changes.

Policy of full disclosure: None.

P-25. Schizophrenia B

P-25-001 Metabolic risk and status with continuous antipsychotic treatment in chronic schizophrenia patients between 2-year period

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Objective: The prevalence of diabetes mellitus in schizophrenic patients is several times higher than that of the general population. In addition, common side effects of atypical antipsychotic treatments for schizophrenia are weight gain and lipid metabolism abnormality. In our previous study of 68 chronic schizophrenic patients using atypical antipsychotics, we reported relatively high levels of resistin and a significant correlation between body mass index (BMI) and Homeostasis Model Assessment-Insulin Resistance (HOMA-IR). We expanded this research in our current 2-year study, examining metabolic laboratory values in chronic schizophrenia patients who used continuous antipsychotic treatment.

Methods: This study was a prospective cohort study. The participants were 42 schizophrenic patients (22 males, 20 females; aged 25–79 years, mean age 52.6±13.4). The Brief Psychiatric Rating Scale (BPRS) and the Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS) were used for medical assessment. Changes in carbohydrate metabolism (C-peptide, resistin, insulin levels, lipid metabolism, HOMA-IR) and changes in physical characteristics (BMI, abdominal girth, the number of metabolic syndrome conditions) were studied over a 2-year period. In addition, single nucleotide polymorphisms (SNP) in the transcriptional regulatory region of the resistin gene were examined.

Results: We found no changes in the mental state of the participants. Moreover, physical changes, such as changes in BMI and abdominal

girth, were not observed. The SNP-420 genotype was not associated with any data. However, there were statistically significant decreases in the mean values of total cholesterol and hemoglobin A1c levels after 2 years.

Conclusion: There were almost no changes in the blood examinations and the physical states of patients with chronic schizophrenia after 2 years of treatment. Research studies observing longer treatment periods are needed to examine how adverse metabolic effects change over time in schizophrenia patients who use continuous antipsychotic treatment.

Policy of full disclosure: None.

P-25-002 Effects of clozapine on dopamine dynamics in the amygdala of stress-sensitive animals

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Objective: Stress can flare up schizophrenic symptoms to cause hypersensitivity in emotional handling the event, so it is meaningful to study the effects of relevant drugs on the dopamine dynamics in the amygdala. We have so far studied using stress-sensitive animals with a special reference to schizophrenia and found that anti-psychotic drugs suppress the dopamine release provoked by fearsome stimulation in the amygdala. To clarify the effects of clozapine commonly given for treatment-refractory schizophrenia, we using animals under conditioned fear stress application attempted to study how clozapine affects the dopamine regulation during fear stimulation in the amygdala.

Methods: Chronic administration of methamphetamine (MAP) results in MAP-sensitization, and we used MAP-sensitized rats as surrogate for stress vulnerability in schizophrenia. Fear conditioning can be formed during stressful environment according to the classical conditioning theory and was widely applied for research of psychiatric disorders. The variations of dopamine levels in the amygdala were measured with time using microdialysis and HPLC (high-performance liquid chromatography).

Results: A single dose of clozapine was identified to suppress the fear stimulation-induced excess of dopamine release in the amygdala more significantly in the stress-sensitive model than in the saline control. However, clozapine did not affect any baseline dopamine levels in the stress-sensitive models.

Conclusion: In our series of studies we have so far demonstrated that anti-psychotic agents suppress the fear stimulation-induced excess of dopamine release in the amygdala either in normal or MAP-sensitized rats. However, these agents suppress dopamine excessive release after fear stimulation conditioning by changing the dopamine baseline levels. In stress-sensitive models, clozapine suppresses the excessive release of dopamine after stimulation conditioning without changing the dopamine baseline levels, suggesting that the results were different from other anti-psychotic drugs. We have already reported similar results with valproate (VPA), and it is warranted to compare clozapine with VPA to elucidate the emotion-stabilizing action of these agents.

Policy of full disclosure: None.

P-25-003 Seizures, EEG abnormalities, and clinical response during clozapine therapy in Japanese patients with schizophrenia

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Objective: Clozapine is effective against treatment-resistant schizophrenia and was introduced to Japan in 2009. Clozapine-induced seizures are more frequent than agranulocytosis, and electroencephalography (EEG) abnormalities are even more common. Because clozapine efficacy varies among individuals and races, there is a need to determine the predictive factor of treatment-response and side effects of clozapine in a Japanese population. Here, we describe EEG abnormalities and seizures associated with clozapine treatment in Japanese schizophrenia and compare EEG results and total score of positive and negative syndrome scale (PANSS (T)) before and after treatment.

Methods: Twenty patients with treatment-resistant schizophrenia according to Diagnostic and Statistical Manual of Mental Disorders IV criteria were enrolled in this study, including 4 males and 16 females. EEGs were obtained prior to clozapine treatment, when seizures occurred, and every 4 weeks. PANSS (T) were used to determine clozapine treatment outcome and were compared at baseline and last observation.

Results: All patients had normal baseline EEGs, and 10 patients (50%) later showed EEG abnormalities. There were no significant differences between the EEG normal and EEG abnormal groups in mean age, gender, mean clozapine dose, or length of treatment with clozapine. Six patients (30%) experienced seizures; one with both tonic-clonic and myoclonic, one with tonic-clonic and four with myoclonic seizures. The mean baseline PANSS (T) scores were not significantly different between the EEG normal and EEG abnormal groups, but the mean score in the EEG abnormal group was significantly lower than that in the EEG normal group at the final follow-up. The response rate of the EEG abnormal group was higher, albeit not significantly, than that of the EEG normal group.

Conclusion: Clozapine is more likely to cause seizures in the Japanese population. EEG abnormalities appeared after clozapine treatments are associated with a good clinical response to clozapine.

Policy of full disclosure: This work was supported by Health and Labor Sciences Research Grant Number 3000000301.

P-25-004 Association study of methamphetamine- and phencyclidine-responsive gene, WD repeat domain 3, in schizophrenia

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Objective: Methamphetamine, an indirect dopamine agonist, and phencyclidine, an antagonist of the N-methyl-D aspartate type glutamate receptor, are known to cause schizophrenia-like symptoms only after adolescent period. Previously, by using a microarray technique, we found that cortical gene expression of WD repeat domain 3 (WDR3) protein was up-regulated in the adult but not in infant rats by these schizophrenomimetics. WDR3 and other related proteins are the nuclear proteins presumably involved in various cellular activities, such as cell cycle progression, signal transduction, apoptosis, and gene regulation. To further elucidate molecular pathophysiology of schizophrenia, we have examined genetic association of WDR3 in schizophrenia.

Methods: We examined 11 single nucleotide polymorphisms (SNPs) of human WDR3 gene, using an 1808 schizophrenics and 2170 matched controls from Japanese population. Additionally, for the family-based association study 204 patients and their parents were examined. All the study was approved by ethics committees of the institutes. All participants gave informed and written consent to participate in the study.

Results: In a genotypic test a nominally significant association with schizophrenia was observed in one SNP. By additional stratification analysis, we found one SNP showed a significant correlation with female schizophrenia. Furthermore, four SNPs displayed nominally significant association with certain onset-age groups of schizophrenia in female and male schizophrenics. In a block-based haplotype analysis, one block showed nominal association with schizophrenia. In female, same block showed a significant association.

Conclusion: Our findings suggest that WDR3 gene may be a susceptibility factor of female and inclinable specific onset ages of schizophrenia. One SNP, which is located in CTCF binding site of 5′ upstream of WDR3 gene, showed a significant association with female schizophrenics. The polymorphism of this site might be linked to the insulator function/dysfunction of the WDR3 and flanking cluster genes. In conclusion, WDR3 might be involved in the molecular basis of schizophrenic pathology.

Policy of full disclosure: None.

P-25-005 Transcriptomic evidence for immaturity of the prefrontal cortex in patients with schizophrenia

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Objective: Schizophrenia, a severe psychiatric disorder, has a lifetime prevalence of 1%. The exact mechanisms underlying this disorder are still unknown, though theories abound. Recent studies suggest that particular cell types and biological processes in the schizophrenic cortex have a pseudo-immature status, in which the molecular properties are similar to those in normal immature brain. However, whether the maturational state of a certain brain region as a whole is affected in schizophrenia is not known. Here, we show that the schizophrenic prefrontal cortices (PFC) resemble juvenile PFC in terms of genome-wide expression profile.

Methods: We conducted a gene expression meta-analysis in which expression patterns that are altered in the dorsolateral PFC (DLFC) and the medial PFC (MFC) of schizophrenia patients were compared with those in the corresponding regions of developing normal human brains.

Results: We found that overall gene expression patterns in the schizophrenic PFC resemble those in the normal immature PFC. Furthermore, we showed that more than half of the common gene alterations in schizophrenic and developing PFC could be derived from maturational abnormalities of fast-spiking interneurons, astrocytes, and oligodendrocytes. Additionally, we found that developing human PFC shows a gene expression pattern similar to that of the PFC of naive Schnurri-2 knockout

mice, an animal model of schizophrenia with good face and concept validity, suggesting that the juvenile-like gene expression patterns observed in the schizophrenic PFC may not be due to medication.

Conclusion: Collectively, our results provide strong evidence that pseudo-immaturity of PFC resembling that of the juvenile brain is an endophenotype for schizophrenia.

Policy of full disclosure: None.

P-25-006 Effects of n-acetylcysteine on clinical symptoms in subjects with at-risk mental state: A case series

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Objective: The safer preventive intervention of psychosis in subjects with at-risk mental state (ARMS) is warranted. Given that N-acetylcysteine (NAC), a glutathione precursor, has neuroprotective effects, its preventive use in psychosis merits investigation.

Methods: Four subjects with subthreshold psychosis were given NAC (2000 mg/day) as supplementation for 12 weeks. Clinical evaluations were conducted at baseline, 12- and 24-weeks. The primary outcome measure was changes in the Scale of Prodromal Symptoms (SOPS). Secondary outcome measures included the Brief Assessment of Cognition in Schizophrenia-Japanese language version (BACS-J), the Schizophrenia Cognition Rating Scale (SCoRS), UCSD Performance-based Skills Assessment-Brief (UPSA-B), Schizophrenia Quality of Life Scale-Japanese version (SQLS-J) and magnetic resonance spectroscopy. This work was supported by JSPS Grant-in-Aid for Young Scientists (B) 24791239. This study protocol was approved by the bioethics committee of St. Marianna University School of Medicine, and written informed consent was received from all participants.

Results: NAC improved the SOPS total score from baseline to endpoint (43.0±13.0 to 22.8±22.2). Three subjects no longer met the criteria of ARMS at endpoint. In addition, improvements in the BACS-J composite z-score (from −0.58±1.17 to 0.16±0.91), the SCoRS and the SQLS-J score were observed, but the UPSA-B score did not change. The N-acetylaspartate/creatine ratio in the dorsolateral prefrontal cortex was higher in subjects who didn't meet the criteria of ARMS at endpoint compared with that in subjects who remained ARMS. No serious adverse events were observed during the trial.

Conclusion: This is the first report which examined the effects of NAC on clinical symptoms in subjects with ARMS. NAC may have beneficial effects on psychophathological symptoms, cognitive functions, functional capacity and subjective QOL. Thus, NAC may offer a safe and efficacious strategy for improving clinical symptoms in subjects with subthreshold psychotic states.

Policy of full disclosure: Dr. Miyake has received speaker's honoraria from Dainippon Sumitomo and Otsuka, and has received research support from KAKENHI and research group for schizophrenia. Dr. Miyamoto has received advisory board honoraria from Dainippon Sumitomo. Dr. Yamaguchi has received advisory board and/or speaker's honoraria from Daiichi Sankyo, Eizai, Eli Lilly, Janssen, Otsuka, and Takeda. No other authors have any conflicts of interest.

P-25-007 Clinical and biological correlates of resilience in patients with schizophrenia: A cross-sectional study

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Objective: Resilience refers to the process of adapting well in the face of significant risk and adversity (e.g. traumatic life events). However, little is known about factors that bring about resilience in patients with severe mental illness. The objective of this cross-sectional investigation was to identify clinical and biological correlates of resilience in patients with schizophrenia.

Methods: Clinically stable outpatients with schizophrenia (DSM-IV) were included. Subjective resilience was assessed using the Resilience Scale (Wagnild and Young 1993). Other clinical variables included sociodemographic data, premorbid adjustment, premorbid intelligence, duration of illness, psychopathology, insight, chlorpromazine-equivalent doses of antipsychotics, drug attitude, personal and social performance, hopelessness, internalized stigma, quality of life (QOL), and self-esteem. Furthermore, as candidate biomarkers of resilience, blood samples were assessed for adrenocorticotropic hormone (ACTH), cortisol, and high-sensitivity C-reactive protein (hs-CRP) levels, while saliva samples were assessed for alpha-amylase concentrations.

Results: Fifty-six outpatients were assessed between April 2013 and January 2014 (mean±SD age, 45.9±10.0 years; duration of illness, 19.4±10.6 years; 22 males; all Japanese). On a scale of 25–175 with higher scores indicating higher resilience, mean±SD total scores of resilience amounted to 110±25 (range: 46–170). Spearman's rank correlation coefficient showed that resilience was positively correlated to self-esteem and QOL, while negatively correlated with internalized stigma, hopelessness, and poor premorbid adjustment. Other variables, including biological markers, showed no statistically significant correlations with resilience. In a stepwise multiple regression analysis, the model including self-esteem (Beta=0.746, p=0.000) and hs-CRP (Beta=0.255, p=0.009) best explained resilience, with the adjusted R-squared amounting to 0.530.

Conclusion: Resilience in patients with schizophrenia correlated positively with self-esteem and QOL, and negatively with internalized stigma, hopelessness, and poor premorbid adjustment. Further studies with larger sample sizes are warranted to elucidate the theoretical construct and biological bases of resilience in patients with schizophrenia.

Policy of full disclosure: None.

P-25-008 Effect of aripiprazole on cognitive function and functional capacity in antipsychotic-naïve first-episode schizophrenia: First report

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Objective: Cognitive impairment is a core feature of schizophrenia and is present early in the course of the illness. Impairments in cognitive functioning are correlated with impaired functional capacity. The purpose of this study was to evaluate the short-term effects of aripiprazole, an atypical antipsychotic, on cognitive function and functional capacity in first-episode schizophrenia.

Methods: Thirteen antipsychotic-naïve patients with first-episode schizophrenia participated in the study. Aripiprazole (3–30 mg/day) was given in an open label design for 8 weeks. Clinical evaluations were conducted at baseline and 8 weeks after the start of treatment. The main outcome measure was change in cognitive function assessed by the Brief Assessment of Cognition in Schizophrenia (BACS-J). Secondary outcome measures included the Schizophrenia Cognition Rating Scale (SCoRS), UCSD Performance-based Skills Assessment-Brief (UPSA-B), the Positive and Negative Syndrome Scale (PANSS) and the Clinical Global Impression-Severity of Illness Scale (CGI-S). This study protocol was approved by the bioethics committee of St. Marianna University School of Medicine, and written informed consent was received from all participants.

Results: Ten patients (3 males and 7 females; mean age, 32.2±6.4 years) completed the study. One patient dropped out, and two patients are in progress. The mean daily dose of aripiprazole was 6.9±6.6 mg/day at 8 weeks. Significant improvements from baseline to endpoint were observed for verbal memory and verbal fluency on the BACS-J, the communication domain on the UPSA-B, the SCoRS score, and all subscales on the PANSS and CGI-S ($p<0.05$).

Conclusion: These results suggest that aripiprazole can improve psychopathological symptoms and some types of cognitive function and functional capacity which may be associated with verbal communication in first-episode schizophrenia. We will present the data of more cases in the congress.

Policy of full disclosure: None.

P-25-009 Blonanserin ameliorates phencyclidine-induced impairment of visual recognition memory (2): Involvement of dopamine-D_1 receptor-PKA signaling

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Objective: Blonanserin exhibits higher affinity for dopamine-$D_{2/3}$ than for serotonin 5-HT_{2A} receptors. It ameliorates cognitive impairment by augmentation of dopaminergic neurotransmission due to inhibition of both

dopamine-D_3 and serotonin 5-HT_{2A} receptors of the medial prefrontal cortex (mPFC) in mice administered phencyclidine [PCP; a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist] repeatedly, as an animal model of schizophrenia. Cognitive impairments in mice administered PCP repeatedly, which is accompanied by dysfunction of the dopamine-D_1 and/or NMDA receptors in the mPFC. However, the molecular mechanism of ameliorating effect of blonanserin remains unclear. In the present study, we investigated the postsynaptic mechanisms underlying the effect of blonanserin on cognitive impairment in PCP-administered mice.

Methods: The visual recognition memory and the levels of phosphorylated NR1 (an essential subunit of NMDA receptors) [Ser^{897} and Ser^{896} phosphorylate by a protein kinase A (PKA) and PKC, respectively] in the mPFC were evaluated by the novel object recognition test (NORT) and western blot analysis, respectively.

Results: The ameliorating effect of blonanserin on PCP-induced cognitive impairment was antagonized by SCH23390, a dopamine-D_1 receptor antagonist, and H-89, a PKA inhibitor. The levels of NR1 phosphorylated at Ser^{897} by PKA in the mPFC of PCP-administered mice after a NORT training session were significantly decreased, compared to those in saline control mice. The phosphorylation levels in the PCP-administered mice were raised by blonanserin, the effect being blocked by SCH23390. There were no differences in the levels of NR1 phosphorylated at Ser^{896} by PKC in any group.

Conclusion: Our findings suggest that dopamine-D_1 receptor-PKA signaling is required for the ameliorating effect of blonanserin on cognitive impairment. Additionally, activation of NMDA receptors in the mPFC through dopamine-D_1 receptor-PKA, but not PKC, signaling is also critical for recognition memory in PCP-administered mice.

Policy of full disclosure: None.

P-25-010 Translating study results into real-world psychiatric practice: An experience in a male, locked, non-acute unit serving for persistently ill patients over one year

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Objective: The authors, previously reported on the effectiveness of antipsychotic augmentation strategies in severely afflicted populations, herein describe an experience in a male, closed psychiatric unit over one year.

Methods: The unit is a non-acute one serving for persistently and severely ill patients in serious needs. This study was approved by Inokashira Hospital. Psychopharmacotherapy of 60 patients (53 with schizophrenia (ICD-10), mean+/−S.D. age 58.4+/−13.0 y.o., duration of illness 30.5+/−15.0 years, approximate duration of admissions 19.1+/−14.4 years) who gave informed consent and were treated for more than three consecutive months in the unit during F.Y. 2013 will be critically evaluated. Clinical evaluation was routinely performed with the CGI and FACT-Sz.

Results: Thus far, compared to the baseline (March 2013 or at the time of admission to the ward), the number and dose of antipsychotics was reduced from 1.80 to 1.03 and 923 mg to 580 mg, respectively. The number of total psychotropics was also significantly minimized from 4.75 to 2.12. Overall, the CGI-Severity and FACT-Sz improved slightly from 5.80 to 5.45 and 29.2 to 33.4, respectively. Likewise, the CGI-Improvement was 4 (i.e., no change) for 36 patients, 3 (minimally better) for 19 patients, and 2 (much better) for 5 patients. Twenty-one patients were successfully treated with an antipsychotic with/without a benzodiazepine (prescribed in 28 patients, mostly lorazepam) or an antiparkinsonian drugs (prescribed in only three patients). Twenty-one patients needed adjunctive valproate (average blood levels 95.9+/−22.1 microg/ml) and nine patients used lithium (0.631+/−0.255 mEq/l). However, only seven patients (11.7%) needed two antipsychotics simultaneously.

Conclusion: Optimization of psychopharmacotherapy is possible in the real-world for difficult patients and, while augmentation of an antipsychotic with mood stabilizers is frequently needed, antipsychotic polypharmacy should be exceptional even in a challenging population.

Policy of full disclosure: The authors have declared that there are no conflicts of interest in relation to the subject of this study. Dr. Suzuki has received manuscript or speaker#s fees from Astellas, Dainippon Sumitomo, Eli Lilly, Elsevier Japan, Janssen, Meiji Seika, Novartis, Otsuka, and Weily Japan. Dr. Uchida has received grants from Pfizer, Astellas Pharmaceutical, Eisai, Otsuka Pharmaceutical, GlaxoSmithKline, Shionogi, Dainippon-Sumitomo Pharma, Eli Lilly, Mochida Pharmaceutical, Meiji-Seika Pharma, Janssen Pharmaceutical, and Yoshitomi Yakuhin and speaker#s honoraria from Otsuka Pharmaceutical, Novartis Pharma, Eli Lilly, Shionogi, GlaxoSmithKline, Yoshitomi Yakuhin, Dainippon-Sumitomo Pharma, Meiji-Seika Pharma, and Janssen Pharmaceutical within the past three years. Dr. Tsunoda has nothing to disclose. Dr. Mimura has received grants or speaker#s honoraria from Asahi Kasei Pharma, Astellas Pharmaceutical, Daiichi Sankyo, Dainippon-Sumitomo Pharma, Eisai, Eli Lilly, GlaxoSmithKline, Janssen Pharmaceutical, Meiji-Seika Pharma, Mochida Pharmaceutical, Novartis Pharma, Otsuka Pharmaceutical, Pfizer, Shionogi, and Yoshitomi Yakuhin within the past two years.

P-25-011 Effect of antipsychotics on telomere length in the hippocampus

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Objective: Recently, leukocyte telomeres in schizophrenia patients have been reported to be shorter than that in healthy subjects. Several lines of evidence suggested that telomere shortening was induced by biophysical and psychological stress, especially during neurodevelopmental period that is thought to be causative for schizophrenia. Additionally, chronic stress exposure to mice suppressed neurogenesis in the hippocampus accompanied with decrease of telomerase expression, leading to depression-like and negative symptom-like behaviors. The behavioral deficits were also induced by treatment of telomerase inhibitor in hippocampus. Although these findings suggest the association between telomere and schizophrenia, the molecular mechanism remains unclear.

Methods: We checked leukocyte telomeres in 42 patients with schizophrenia (Male/Female=23/19, Ave. age=49.81) and 56 healthy subjects (Male/Female=30/26, Ave. age=46.84). Telomere length was measured by quantitative PCR as described previously (Cawthon et al. 2009) with minor modifications. In mice study, C57BL/6J mice were administrated with antipsychotics and some antagonists for 2 weeks from the age of 8 weeks.

Results: We first investigated the lengths of leukocyte telomeres using Japanese schizophrenia patients and discovered that the telomeres were indeed shortened as previous reports in American and European subjects with schizophrenia. Next, to evaluate the effect of antipsychotics on telomere length, we had treated mice with several types of antipsychotics for 2 weeks and found that treatment of atypical antipsychotics, such as risperidone, olanzapine and aripiprazole, but not typical antipsychotics, haloperidol, elongated the telomere length in the hippocampus. Moreover, we found that the effect of atypical antipsychotics on telomere length might be regulated by serotonin system.

Conclusion: Our findings suggest the possibility that atypical antipsychotics improve negative symptom, at least partially, through the modulation of telomere length.

Policy of full disclosure: None.

P-25-012 Is sustained dopamine D2 receptor blockade above 65% necessary for maintenance treatment of schizophrenia? A single-blind, randomized, controlled study

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Objective: While 65–80% blockade of dopamine D2 receptors with antipsychotics optimizes therapeutic efficacy in the acute phase of schizophrenia, it is unclear as to whether it is necessary to keep D2 blockade within this therapeutic window for the maintain treatment. The objective of this study was to examine whether this therapeutic window also would apply for the maintain treatment.

Methods: In this single-blind, 52-week, randomized controlled trial, clinically stable patients with schizophrenia (DSM-IV) treated with risperidone or olanzapine were randomly assigned to the continuous D2 blockade group (i.e. a trough D2 blockade of >65%) or intermittent D2 blockade group (i.e. a peak D2 blockade of >65% with a trough level of <65%). Plasma antipsychotic concentrations at trough that are expected to result in 65% D2 blockade are 15.2 ng/mL and 19.3 ng/mL for risperidone and olanzapine, respectively, according to the model that we recently developed. Oral doses that correspond to those plasma antipsychotic concentrations at trough will be estimated for each individual, using the mixed effect population pharmacokinetic approach. According to the group assigned, antipsychotic doses were individually titrated. Psychopathology and side effects were assessed at the baseline and one year with the Positive and Negative Syndrome Scale (PANSS), the Simpson-Angus Scale (SAS), the Barnes Akathisia Rating Scale (BAS), and the Abnormal Involuntary Movement Scale (AIMS).

Results: Sixty-eight patients were enrolled (mean±SD age, 55.4±14.9; 41 men; 33 and 35 subjects on risperidone and olanzapine, respectively). 26 (76.5%) and 31 (91.2%) subjects successfully completed the study in

the continuous D2 and intermittent D2 groups, respectively, without any significant difference. No significant differences were found in changes in PANSS total score (−0.6 vs. −1.5), SAS, BAS or AIMS between the continuous D2 and intermittent D2 groups.

Conclusion: Sustained dopamine D2 blockade above 65% may not be necessary for the maintain treatment of schizophrenia.

Policy of full disclosure: None.

P-25-013 Postnatal development of patterns of basal and schizophrenomimetic phencyclidine-induced gene expression in the rat neocortex

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Objective: The onset of schizophrenia and the schizophrenomimetic effects of N-methyl-D-aspartate (NMDA) receptor (NMDAR) antagonists usually occur after adolescence. These clinical observations indicate suggest that schizophrenia-related neuron circuits and molecules in the brain could exhibit development-dependent responses to NMDAR antagonists.

Methods: To get an insight into the molecular mechanisms underlying the above clinical observations and onset of schizophrenia, we have studied developmental changes in the patterns of brain gene expression following no treatment (basal expression) or systemic application of phencyclidine (7.5 mg/kg, subcutaneously) in the developing rats from postnatal days 8 to 77. To this end, we employed a DNA microarray and a quantitative RT-PCR method. The present animal experiments have been approved by the ethics committees of the Tokyo Medical and Dental University.

Results: DNA microarray analyses have revealed that prominent changes in overall gene expression profiles after the PCP injection occurs across the critical period around postnatal weeks 3 for the development of adult-type PCP-induced abnormal behavior that has been considered to be a model for schizophrenia. PCP, at least, caused an increase (PCP/saline control ratios more than 1.2) and decrease (PCP/saline control ratios less than 0.8) in the expression of 18 and 18 genes, respectively, in the neocortex only after the critical period. The overall patterns of basal gene expression in the neocortex also displayed an inflection period around postnatal week 3.

Conclusion: These data further support our view that the neocortical genes exhibiting the critical period-related alterations in basal expression and responsiveness to PCP could compose the molecular cascades that are involved in the pathophysiology of schizophrenia. These genes might malfunction in the schizophrenia-related neocortical circuits after adolescence,

Policy of full disclosure: None.

P-25-014 The improvement of social functioning in schizophrenic patients treated with paliperidone extended-release: 12-month observational surveillance in real clinical practice with 1405 patients

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Objective: To demonstrate the effectiveness of PAL-ER on social functioning of schizophrenia in the real world, we conducted a 12-month observational surveillance in real clinical practice with 1405 Japanese schizophrenic patients.

Methods: This open-label, observational, multicenter surveillance in real clinical practice was performed for a 12-month observation period. The primary endpoint was changes of social functioning estimated by Social and Occupational Functioning Assessment Scale (SOFAS) from baseline to the end of observation period (using last-observed-carried forward: LOCF). Secondary endpoint was improvement of symptoms estimated by Clinical Global Impression-Schizophrenia (CGI-SCH). All treatment-emergent adverse events (TEAEs) and adverse drug reactions were also collected. The protocol was reviewed by internal review board members including the ethical point of view and was approved by Pharmaceuticals and Medical Devices Agency.

Results: Discontinuation rate calculated by Kaplan-Meier method was 34.7%. In this surveillance, we found that PAL-ER treatment significantly improved the social functioning of schizophrenia patients assessed by SOFAS ($p<0.001$ by signed Wilcoxon test). Among the treated patients, 52.8% were improved and 5.6% were worsened in SOFAS score. The patients who had more than 60 in SOFAS score represented slightly disable but generally well in social functioning, and this proportion of patients increased from 3.3% at baseline to 24.0% at 12-month by the treatment. Also, 55.3% of PAL-ER treated patients showed improvement of more than 1 scale in CGI-SCH at LOCF compared to baseline. Adverse drug reactions were reported in 414 (29.5%) patients in total; most common were hyperprolactinemia (6.4%), somnolence (5.2%), fatigue (4.2%), and akathisia (2.6%). Twelve deaths were occurred and serious TEAEs were reported in 8.8% patients. No new safety concerns were observed.

Conclusion: This is a first report showing that PAL-ER treatment improved the social functioning in Japanese schizophrenic patients in real clinical practice.

Policy of full disclosure: All authors are employees of Janssen Pharmaceutical K.K.

P-25-015 Effects of escitalopram on the amygdala dopamine release in emotional processing: A specific effect in the methamphetamine-sensitized rats

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Objective: Escitalopram (ESCIT) has the highest affinity for the human serotonin transporter. Although SSRI typically used in the treatment of depression and anxiety disorders, how such distinguish profile account for their therapeutic action has not been fully clarified yet. In this study, to investigate the effect of SSRI in emotional processing, we examined the effects of the ESCIT on the dopamine (DA) levels and on excessive increase of DA levels in response to a conditioned fear stimulus (CS) in the amygdala of methamphetamine (MAP) -sensitized rats, in which model animals the excessive increase of DA levels are a biological marker of hypersensitivity and vulnerability to psychological stress.

Methods: Male Sprague-Dawley rats received 2 mg/kg/day of MAP for 10 days, and then a fear-conditioning was performed in which tone conditioned stimulus was paired with electrical foot shock. The extracellular DA levels in the amygdala were measured using in vivo microdialysis. During microdialysis, rats were injected to ESCIT (5 mg/kg) intraperitoneally and then after 80 min followed by CS.

Results: The basal extracellular DA levels were higher in the amygdala of MAP-sensitized rats compared to un-sensitized rats. ESCIT treatment significantly increased the DA levels in the amygdala in un-sensitized rats. However, the increased DA elicited by ESCIT was not shown in the MAP-sensitized rats. The CS subjection significantly increased amygdala DA levels, which was greater for MAP-sensitized rats than for un-sensitized rats. ESCIT treatment significantly suppressed the CS induced excess DA release in the amygdala of MAP-sensitized rats.

Conclusion: These results suggest that the therapeutic effect of SSRI on depression and anxiety disorders may involve modulation of amygdala DA release in emotional processing. In addition, the specific effect of SSRI on DA levels shown in MAP-sensitized rats may imply a part of mechanisms for beneficial effect on vulnerability to psychological stress.

Policy of full disclosure: None.

P-25-016 Identification of developmentally regulated NMDA receptor antagonist phencyclidine-responsive transcripts in the rat brain

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Objective: Schizophrenic and similar psychotic symptoms induced by an NMDA-type glutamate receptor antagonist, phencyclidine (PCP), usually develop during or after adolescence. Adult-type behavioral disturbance following NMDA receptor antagonist application in rats is observed as well only after a critical period at around 3 postnatal weeks. To obtain further insights into the molecular basis of schizophrenia, we have investigated the gene expression profiles after acute PCP injection at different developmental stages in rats.

Methods: Male Wistar rats at different postnatal days (PD) were administered with PCP. After 1 h, total RNA in cerebral neocortex and thalamus of the animals was isolated and applied for DNA microarray analysis to determine the development-dependent PCP-induced genes. All the study was approved by the ethical committee for animal experiments of the Institute.

Results: We have identified several PCP-responsive genes from the rat brain regions only after the developmentally critical period as novel candidates for the schizophrenia-related molecules. We next characterized a PCP-responsive non-coding transcript, prt6. The prt6 mRNA in thalamus of adult rats was rapidly enhanced and peaked at 1–6 hours, then returned to the basal level within 24 hours. By the acute injection of another non-competitive NMDA receptor antagonist, MK-801, and a

schizophrenomimetic dopamine agonist, methamphetamine, the expression level of prt6 mRNA was significantly increased.

Conclusion: The present study indicates that prt6 may be a key molecule in the pathophysiology of the onset of schizophrenic symptoms. Possible miss regulation of the target gene(s) expression for microRNA and/or other non-coding RNA fragments in the prt6 transcript may be mutually associated with maturation of certain brain neuron circuits and molecular networks in schizophrenia.

Policy of full disclosure: None.

P-25-017 Effect of aripiprazole on subjective experience in antipsychotic-naïve first-episode schizophrenia: First report

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Objective: Subjective experience under antipsychotic treatment may be associated with adherence and functional outcome in schizophrenia. The purpose of this study was to evaluate the short-term effects of aripiprazole on subjective experience in first-episode schizophrenia.

Methods: Thirteen antipsychotic-naïve patients with first-episode schizophrenia participated in the study. Aripiprazole (3–30 mg/day) was given in an open label design for 8 weeks. Clinical evaluations were conducted at baseline and 8 weeks. The primary outcome measure was changes in subjective well-being assessed by the Subjective well-being under neuroleptic drug treatment short form-Japanese version (SWNS-J). Secondary outcome measures included the Schizophrenia Quality of Life Scale-Japanese version (SQLS-J) and the Positive and Negative Syndrome Scale (PANSS). Safety assessments included laboratory tests, body weight, Body Mass Index (BMI), and the Drug Induced Extra-Pyramidal Symptoms Scale (DIEPSS). This study protocol was approved by the bioethics committee of St. Marianna University School of Medicine, and written informed consent was received from all participants.

Results: Ten patients (3 males and 7 females; mean age, 32.2±6.4 years) completed the study. One patient dropped out, and two patients are in progress. The mean daily dose of aripiprazole was 6.9±6.6 mg/day at 8 weeks. Significant improvements from baseline to endpoint were observed for self-control and social integration on the SWNS-J, psychosocial score on the SQLS-J, and all subscales on the PANSS. In the laboratory tests, high-density lipoprotein cholesterol significantly increased, and fasting blood sugar significantly decreased from baseline within the normal range. Although mean body weight and BMI increased from baseline, the rate of weight gain was only 0.4%. There was no significant change in the DIEPSS score.

Conclusion: These results suggest that aripiprazole can improve psychopathological symptoms and some types of subjective experience in first-episode schizophrenia. We will present the data of more cases in the congress.

Policy of full disclosure: None.

P-25-018 Interaction between paliperidone and carbamazepine

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Objective: This aim of this study was to determine the impact of carbamazepine on the pharmacokinetics of paliperidone.

Methods: Six schizophrenic patients initially received a 6–12 mg/day dose of paliperidone alone. Subsequently, a 200 mg/day dose of carbamazepine was administered, and the carbamazepine dose was increased to 400 mg/day and then 600 mg/day. Plasma concentrations of paliperidone before and after carbamazepine co-administration were quantified using LC/MS/MS.

Results: Carbamazepine significantly reduced the plasma concentration of paliperidone. The plasma concentration of paliperidone at baseline and with co-administration of 200, 400, and 600 mg/day were 45.8±11.7, 26.9±13.7, 17.1±8.2, and 15.9±7.6 ng/ml, respectively. The concentration of paliperidone with carbamazepine co-administration at doses of 200, 400, and 600 mg/day were 55.7±20.7, 36.1±12.2, and 33.6±10.4%, respectively, of baseline. This effect occurred even at the carbamazepine dosage of 200 mg/day and reached a plateau at dosages higher than 400 mg/day. However, carbamazepine co-administration exacerbated the psychotic symptoms in some patients.

Conclusion: The results of the present study suggest that adjunctive treatment with carbamazepine reduces the concentration of paliperidone in a dose-dependent manner, most likely because of the induction of several drug metabolyzing enzyme and several drug transporters.

Policy of full disclosure: None.

P-25-019 The differences of cognitive deficits in chronic schizophrenia on long-term treatment with typical and atypical antipsychotics

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Objective: Cognitive deficits have been presented in the prior to the onset of other symptoms of schizophrenia and generally persisted during the course of the disease. Whether cognitive function is affects by antipsychotic treatment during the course of schizophrenia is still debated. This study aimed to examine the effect of long-term treatment of antipsychotic drugs on cognitive function in patients with chronic schizophrenia.

Methods: The study assessed cognitive function in 395 healthy controls and 438 patients with chronic schizophrenia on long-term treatments with antipsychotics, including mainly monotherapy with clozapine (n=224), risperidone (n=99) and typical antipsychotics (n=115).

Results: Cognitive test scores were significantly lower in all patient groups than healthy controls on all scales (all $p<0.001$) except for visuospitial/constructional index. Clozapine treatment had significantly lower immediate memory and delayed memory than typical antipsychotics (all $p<0.01$). Clozapine treatment had better language index than risperidone ($p<0.01$).

Conclusion: Patients with chronic schizophrenia performed significant cognitive deficits than healthy controls in all examined cognitive domains except for the visuospitial/constructional index. Cognitive deficits in patients with chronic schizophrenia were significantly influenced by different type's antipsychotics treatment. Clozapine treatment had worse immediate memory and delayed memory than typical antipsychotics, and better language performance than risperidone.

Policy of full disclosure: None.

P-25-020 Effect of pharmaceutical care by pharmacists on medication therapy in patients with chronic schizophrenia

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Objective: Despite of contradictory evidence for effectiveness, use of two or more antipsychotics, antipsychotics polypharmacy, is given in about one third patients with chronic schizophrenia. Polypharmacy is raised some problems, including adverse effects and patient safety. On the other hand, pharmacists have responsibility to check the prescription and discuss with physician and other health-care providers, and then pharmacists should propose the optimal formulation. If these functions of pharmacists work precisely, the problems may be prevented. Therefore, in this study, we examined whether continuous pharmaceutical cares are useful for the physicians' prescriptions in patients with schizophrenia or not.

Methods: Subjects are 78 in-patients with chronic schizophrenia treated to antipsychotics therapy in Sawa hospital in Osaka, Japan. The participants were divided into two groups; continuous pharmaceutical intervention group (n=26) and non-intervention group (n=52). The pharmaceutical cares are as follow; patients' education about medicine and disease, monitoring side effects, up to these points for patients. To physicians, request the blood test, discuss to prescription formula. We performed intervention as appropriate. The items of survey are as follow; the doses of antipsychotics, anti-Parkinsonian, and benzodiazepines, the number of antipsychotics and anti-Parkinsonian, and the rate of concurrent anti-Parkinsonian, benzodiazepines, and mood stabilizers.

Results: In this study, continuous intervention for a year, the dose and the number of antipsychotics and the number of anti-Parkinsonian was significantly lower in intervention than in non-intervention.

Conclusion: Medication therapy is one of the most important treatments for schizophrenia although there are some problems in medication therapy such as adverse effects. Pharmaceutical intervention by pharmacists could make prescriptions by physicians optimize and/or simplify, including in the medicines for the adverse effects and adjuvant medications. As indicated above, it might be suggested that clinical practice should be taken full advantage of pharmacists' ability to medication therapy for schizophrenia.

Policy of full disclosure: None.

P-25-021 Blonanserin ameliorates phencyclidine-induced impairment of visual recognition memory (1): involvement of dopamine-D_3 receptors

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Objective: Blonanserin shows a binding profile unique among the atypical antipsychotic drugs (APDs) in that it exhibits a higher affinity for dopamine-$D_{2/3}$ receptors than for serotonin 5-HT_{2A} receptors. Clinically, blonanserin exhibits APD properties, with efficacy against positive symptoms, negative symptoms, and cognitive impairments in schizophrenia. In animal studies, blonanserin has shown activity in reducing several psychobehavioral abnormalities in animal models of schizophrenia. However, the effect of blonanserin on the cognitive impairment and involvement of dopamine-D_3 receptors in its effect remain unclear. In the present study, we investigated the effect of blonanserin on cognitive impairment in the animal model of schizophrenia, in comparison with that of olanzapine, and elucidated further the involvement of dopamine-D_3 receptors in this model.

Methods: The mice received phencyclidine (PCP), a non-competitive NMDA receptor antagonist, (10 mg/kg/day, *s.c.*) once a day for 14 consecutive days, as an animal model of schizophrenia. The visual recognition memory and extracellular dopamine levels in the medial prefrontal cortex (mPFC) were evaluated by the novel object recognition test (NORT) and microdialysis experiment, respectively.

Results: Blonanserin (3 mg/kg, *p.o.*), as well as olanzapine (3 mg/kg, *p.o.*), significantly ameliorated PCP-induced impairment of visual recognition memory, as demonstrated by NORT, and increased the extracellular dopamine levels in the mPFC. Both these effects of blonanserin were antagonized by DOI, a serotonin 5-HT_{2A} receptor agonist, and 7-OH-DPAT, a dopamine-D_3 receptor agonist, whereas the effects of olanzapine were antagonized by DOI, but not by 7-OH-DPAT.

Conclusion: Our conclusion is that blonanserin ameliorates PCP-induced cognitive impairment by antagonizing dopamine-D_3 receptors, in addition to serotonin 5-HT_{2A} receptors, and thereby stimulates release of dopamine in the mPFC, and shows a unique pharmacological efficacy different from that of olanzapine.

Policy of full disclosure: None.

P-25-022 Schizophrenic patients have a high prevalence of clinical and laboratory markers of low plasminogen activators and/or plasmin activity

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Objective: To assess the prevalence of markers of reduced activity of plasminogen activators/plasmin in schizophrenics. Schizophrenics exhibit hippocampal atrophy. Plasminogen activators and plasmin mediate different processes that culminate in neuronal excitotoxicity prevention and hippocampal neurogenesis.

Methods: Study population consisted of 70 schizophrenics (DSM-IV) and 98 age-matched controls without psychiatric diagnosis. Exclusion criteria for patients and controls comprised pregnancy, puerperium, estrogen use or anticoagulation within one month preceding sampling. Twenty-nine outpatients and 41 inpatients, aged 18–72 years (mean 42 +/−11), were recruited at a university hospital. Thirty percent were taking atypical antipsychotics.

Results: Clinical indicators suggestive of reduced activity of plasminogen activators/plasmin, highly prevalent among schizophrenics, included: a history of ischemic stroke <50 years or deep-venous thrombosis (14% versus 2% of controls), severe dysmenorrhea during early adolescence (50% versus 12%), and any stillbirth or preterm delivery due to severe placental insufficiency in psychotropic-naïve women (50% versus none). All but three patients had positive laboratory markers (1–6, mean 2.1), including persistent antiphospholipid antibodies, usually lupus anticoagulant or IgM anticardiolipin antibody in medium/high titer (30% versus none); low free-protein S (22% versus none, range 32–66%); >20% increase in fasting insulinemia with normal glucose levels (44% versus 11%, range 13.8–119 mcU/mL); >20% increase in homocysteine levels (27% versus 5%, range 13.6–59 mcmol/L); and a PAI-1 4G allele (60% versus 48%). Of the hyperhomocysteinemic patients, 25% had two or more alleles of the methylenetetrahydrofolate reductase C677T or A1298C polymorphisms. Schizophrenics studied during acute episodes and refractory patients exhibited the highest number of laboratory markers. Non-significant variables were: heterozygous prothrombin G20210A (2% versus 1%), heterozygous factor V Leiden (3% versus 2%), antithrombin III and protein C deficiency (not detected).

Conclusion: Our findings suggest that protocols aiming at normalizing plasminogen activators/plasmin activity may offer new pharmacological tools for treating schizophrenia (Faperj E.26/110.643/2012).

Policy of full disclosure: None.

P-25-023 Sustained psychosis remission with warfarin therapy

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Objective: To explain why five patients with schizophrenia or schizoaffective disorders (DSM-IV) and recurrent deep vein thrombosis attained remission of psychotic symptoms after months on warfarin therapy and remain free of psychotropic medication from 2–11 years. None of these patients displayed any ischemic brain injury on neuroimaging studies.

Methods: The model that better explains the reduction of hippocampal volume, commonly seen in patients with schizophrenia and schizoaffective disorders, includes a trigger and a predisposing condition. The trigger is exemplified by illicit drugs or traumatic events that promote release of substances harmful to the neurons, such as glucocorticoids or noradrenalin. Predisposing factors comprise inherited or acquired factors that may impair hippocampal neurogenesis or neuronal plasticity. The Medical Subject Headings hippocampus AND "neuronal plasticity" OR neurogenesis were entered in Pubmed with every component of the coagulation and fibrinolytic pathways to search for proteins capable of preventing thrombotic events and also of mediating hippocampal regeneration.

Results: The search yielded only one match: tissue-plasminogen activator (tPA). Clot-buster tPA is involved with synaptic remodeling, neuronal plasticity and hippocampal neurogenesis required for brain repair after stress. All five patients had more than one thrombophilia diagnosis associated with reduced activity of tPA, including fasting hyperinsulinemia, hyperhomocysteinemia, prothrombin G20210A polymorphism, PAI-1 4G allele or antiphospholipid antibodies, such as a strong lupus anticoagulant. Biochemical abnormalities seen in schizophrenia and related to low tPA activity include: deficient dopamine transmission at D1 receptors in the prefrontal cortex, impaired cleavage of brain-derived neurotrophic factor precursor (pro-BDNF) to antiapoptotic mBDNF, abnormal N-methyl-D-aspartate receptor-mediated signaling, reduced Akt phosphorylation, and abnormal activation of reelin. An increased prevalence of both thromboembolic and psychotic events is seen in conditions characterized by low tPA activity, such as the puerperium, confinement and chronic inflammatory disorders. Warfarin increases tPA levels.

Conclusion: Our findings suggest that normalization of tPA activity may provide a new strategy for the treatment of schizophrenia.

Policy of full disclosure: None.

P-25-024 Contributions of medial prefrontal cortex and dorsomedial striatum to working memory capacity in rats

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Objective: Working memory enables storage and manipulation of information necessary for higher order cognition and is disrupted in psychiatric disorders such as schizophrenia. Capacity, one facet of working memory, has been identified as requiring more basic research before being included in the translational battery of the Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) initiative. Working memory capacity is often assessed by measuring the span or number of stimuli that can be retained in working memory. The objective of the present experiments was to test if temporary inactivation of medial prefrontal cortex (mPFC) or dorsomedial striatum (dmSTR) reduced working memory capacity using an odor span task (OST) in rats.

Methods: Male Long Evans rats were trained to perform the OST. Briefly, the task requires rats to remember an increasing span of different odors to receive food reward using a serial delayed non-matching to sample procedure. Following training, rats were implanted with cannulae dorsal to the mPFC and dmSTR. The rats were then tested on the OST following infusions of either saline or the GABA receptor agonists muscimol and baclofen into the mPFC (bilateral), dmSTR (bilateral), or a unilateral infusion into each area in opposite hemispheres (disconnection procedure) in a counterbalanced order.

Results: Rats showed average spans between 8 and 12 odors at the end of training and following saline infusions. Temporary inactivation of either the mPFC (2.67 odors) or dmSTR (5.64 odors) profoundly impaired performance of the task only on the day of infusion. Critically, the

disconnection procedure also significantly reduced odor span (1.74 odors). Latency to retrieve the food reward during the task was not affected by any of the treatments.

Conclusion: These data define a neural circuit including the mPFC and dmSTR that supports odor span capacity in rats.

Policy of full disclosure: None.

P-25-025 NS1738, a positive allosteric modulator of Alpha7 nicotinic receptors, as adjunctive treatment in schizophrenia. An experimental study

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Objective: Preclinical and clinical studies with α7 nicotinic acetylcholine receptor (nAChR) agonists show promising results for the treatment of cognitive deficits in schizophrenia, but positive allosteric modulators (PAMs) of the α7 nAChR may provide a rational alternative. Here we examined in the rat, the effects of the α7 PAM NS1738 on brain dopaminergic and noradrenergic cell firing and cognitive functioning. Adjunctive treatment with NS1738 to risperidone was examined for antipsychotic efficacy and effects on cortical glutamatergic NMDA receptor-mediated neurotransmission.

Methods: We examined antipsychotic efficacy using the CAR test, the effect on cognition using the novel object recognition (NOR) test, the effect on cell firing in the ventral tegmental area (VTA) and locus coeruleus (LC) using extracellular single-cell recording in vivo and the effects on NMDA receptor-mediated currents in pyramidal neurons in the medial prefrontal cortex (mPFC) using intracellular electrophysiological recording in vitro.

Results: NS1738 increased both firing rate (0.1 mg/kg i.v.) and in particular burst firing (0.05–0.1 mg/kg i.v.) of dopaminergic cells in the VTA, whereas no effect was seen on noradrenergic cells in the LC. Furthermore, NS1738 (1 mg/kg s.c.) significantly improved recognition memory. Addition of NS1738 (1 mg/kg s.c.) to a low dose of risperidone (0.25 mg/kg i.p.) enhanced the antipsychotic-like effect in the CAR model. Whereas neither risperidone (10 nM) nor NS1738 (500 nM) produced any effect when administered alone, the combination potentiated NMDA-induced currents in pyramidal cells in the mPFC.

Conclusion: The present results propose that in combination with an α7 PAM, a dose reduction of antipsychotic drugs such as risperidone may be achieved, yet with maintained antipsychotic effect. Moreover, the combination of NS1738 and risperidone in concentrations which were ineffective when given alone, enhanced cortical glutamatergic NMDA receptor-mediated transmission, an effect which may contribute to improve cognition and negative symptoms.

Policy of full disclosure: Grants/research support of Torgny H. Svensson: The Swedish Research Council, The Karolinska Institutet, Stockholm (Sweden), The Brain Foundation (Sweden), AstraZeneca, Organon, Schering-Plough, Merck Sharp and Dome, Lundbeck, Otsuka, Astellas; Consultant/advisory board: AstraZeneca, Janssen, Lundbeck, Otsuka, Merck Sharp and Dome, Organon, Pfizer, Carnegie Health Care Funds (Sweden).

P-25-026 Association between FAT gene and schizophrenia in the Korean population

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Objective: The aim of this study was to investigate the genetic association of the FAT gene with schizophrenia in the Korean population, as well as analyzing the association of FAT gene with clinical variables.

Methods: Four variants within the FAT gene were investigated in 189 patients with schizophrenia and 119 healthy controls(rs2306987 A/C, rs2306990T/C, rs2637777 G/T, and rs2304865 G/C).

Results: Significant association at the rs273777 with schizophrenia was observed; however, rs2306987, rs2306990, and rs2304865 were not associated with schizophrenia. Haplotype analyses revealed that the haplotype A/T/T/G was associated with a significantly protective effect. Sliding window analysis (rs2637777 G/T and rs2304865 G/C) revealed the more common T/G haplotype, included in the A/T/T/G protective combination, showed a small protective effect, in particular the effect wasdue to the rs273777T variant (minor allele).

Conclusion: The present finding suggests that FAT polymorphism may play a putative role in the susceptibility to schizophrenia in the Korean population. Further studies using a larger number of subjects should be performed to determine whether the FAT gene polymorphism may be truly involved in the development of schizophrenia.

Policy of full disclosure: None.

P-25-027 Disturbance of facial mimicry in schizophrenia

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Objective: Emotional facial expression is an important mechanism contributing to the experience of empathy, identified as a key predictor of social function. Although the existence of empathy dysfunction in schizophrenia is generally accepted, direct evidence exists very limitedly. The aim of this study was to evaluate the disturbance of empathy through rapid facial mimicry by using electromyography.

Methods: 25 patients with schizophrenia were enrolled in the study. They were presented with stimuli portraying happy, angry, sad facial expressions. Participants were requested to recognize the stimuli while electromyographic activities of corrugator, zygomaticus muscles were recorded. The EMG activity and heart rate were compared with those of 24 control subjects matched for age, duration of education, IQ and gender. Empathic abilities of the participants were assessed with the empathy contagion scale and interpersonal reactivity index. A neuropsychological battery, including positive and negative syndrome scale, the Korean – Weschler adult intelligence scale was also administered.

Results: There was no significant difference in any of the demographic variables of the two groups. The patients with schizophrenia had a significant deficiency in empathy based on the IRI and the EC. The healthy control group displayed a distinct pattern of EMG responding consistent with a typical mimicry response such as greater zygomaticus activity in response to happy faces, and greater corrugator activity to angry and sad faces. In contrast to controls, schizophrenia patients did not show electromyographic response to happy, angry, sad facial expressions. The activity of zygomaticus muscle was negatively correlated with personal distress in angry face, and positively correlated with personal distress in happy face. A negative correlation was observed between PANSS score and EC.

Conclusion: We could identify that schizophrenia patients are impaired in capacity of facial mimicry, as indicator of affective empathy in both positive and negative emotions. These results suggest that a considerable proportion of decreased facial mimicry in schizophrenia might be influences to social interaction.

Policy of full disclosure: None.

P-25-028 Associations of obsessive-compulsive symptoms with clinical features and neurocognitive functioning in patients with schizophrenia according to the stage of illness

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Objective: To investigate the associations of comorbid obsessive#compulsive symptoms (OCS) with neurocognitive functioning and psychopathology in people with schizophrenia according to stage of illness.

Methods: A total of 163 people with schizophrenia who were receiving risperidone monotherapy were enrolled. Comorbid OCS were assessed using the Yale#Brown Obsessive Compulsive Scale (YBOCS), and subjects with a score of 10 or higher constituted the OCS group. Neurocognitive functioning, psychopathology, and quality of life were compared according to the presence of OCS in the total population and among populations with<5 and #5 years of illness duration.

Results: A total of 30 patients (18.4%) had OCS. In the early-stage group (duration of illness<5years), the learning index on the verbal learning test was significantly higher in the OCS than in the non-OCS group. In the chronic-stage group (duration of illness#5 years), the backward digit span was significantly lower in the OCS than in the non-OCS group. In both stages of illness groups, scores on positive and general psychopathology subscales and total Positive and Negative Syndrome Scale, Calgary Depression Scale for Schizophrenia, and Beck Depression Inventory scores were significantly higher in the OCS than the non-OCS subgroup. Additionally, the Subjective Well-being under Neuroleptic Treatment-Short Form score was significantly lower in the OCS than in the non-OCS group.

Conclusion: The relationship between OCS and neurocognition in patients with schizophrenia is dependent on stage of illness. However, schizophrenia patients with OCS had greater psychotic and depressive symptoms and poorer quality of life regardless of illness stage.

Policy of full disclosure: This work was supported by a grant (CRI10012-1) of the Chonnam National University Hospital Research Institute of Clinical Medicine. Data collection was supported in part by

investigator-initiated grants from Korea Otsuka Pharmaceutical, Sanofi-Aventis Korea, and Janssen Korea. The funding sources had no further role in study design; in the analysis and interpretation of data; in the writing of the manuscript, and in the decision to submit the article for publication.

P-25-029 Comparison of attitudes toward long-acting injectable antipsychotics among psychiatrists and patients

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Objective: The current prescription rate of long-acting injectable antipsychotics (LAI) is <1% in Korea. This study aimed to investigate the reason for LAI underuse by surveying the attitudes toward LAI among psychiatrists and patients receiving LAI.

Methods: A total of 173 psychiatrists and 99 patients receiving LAI participated in the survey. Participating psychiatrists were divided into two groups according to experience with prescribing LAI to at least 10 patients.

Results: The two psychiatrist groups did not differ significantly in terms of sociodemographic characteristics and clinical practice patterns. However, the group with higher experience more frequently provided explanations regarding LAI to their patients and was more satisfied with the use of LAI than the group with less experience. Acceptance rates of patients to the recommendation for LAI treatment and satisfaction of psychiatrists with the outcome of LAI were also significantly higher in the group with higher experience. Psychiatrists with less experience with LAI were more negative toward LAI than patients receiving LAI as well as psychiatrists with higher experience.

Conclusion: Attitudes of psychiatrists toward LAI were closely related to the use of LAI. The negative attitude and reluctance of psychiatrists, rather than patient resistance, may contribute to the underuse of LAI. To enhance the use of LAI, more information based on scientific evidence should be provided to psychiatrists to reduce their prejudice against LAI, and the positive experiences of both patients receiving LAI and colleagues should be shared with them.

Policy of full disclosure: This study was supported in part by an investigator-initiated grant from Janssen Korea Co. Ltd. The funding source had no further role in study design; in the analysis and interpretation of data; and in the decision to submit the article for publication. Representatives of the company were allowed to comment on the report, but the final approval of content was retained by the investigators exclusively.

P-25-030 Effects of antipsychotic drugs on the expression of synapse-associated proteins in the frontal cortex of rats subjected to immobilization stress

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Objective: Regulation of synaptic plasticity has been implicated in the cognitive impairment and treatment of schizophrenia. The present study examined the effects of three antipsychotic drugs, olanzapine, aripiprazole, and haloperidol, on the expression of synapse-associated proteins in the frontal cortex of rats with and without immobilization stress.

Methods: Rats were subjected to immobilization stress 6 h/day for 3 weeks. The effects of two atypical antipsychotic drugs, olanzapine (2 mg/kg) and aripiprazole (1.5 mg/kg), on expression of serine9-phosphorylated GSK-3 beta, Beta-catenin, BDNF, PSD-95, and synaptophysin were determined by Western blotting. A typical antipsychotic drug, haloperidol (1.0 mg/kg), was used for comparison.

Results: Immobilization stress significantly decreased the expression of phosphorylated GSK-3 beta, Beta-catenin, BDNF, PSD-95, and synaptophysin in the frontal cortex (all $p<0.01$). Chronic administration of olanzapine and aripiprazole significantly attenuated the immobilization stress-induced decrease in the levels of these proteins ($p<0.05$ or $p<0.01$), whereas chronic administration of haloperidol did not in this regard. Additionally, chronic administration of olanzapine ($p<0.05$) and aripiprazole ($p<0.01$) significantly increased levels of phosphorylated GSK-3 beta under normal conditions without stress, and chronic administration of aripiprazole also increased BDNF levels under this condition ($p<0.01$).

Conclusion: These results indicate that two atypical antipsychotics, olanzapine and aripiprazole, and one typical one, haloperidol, differentially regulate the levels of synapse-associated proteins in the rat frontal cortex. These findings may contribute to neurobiological basis of how olanzapine and aripiprazole improve the cognitive symptoms of patients with schizophrenia by suggesting that their mechanism of action involves up-regulation of synapse-associated proteins.

Policy of full disclosure: None.

P-25-031 Effect of add on aripiprazole on antipsychotic induced hyperprolactinemia

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Objective: To study the effect of add on aripiprazole on antipsychotic induced hyperprolactinemia in patients with schizophrenia/Bi Polar Affective Disorder (BPAD).

Methods: In patients of schizophrenia/BPAD, with clinically suspected antipsychotic induced hyperprolactinemia, serum prolactin levels were measured. For patients who had higher serum prolactin levels (N-10) tablet aripiprazole was added and subsequently serum prolactin levels were repeated over next few months. Standardized mean difference between serum prolactin levels before and after aripiprazole was calculated, with a 95% confidence limit interval.

Results: Aripiprazole had statistically significant effect on reducing the serum prolactin levels [Pre 89.55 ng/ml (SD: 56.42 ng/ml); post 36.42 ng/ml (SD: 24.44 ng/ml; t-3.950; SD: 42.52 ng/ml; $p<0.005$)] in patients with antipsychotic induced hyperprolactinemia on paired sample T test.

Conclusion: Aripiprazole is efficacious in treating antipsychotic induced hyperprolactinemia. Results have to be repeated in studies with larger sample size.

Policy of full disclosure: None.

P-25-032 Treatment patterns of long-acting injectable antipsychotics in the province of quebec

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Objective: The objective of this study was to assess the treatment patterns of long-acting injectable antipsychotics (LAI-AP), notably in terms of treatment persistence and compliance, in a real life setting, using the provincial public drug reimbursement program database of the Régie de l#assurance maladie du Québec (RAMQ).

Methods: Patients with a diagnosis of schizophrenia/schizoaffective disorder, who were incident users (no use in the previous 12 months) of a LAI-AP prescribed between January 1st 2008 and March 31st 2012, at least 20 years old, and with continuous enrolment in the database during the study period were selected. Concomitant use of oral antipsychotics and treatment adherence with LAI-AP were analyzed. Persistence was estimated in terms of treatment duration. Compliance was calculated during the year after the initiation of the LAI-AP using the medication possession ratio (MPR). Patients were considered compliant if they had a MPR of at least 0.80. Treatment compliance to oral antipsychotics used in the year prior the initiation of the LAI-AP was also evaluated.

Results: A total of 1,992 patients met the inclusion criteria. The mean age was 43.5 years (SD=14.3) and 66.2% of the patients were male. A total of 546 patients (27.4%) received an oral antipsychotic at the first date of dispensation of LAI-AP. The average persistence with LAI-AP was 217.2 days (SD=144.2). The mean MPR over the one-year period following the initiation of LAI-AP was 0.58 (SD=0.35) for the overall cohort. 37.5% of patients were compliant, with a MPR of 0.80 or more, while in the year before the initiation of LAI-AP, the compliance with oral antipsychotics was 29.0% ($p<0.001$).

Conclusion: Treatment persistence and compliance represent significant issues in the treatment of schizophrenia/schizoaffective disorders. The initiation of a LAI-AP significantly improved treatment compliance versus oral antipsychotics among these patients.

Policy of full disclosure: This study was supported by Lundbeck.

P-25-033 Healthcare costs before and after initiation of long-acting injectable antipsychotics in the province of Quebec

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Objective: The purpose of this study was to describe the resource use before, and after, initiation of long-acting injectable antipsychotics (LAIAP)

using the provincial public drug reimbursement program database of the Régie de l'assurance maladie du Québec (RAMQ).

Methods: Patients who were incident users (no use in the previous 12 months) of a LAIAP prescribed between January 1st 2008 and March 31st 2012, at least 20 years old, with a diagnosis of schizophrenia/schizoaffective disorder and with continuous enrollment during the study period were selected. Resource utilization and associated costs were analyzed both during the year before LAIAP initiation (preinitiation period) and the year after (postinitiation period).

Results: A total of 1992 patients met the inclusion criteria. The average age was 43.5 years (SD=14.3). In pre-initiation period, 1484 patients had at least one hospitalization, compared to 958 in post-initiation period ($p<0.001$), and the number of days hospitalized was reduced by half (40 days [SD=40] vs. 21 days [SD=30]; $p<0.001$). The number of patients having at least one emergency room visit decreased from 1372 to 813 patients ($p<0.001$), but the number of patients with at least one outpatient clinic visit increased from 1572 to 1726 patients ($p<0.001$). The pre-initiation inpatient costs were CDN$21312 (SD=27303), compared to CDN$7199 (SD=16419) in post-initiation period ($p<0.001$). The outpatient costs were CDN$1209 (SD=1173) during the pre-initiation period, and CDN$1296 (SD=1284) in the post-initiation period ($p=0.002$), while cost of medication were CDN$1861 (SD=2515) vs. CDN$4595 (SD=3910) ($p<0.001$). Total cost of health care resource, including LAIAP, were CDN$24382 (SD=27234) in the pre-initiation period, compared to CDN $13090 (SD=16987) in the post-initiation period ($p<0.001$).

Conclusion: The initiation of LAIAP resulted in significantly lower health care resource and cost reduction, with the primary driver being a reduction in number of hospitalizations, days of hospitalization and visits to the emergency room.

Policy of full disclosure: This study was supported by Lundbeck.

P-25-034 Improvement on dyslipidemia and negative symptoms by ziprasidone augmentation in clozapine-resistant patients with schizophrenia

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Objective: The object of this study was to evaluate the effectiveness of ziprasidone as an augmentation agent for improving dyslipidemia, psychotic symptoms, and functional outcome in clozapine-resistant patients with schizophrenia.

Methods: A 6-month, prospective, open-label clinical trial was conducted in clozapine-resistant patients with schizophrenia. In every enrolled patient, ziprasidone was added-on to clozapine while maintaining or reducing the daily doses of clozapine during the study period. Dyslipidemia-improving effects were assessed by the mean changes in fasting triglyceride (TG), HDL-cholesterol, and TG to HDL cholesterol ratio(TG/HDL-C). Symptomatic improvement was measured by the mean change of BPRS scores. Improvement in functional outcome was assessed using GAF and PSP sclae.

Results: 48 patients were enrolled (mean aged 42.5±7.5 years; 31.3% women; mean clozapine dose of 431.3±107.0 mg/day) and 39 patients completed this study. The mean augmented dose of ziprasidone was 108.3±43.6 mg/day. Daily dose of clozapine was reduced to 84.5% from the baseline dose in 20 patients, whereas 28 patients maintained the same dose of clozapine. There were significant improvements in lipid profile, with mean changes of −73± mg/dL in fasting TG and 2.25± in TG/HDL-C, in particular patients with metabolic syndrome at baseline ($p=0.005$). These changes in fasting TG and TG/HDL-C were consistent regardless of whether the daily dose of clozapine was reduced or not. The mean change in BPRS scores was −6.2±5.8 ($p<0.001$). Especially, negative symptoms and affect subscale scores were much more improved; in consequence, functional outcome was improved as well.

Conclusion: Ziprasidone is suggested as a suitable agent for augmentation in clozapine-resistant patients with schizophrenia, in particular those with insulin resistance and dyslipidemia. Additionally, ziprasidone augmentation of clozapine appears to be safe and effective in improving negative-affect symptoms and functional outcome.

Policy of full disclosure: None.

Comparison of the changes in TG to HDL-cholesterol ratio over 6months between patients who reduced daily dose of clozapine and patients who maintained the same dose of clozapine with a separate analysis for patients with MetS and patients without MetS at:

P-25-035 Metabolic syndrome and its impact on health related quality of life and body image in Korean patients with schizophrenia

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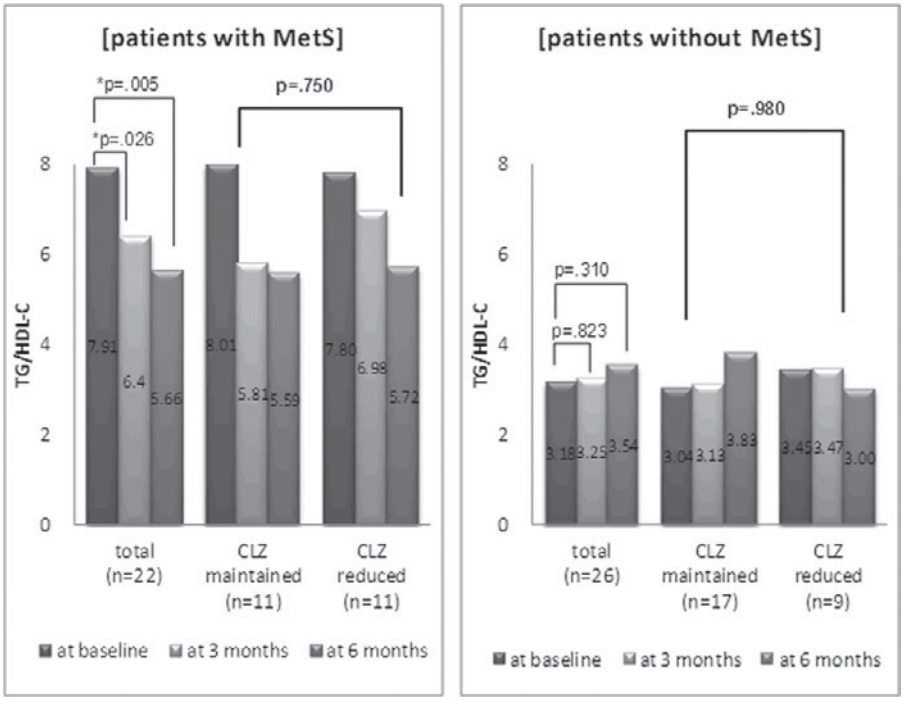
Objective: The use of antipsychotic drugs led to an unequivocal improvement in the medical treatment of schizophrenia. However, treatment with these drugs is associated with important side effects such as metabolic syndrome. Therefore screening and management of metabolic syndrome are important for quality of life in schizophrenia patients. This study aimed to study the prevalence of metabolic syndrome and its impact on health related quality of life (HRQoL) in patients with schizophrenia.

Methods: The subjects were 81 in-patients with schizophrenia who were diagnosed as schizophrenia by DSM-IV criteria. For each subject, anthropometric index and laboratory parameters were measured. Metabolic syndrome defined by NCEP ATP III and HRQoL were measured by Short-Form 36 Health Survey-Korean (SF-36-K). Body image was measure by Body Image Index. Statistical analysis was done using SPSS 12.0 for Window. Statistical significance was set at $p<0.01$.



Results: Of patients, 24.7% had metabolic syndrome. Metabolic syndrome was associated with long duration of illness. The patients with metabolic syndrome showed poor QoL., especially role physical and bodily pain in SF-36-K. Also, the patients with metabolic syndrome had negative body image, especially body feature, compared to the patients without metabolic syndrome.

Conclusion: This study suggested that metabolic syndrome is common among patients with chronic schizophrenia. Also it may lead to lowering of QoL and deterioration of body image. So, clinicians should be cautions to aware the increased risk for the metabolic syndrome and intervene actively to prevent and treat metabolic morbidity among chronic patients with schizophrenia.

Policy of full disclosure: None.

P-25-036 Effects of environmental context and drug dose on MK-801 sensitisation in rats

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Objective: The behavioural and neurochemical adaptations associated with N-methyl-D-aspartate (NMDA) receptor antagonist – induced sensitisation are thought to be relevant to the glutamate pathophysiology of schizophrenia. External factors that modulate sensitisation, including drug dose and environmental context, have not been addressed in the MK801 sensitisation rat model. The objective of this study was to determine the impact of these external factors on MK801 sensitisation.

Methods: The first cohort of Sprague-Dawley rats (n=10/group) was assigned to one of four dose treatment groups: saline or MK801 (0.1, 0.25 and 0.5 mg/kg). To induce sensitisation rats were administered 7 daily injections of MK801 and a challenge dose of the drug after a 5-day period of abstinence. The second cohort of rats (n=8/group) received 7 daily injections of MK801 (0.25 mg/kg) in one of two environmental contexts, test or home cage, and was challenged with either MK801 (0.25 mg/kg) or saline in the test cage. Additionally, we analysed the protein expression of the NR1, NR2A & 2B NMDA receptor subunits in the nucleus accumbens, a key region associated with expression of sensitisation.

Results: MK801 induced sensitisation was significantly affected by dose ($p<0.05$), whereby only the intermediary (0.25 mg/kg MK801) treatment group developed locomotor sensitisation. However, there was no effect of context on locomotor sensitisation to MK801 (0.25 mg/kg). Furthermore, conditioned locomotion was not evident in rats treated with MK801 in the test cage and challenged with vehicle. MK801 induced locomotor activity did not correlate to the protein expression of NR1, NR2A or 2B subunits.

Conclusion: These results demonstrate that MK801 induced sensitisation is highly dependent on the drug dose but not the environmental context in which the drug is administered. Future studies aim to elucidate the role of non-NMDA glutamatergic receptors in MK801 sensitisation, which may pave the way for a better understanding of glutamates role in schizophrenia.

Policy of full disclosure: None.

P-25-037 Long-term effectiveness and safety of blonanserin in patients with first-episode schizophrenia: A one-year open-label study

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Objective: Schizophrenia is a chronic and debilitating disorder characterized by positive, negative, cognitive, and affective symptoms. The purpose of this study was to evaluate the long-term effectiveness and safety of blonanserin, a second-generation antipsychotic drug developed in Japan, in patients with first-episode schizophrenia.

Methods: Twenty-three antipsychotic-naïve patients with first-episode schizophrenia were treated within an open-label, one-year, rater-blind prospective trial of blonanserin (2–24 mg/day). Clinical evaluations were conducted at baseline and 2-, 6-, and 12-months after the start of treatment. The main outcome measures were changes in subjective well-being and subjective quality of life, as assessed by the Subjective Well-being under Neuroleptic treatment scale Short form-Japanese version (SWNS-J) and the Schizophrenia Quality of Life Scale-Japanese language version (SQLS-J), respectively. Secondary outcome measures included the Positive and Negative Syndrome Scale (PANSS), the Brief Assessment of Cognition in Schizophrenia-Japanese language version (BACS-J), laboratory tests, body weight, and extrapyramidal symptoms. This study protocol was approved by the bioethics committee of St. Marianna University School of Medicine, and written informed consent was received from all participants.

Results: Fourteen patients (60.9%) completed the study. In the intention to treat analysis, significant improvements were observed in several subscales on the SWNS-J, SQLS-J, and BACS-J, and in all subscales on the PANSS. Improvement in depressive symptoms with blonanserin treatment was positively correlated with improvements in subjective well-being and subjective quality of life, as well as certain domains of cognitive function. No significant changes were noted for any safety measure during the one-year study period.

Conclusion: Blonanserin was well tolerated and effective for the treatment of first-episode schizophrenia in terms of subjective wellness, cognition, and a wide range of pathological symptoms. Thus, blonanserin may be a promising candidate as a first-line antipsychotic for first-episode schizophrenia.

Policy of full disclosure: Dr. Tenjin has received speaker's honoraria from Dainippon Sumitomo. Dr. Miyamoto has received advisory board honoraria from Dainippon Sumitomo. Dr. Miyake has received speaker's honoraria from Dainippon Sumitomo, Eli Lilly, Mitsubishi Tanabe, Otsuka, and Yoshitomi. Dr. Sumiyoshi has received advisory board and/or speaker's honoraria from Dainippon Sumitomo, Eli Lilly, Mitsubishi Tanabe, Yoshitomi, and Takeda. Dr. Yamaguchi has received advisory board and/or speaker's honoraria from Daiichi Sankyo, Eizai, Eli Lilly, Janssen, Otsuka, and Takeda. No other authors have any conflicts of interest.

P-25-038 Impact of once- versus twice-daily risperidone and olanzapine dosing on clinical outcomes: Findings from the catie schizophrenia study

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Objective: The objective of this study was to evaluate the impact of once- vs. twice-daily dosing of risperidone and olanzapine on clinical outcomes in patients with schizophrenia.

Methods: Data from phase 1 of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia study were used in this post hoc analysis. Patients with schizophrenia (DSM-IV) were randomly allocated to treatment with risperidone (1.5–6.0 mg/day) or olanzapine (7.5–30 mg/day), and were also randomly assigned to once-daily (N=173 or 169, respectively) or twice-daily (N=168 or 167, respectively) dosing and followed over 18 months. Discontinuation rate and time to discontinuation were used as primary outcome measures to compare the two groups. The following secondary outcome measures were also analyzed; efficacy: symptoms and quality of life, safety: extrapyramidal symptoms, body weight, and adverse events, other: medication adherence, attitude toward medication, and concomitant psychotropic medications.

Results: We found no significant difference in discontinuation rates and time to discontinuation between once- and twice-daily dosing groups ($P>0.05$) in total patients receiving risperidone and olanzapine, or patients receiving risperidone or olanzapine. Once-daily dosing group demonstrated significantly lower mean daily doses of risperidone and olanzapine across phase 1 ($P=0.046$ and 0.003, respectively), and a lower rate of sleepiness in total patients ($P=0.004$) compared to twice-daily dosing group. No significant differences were found in any other outcome measures between once- and twice-daily dosing groups in total patients.

Conclusion: We found no differences in effectiveness and efficacy outcomes between once- and twice-daily dosing for risperidone and olanzapine. However, in view of the lower mean dose and better side effect profile, it may be advisable to adhere to a once-daily dosing regimen.

Policy of full disclosure: Dr. Takeuchi has received fellowship grants from CAMH foundation, the Japanese Society of Clinical Neuropsychopharmacology, and Astellas Foundation for Research on Metabolic Disorders, speaker's fees from Dainippon Sumitomo Pharma, Eli Lilly, GlaxoSmithKlein, Janssen Pharmaceutical, Meiji Seika Pharma, and Otsuka Pharmaceutical, and manuscript fees from Dainippon Sumitomo Pharma within the past 5 years. Mr. Fervaha has no competing interests to disclose. Dr. Lee has received consultant fee from Roche within the past 5 years. Dr. Agid has received speaker's honoraria from, Eli Lilly, Janssen-Ortho (Johnson & Johnson), Lundbeck, Novartis, Sepracor Inc. US., and Sunovion, and consultant fees from BMS, Eli Lilly, Janssen-Ortho (Johnson & Johnson), Lundbeck, Novartis, Otsuka, Roche, Sepracor, and Sunovion, and research support from Janssen-Ortho (Johnson & Johnson), Otsuka, and Pfizer, Inc. within the past 5 years.

Dr. Remington has received research support from Novartis, Medicure, and Neurocrine Bioscience, consultant fees from Roche, and speaker's fees from Novartis. He holds no commercial investments in any pharmaceutical company within the past 5 years.

P-26. Post-traumatic stress disorders

P-26-001 Atypical antipsychotics in the treatment of posttraumatic stress disorder

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Objective: This study reviewed extant published articles on the efficacy and safety of atypical antipsychotics for the treatment of posttraumatic stress disorder.

Methods: We performed a literature search using PubMed, EMBASE, and the Cochrane database in January 2013. Selection criteria for this review included prospective, controlled studies using validated rating scales of posttraumatic stress disorder symptoms in the management of posttraumatic stress disorder.

Results: A total of 12 prospective, controlled studies were included in this review. This review found that atypical antipsychotics are effective and safe in treating posttraumatic stress disorder, even though there were some negative findings. In particular, atypical antipsychotics also seem to be effective in treating anxiety, depression and psychotic symptoms frequently accompanied by PTSD.

Conclusion: This review found that atypical antipsychotics appeared to be effective and tolerable in the management of PTSD, even though the evidence was limited.

Policy of full disclosure: None.

P-26-002 Association between D2 Dopamine Receptor(DRD2) gene and posttraumatic stress disorder

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Objective: Evidences from recent studies support the role of a genetic factor in Posttraumatic Stress Disorder (PTSD) development. The first aim of this study is to investigate the association between Dopamine D2 receptor (DRD2) TaqI A polymorphism and PTSD. The second aim is to examine the association between DRD2 TaqI A polymorphism with clinical symptoms in PTSD.

Methods: 189 Vietnam veterans were collected for this study, among whom 99 were PTSD patients and 90 were control subjects. DRD2 TaqI A polymorphism were determined by PCR method. Several standardized research scales were used for the clinical assessment of PTSD, including the combat exposure scale (CES), clinician administered PTSD scale (CAPS), Beck depression inventory(BDI), clinical global impression (CGI).

Results: In this study, the PTSD patients were not significantly different from the controls in respect to the DRD2 genotype distribution, the frequency and prevalence of A1 allele, or the frequency of heterozygotes. In PTSD patients, patients group with A1 allele (A1A1, A1A2) had higher scores for the total CAPS score ($p=0.044$), avoidance symptoms score of CAPS ($p=0.016$) and BDI ($p=0.024$) than those without A1 allele (A2A2).

Conclusion: We couldn't find association between Dopamine D2 receptor (DRD2) TaqI A polymorphism and PTSD. But A1 allele of DRD2 seem to have influence on avoidance symptoms in PTSD patients.

Policy of full disclosure: None.

P-26-003 PTSD, outcome and its up to date treatments

H. Rabbani. *Paris, France*

Objective: Based on our teaching experiences, observations and clinical researches in the Mental Health Center, we present the psychopathological and psycho-social effects of post-traumatic stress disorder (PTSD) (caused by wars or catastrophic stressful life events) then its different methods of treatment.

Methods: Since world war II, large studies were made in France, USA, Canada and in some other European countries by researchers (Goldberger L. 1982, Lazarus R.S. 1985, Lomranz J.1990 and others) on this area. Recently the study of PTSD has become one of the principal themes of congresses.

Results: The therapy of the patients, particularly women (Rabbani H. San Francisco 1998) in some cases: eg. divorce, forced immigration, (Rabbani H. 1991) and separation or faced to the catastrophic events (human or natural) and suffering from depression and trauma, is not so easy. In one side, the medical and psycho pharmacotherapy (antidepressants with their chemical substances), and psychosocial treatments: music, occupational therapy, sports, physical activities etc. on the other side, are recommended. Today, depression and trauma resulting from many factors (Rabbani H. Salpêtrière 2007) are widespread in the world. Alas! because of so many reasons: sociopolitical and environmental changes, acts of terrorism, injustice, wars and violence (Rabbani H. Istambul 2003 Mc Gill 2012) etc. there is likelihood that the frequency of anxiety, depression and trauma will increase in the future. The efficiency of some antidepressants such as imipramine, paroxetine (Rabbani H. 2008 Munich) and others (eg. antidepressant properties of ketamine) recently presented by H. Lôo R. Gaillard et al 2014, is well established; however, medical treatment, in spite of its side effects, as indicated also several authors (Stein H.B. et al 2002, Gourion D. et al 2007) is pertinent.

Conclusion: Meanwhile, in parallel of medical and pharmacotherapy, we must note that the psychosocial and family cares in collaboration with psychologists and social workers can be more efficient in reduction or improvement of PTSD.

Policy of full disclosure: None.

P-26-004 The effect of early post-stressor intervention with agomelatine on behavioral and molecular responses in an animal model of post-traumatic stress disorder

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Objective: Long-term behavioral, molecular and morphological effects of agomelatine, a melatonergic agonist (MT1/MT2) and 5HT2C antagonist with antidepressant and anxiolytic and re-synchronizing effects were assessed in an animal model of posttraumatic stress disorder (PTSD).

Methods: Adult male Sprague-Dawley rats were exposed to the predator scent stress (PSS) (10 min), and 1 h later treated acutely with agomelatine (50 mg/kg i.p.) or vehicle on Day1 (D1). Rats were assessed in the Elevated plus-maze (EMP) and acoustic startle response (ASR) on D8, freezing behavior after situational reminder cue was done on (D9) and rats were sacrificed 24 h after. Serum corticosterone and the dexamethasone suppression test were used to assess the stress response and HPA axis feedback inhibition. Neurons from hippocampus (CA1, CA3, and DG) were reconstructed and Sholl analysis and spine density estimation evaluated. Brain expression of BDNF and Per1, Per2 clock genes was analysed.

Results: Agomelatine reversed time spent in the open arms (EPM) decrease and mean startle amplitude increase observed in PPS vehicle-treated rats. Moreover agomelatine decreases prevalence rates of individuals displaying extreme behavioural responses (PTSD-like), cue-induced freezing and PPS#induced corticosterone increases. Agomelatine also normalized BDNF decreases observed in the DG, cortex (layer III), and basolateral amygdala (BLA) of PPS rats. In line with this, agomelatine-treated stressed animals displayed significantly increased DG and CA1-apical dendritic length and number and reversed the hippocampal neuronal retraction observed in PSS vehicle-treated rats. As regards clock genes expression, agomelatine normalized Per1 increases observed in the CA3, Suprachiasmatic nucleus (SCN) and BLA of PPS rats and Per2 increases observed in the CA1, SCN and BLA of PPS rats.

Conclusion: The data provides initial evidence that a single dose of agomelatine administered in the acute aftermath of stress promotes recovery while promoting enhanced neuronal and synaptic plasticity and connectivity in the secondary prevention of PTSD in this model.

Policy of full disclosure: None.

P-27. Neurodegeneration B

P-27-001 Pharmaceutical therapy for behavioral and psychological symptoms of dementia (BPSD) in inpatients

J. Uno. *Fujita Kokoro Care Center, Toyoke Aichi, Japan*

Objective: Although Behavioral and Psychological Symptoms of Dementia (BPSD), such as hallucination, delusion, aggressiveness, disquieting are treated with central symptoms of dysfunction of recognition by pharmaceutical therapy in dementia, there is few repots of clinical survey. This article reports the survey of pharmaceutical therapy for BPSD with inpatients in our hospital and we reexamined the pharmaceutical therapy in BPSD.

Methods: The patients with dementia (ICD-10: F0) hospitalized at Okehazama Hospital Fujita Kokoro Care Center between 1/4/2012 and 31/3/2013 were enrolled in the survey. The symptoms of BPSD and the

names of the drugs and doses for the treatment of BPSD were studied from the patient's case record.

Results: The subjects number (M/F) who were enrolled in the study were 150 (72/78), and average age was 78.5 (46#99) and average hospitalized days were 147(2#3, 516). BPSD were recorded in 64.0% of subjects and main symptoms were below: agitation, hallucination, abnormal behavior, and resistance. The drugs for the treatment of dementia were prescribed in 31.1% of the subjects and antipsychotics, Yokukansan, anxiolytics/hypnotics, and mood stabilizers were below: 82.3%, 34.4%, 19.8%, 22.9%, respectively. The prescription rate of antipsychotics were higher in order: Risperidone>Quetiapine>Olanzapine>Aripiprazole.

Conclusion: The study revealed that about 64.0% in inpatients with dementia in our hospital have symptoms of BPSD and they have short hospitalized periods also. If we could control the symptoms of BPSD, they can leave out the hospital as soon as possible. The main symptoms of BPSD were agitation, hallucination, abnormal behavior, so the drugs to treat BPSD were mainly used antipsychotics for the purpose of sedation. As FDA revealed that the use of antipsychotics makes the death rates higher, we pharmacists engaged in psychiatric care should actively commit themselves as a professional of drugs to ensuring appropriate prescriptions in order to get maximum merits of antipsychotics.

Policy of full disclosure: None.

P-27-002 Epidemiological and clinical profile of Alzheimer's dementia in Upper Egypt

H. El Tallawy[1], W. Farghaly[1]. [1]*Assiut University, Assiut, Egypt*

Objective: Objective of this work was to estimate the prevalence of AD in Upper Egypt and the associated possible risk factors.

Methods: Subjects and methods: All subjects at the age of 50 years and more (n=12,508) who have been living in Al Khargah district; New Valley Governorate (n=8,173 out of 62,583) or Al Quseir city; Red sea Governorate (n=4,335 out of), for at least 6 months, at the time of interview were included in this study. All inhabitants were screened in a door to door manner using a short standardized Arabic screening questionnaire and modified MMSE, by 6 specialists of neuropsychiatry. Suspected cases were subjected to full clinical examination, psychometric assessment using the Cognitive Abilities Screening Instrument, Instrumental Activities of Daily Living Scale, Geriatric Depression Scale, Hachinski Ischemic Score, DSMIV- TR diagnostic criteria, neuroimaging, and laboratory investigations when indicated.

Results: One hundred twenty six cases were diagnosed as having AD with a prevalence rate of 1% for population aged 50 years and more. It was estimated that 7.9% of the cases were early onset dementia (<65 years of age), while 92.1% were late onset AD (>65 years). The prevalence increased steeply with age to a maximum of 9.74% for those aged >80 years. It was higher among females (1.265%) than males (0.93%). Staging of dementia cases revealed that 41.3% of cases are of mild severity. Probable associated risk factors in order of frequency were hypertension (14.3%), positive family history of AD (13.5%), smoking (10.3%), diabetes mellitus (8.7%), epilepsy prior to dementia (5.6%). Among symptomatic presentation impaired self care was recorded among 88.1% of cases, memory impairment in 84.1%, while behavioral changes were reported among 48.4%.

Conclusion: Prevalence of AD in Upper Egypt was 1% with more than 40% of cases are of mild severity. Door-to-door survey is the best method in, developing countries, for early detection of those mild cases.

Policy of full disclosure: None.

P-27-003 Blood endotoxin in patients with AD, acetyl choline metabolic enzymes, BDNF level changes and significance of research

B. Han[1], F. Wu[2], D. Han[2], Q. Sun[1], X. Shan[1]. [1]*The General Hospital of CAPF, Peking, China;* [2]*Shanxi Medical University, Taiyuan City, China*

Objective: Observe whether accompanied by IETM in patients with AD, further explore AChE, ChAT, and the role of BDNF in AD mechanism, proved to play an important role in AD. Provide new way for the onset of the new prevention and treatment of AD.

Methods: Research object and grouping: from August 2011 to October 2012 will conform to the standard of from Department of Outpatient and Ward of Department of Neurology or Department of Outpatient and Ward of Department of Psychiatry in Shanxi Province, 70 old people as the research object, such as divided into AD group and control group. Neuropsychological tests: MMSE and ADAS-cog. LPS level was detected by Chromogenic End-point Tachypleus Amebocyte Lysate (CE TAL), AChE, ChAT and BDNF level was detected by ELISA.

Results: MMSE scores in the AD group were significantly lower than the control group; ADAS-Cog scores in the AD group was significantly higher than the control group. LPS levels in AD group was significantly higher than the control group; AChE levels higher than the control group, ChAT level significantly lower than the control group; Serum BDNF levels in AD group was significantly lower than the control group. The AD group LPS, BDNF, ChAT, and content of AChE after statistical analysis found that the LPS under 0.20 Eu/ml, BDNF, ChAT and AChE content fell sharply, while LPS above 0.20 Eu/ml, BDNF, ChAT and AChE content basic similar. By control LPS, BDNF, ChAT and AChE content statistics analysis, found that among various variables found no correlation exists between variables.

Conclusion: In the AD patients with IETM. The experiment based on the research of the AChE, ChAT, BDNF and combining the research previously of TNF alpha and A beta and Tau protein of observation, put forward the "IETM may be AD A new risk factor in the process of happen?" Key words Intestinal endotoxemia; Alzheimer's disease; LPS; AChE; ChAT; BDNF.

Policy of full disclosure: None.

P-27-004 Effect of endotoxin on brain cell apoptotic in aging rats

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Objective: To study dyofunction clearing endotoxin and its effect on brain cells in aging rats.

Methods: Endotoxin and tumor necrosis factor-# content of plasma were determined in normal and after endotoxin infection of 24 month old and 6 month old rats. Effect of endotoxin and tumor necrosis factor-# on free Ca## in brain cells were observed in vitro, and apoptosis of brain cells were examined by flow cytometer.

Results: The level of endotoxin in plasma were much higher in 24 month old rats than those of 6 month old rats in both normal and after endotoxin injection groups, buttumor necrosis factor-# was increased significantly only after endotoxin injection. Tumor necrosis factor-# was elevated significantly free Ca## in brain cells, and after endotoxin injection via portal vein apoptosis of brain cells were developed.

Conclusion: Increased plasma endotoxin toxin and tumor necrosis factor-# in 24 month old rats contributed to elevation of [Ca##]i in brain cells and apoptosis, and the mechanism might involes changes of brain microecological environment induced by altered cytokins. [Key words] Endotoxin; tumor necrosis factor-#;Apoptosis; Rat.

Policy of full disclosure: None.

P-27-005 Effects of IETM on learning memory ability and hippocampal gene expression of APP and PS1 in rats with Alzheimer's disease

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Objective: To investigate the effect of intestinal endotoxemia (IETM) on learning and memory ability in rats with Alzheimer's disease (AD) and its possible mechanisms.

Methods: The AD model of wistar rats were produced by injecting D-galactose and AlCl3 intraperitoneally for 90 days. Subsequently, learning and memory ability of the rats were evaluated by Morris water maze; the level of lipopolysaccharide (LPS) and tumor necrosis factor-# (TNF-#) were determined by ELISA; the apoptotic neuron was detected by (TUNEL); hippocampal gene expression of amyloid precursor protein (APP) and presenilin1 (PS1) was tested by RT-PCR.

Results: Compared with the normal control group, the model group had longger latency ($P<0.01$) and more error times ($P<0.05$) in Morris water maze test; LPS, TNF-# and PD in AD rats were increased ($P<0.05$); the expression of APP and PS1mRNA in hippocampus were increased (P#0.05).

Conclusion: The rat model of Alzheimer#s disease is accompanied IETM and that may plays an important role in the development of AD. [Key words] Alzheimer's disease (AD); Intestinal endotoxemia (IETM); Lipopolysaccharide (LPS); Tumor necrosis factor-# (TNF-#); Amyloid beta-protein precursor (APP); Presenilin1 (PS1)

Policy of full disclosure: None.

P-27-006 The change of endotoxin, AchE, ChAT and Tau protein in patients with Alzheimer's disease

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Objective: To investigate the change of endotoxin, AchE, ChAT and Tau protein in patients with Alzheimer's disease (AD).

Methods: From January 2011 to January 2012, subjects of patients with AD and healthy elderly were collected from hospital and nursing homes from Taiyuan City, China. Subsequently, cognitive function of the two group subjects were assessed by MMSE and ADAS-Cog. The level of endotoxin was determined by TAL, AchE, ChAT and Tau protein were determined by ELISA.

Results: MMSE score in the patients with AD were significantly lower than the healthy elderly ($P<0.001$), ADAS-Cog score in patients with AD were significantly higher than the healthy elderly ($P<0.001$); patients with AD endotoxin, AchE, ChAT and Tau protein were significantly higher than the healthy elderly ($P<0.05$).

Conclusion: Patients with AD were all accompanied intestinal endotoxemia and that may be a risk factors in the development of AD. [Key words] Alzheimer's disease; Intestinal endotoxemia; endotoxin; AchE; ChAT; Tau protein.

Policy of full disclosure: None.

P-27-007 The role of P38, JNK and NF-KB in LPS activating microglia in Alzheimer disease's rats

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Objective: The study was to explore the role of P38, JNK and NF-KB in LPS activating microglia in Alzheimer disease (AD) Rats which were established by D-galactose and aluminum trichloride (AlCl3).

Methods: Adult Wistar rats were subjected to 90 days of intraperitoneal injection weth D-galactose and AlCl3 to establish the AD model. After the administration, the level of Lipopolysaccharide (LPS) in the serum was determined by tachypleus amebocyte lysate method; the experession of P38, JNK, NF-KB and OX-42 in the brain were determined by Western-blot and Immunofluorescence method.

Results: The expression of OX-42 in the brain of Alzheimer Disease's rats and the control group both have positive fluorescent particles, fluorescence intensity compared the two groups difference have statistical significance. The expression of OX-42 in the brain of AD's rats and the control group both expressed, the difference between groups was not statistically significant; Compared with the control group, the expression of p-P38, p-JNK in the brain of AD's rats were markedly increased. Compared with the control group (34.7±4.6)%, the expression of NF-KB in the brain of AD's rats (51.9±7.6)% were markedly increased, difference have statistical significance.

Conclusion: The P38, JNK and NF-KB played a important role in LPS activating microglia in the AD's rats model which were established by D-galactose and AlCl3. [Key words] Intestinal endotoxemia, Lipopolysaccharide, Alzheimer's disease, P38, JNK, NF-KB.

Policy of full disclosure: None.

P-27-008 Recovery of old (lost) memories in mice genetically designed to mimic Alzheimer's disease

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Objective: The clinical hallmark of Alzheimer's disease (AD) is progressive cognitive decline. Patients first show difficulty forming new memories, then deficits in retrieving older memories. Beta-amyloid (Ab) is implicated in AD and chronically high Ab may induce cell death. This neurodegeneration readily accounts for memory and cognitive impairment observed in later stages of AD. In early stages of AD, however, patients show deficits in forming new memories and high Ab but no detectable cell death. This suggests that high Ab may directly interfere with the synaptic plasticity required for normal memory formation. How Ab impairs memory is unknown. In vitro, high Ab decreases synaptic strength by promoting internalization of postsynaptic AMPA-type glutamate receptors (AMPARs), suggesting some of the memory deficits in AD may be due to excessive AMPAR internalization. Here we investigated the role of AMPAR internalization in the memory deficits observed in several types of mice genetically designed to recapitulate important aspects of AD.

Methods: We examined the effects of acutely or chronically increasing Ab on the ability of mice to form stable memories. We also examined the role of AMPAR internalization in these memory deficits.

Results: Acute or chronic increases in Ab impaired the ability of mice to form stable long-term memory. Importantly, transiently interfering with AMPAR internalization was sufficient to reverse the memory deficits produced by either acute or chronic overexpression of Ab. Memories, even after consolidation, are modifiable. The process of remembering is thought to reactivate memory representations in the brain. The reactivated memory is re-stored in a second wave of consolidation (reconsolidation). Strikingly, similarly disrupting AMPAR endocytosis during a memory reminder enabled the recovery of an otherwise inaccessible memory in mice with chronically high Ab.

Conclusion: Our findings raise the possibility that targeting AMPAR trafficking could restore both the ability to form new memories as well as enable recovery of lost past memories in AD patients.

Policy of full disclosure: None.

P-27-009 Novel 5-HT6 receptor antagonists/D2 receptor partial agonists targeting behavioral and psychological symptoms of dementia

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Objective: All dementia patients suffer from impairment of cognitive functions and up to 90% of them show also behavioral and psychological symptoms (BPSD) such as: depression, anxiety, agitation, aggression, irritability or psychosis. Those symptoms were found to be even more disturbing than cognitive decline and are the most common cause of patients' institutionalization. In view of lack of specific treatments, BPSD have been commonly treated using antipsychotic drugs, which display only partial efficacy. Moreover, they were found to exacerbate preexisting cognitive deficits, as well as cause serious cardiovascular and motor side effects, and thus are not approved for the treatment of BPSD. Therefore, development of an effective and safe therapy of BPSD remains an increasing clinical and social unmet need. Pharmacological studies revealed procognitive role of 5-HT6 receptor (5 HT6R) antagonists, and indicated their potential anxiolytic and antidepressant-like activity Moreover recent clinical findings confirm their utility in treatment of Alzheimer's disease. Similarly, a growing body of evidence suggests the high therapeutical potential of D2 receptor (D2R) partial agonists as both antipsychotic and antidepressant agents, with a favorable safety profile.

Methods: Design, synthesis and pharmacological evaluation of a set of innovative, hybrid molecules acting as 5HT6R antagonists and D2R partial agonists was presented. The series was evaluated for affinity towards 5-HT6, D2 and M1 receptors as well as hERG channels. The lead molecule was tested in models of antidepressant-like (Porsolt test) and anxiolytic-like (Vogel test) activity.

Results: The most promising compounds displayed a desired profile of 5-HT6/D2 activity with negligible affinity for antitargets. The lead compound was significantly active in rat tests, in doses lower than the reference compounds, representing components of its mechanism of action (i.e. selective 5-HT6 antagonism and partial D2 agonism).

Conclusion: These observations provide compelling validation of the applied approach and warrant further studies on this mechanism of action.

Policy of full disclosure: MK is employee of Adamed Ltd. Studies were financed by Adamed Ltd. and Polish Agency for Enterprise Development (PARP). Project nr UDA-POIG.01.04.00-14-055/10-00.

P-28. Neuropathology/post mortem studies

P-28-001 Abnormal fatty acid composition in the frontopolar cortex of affective disorders – Kraepelin's dichotomy still alive

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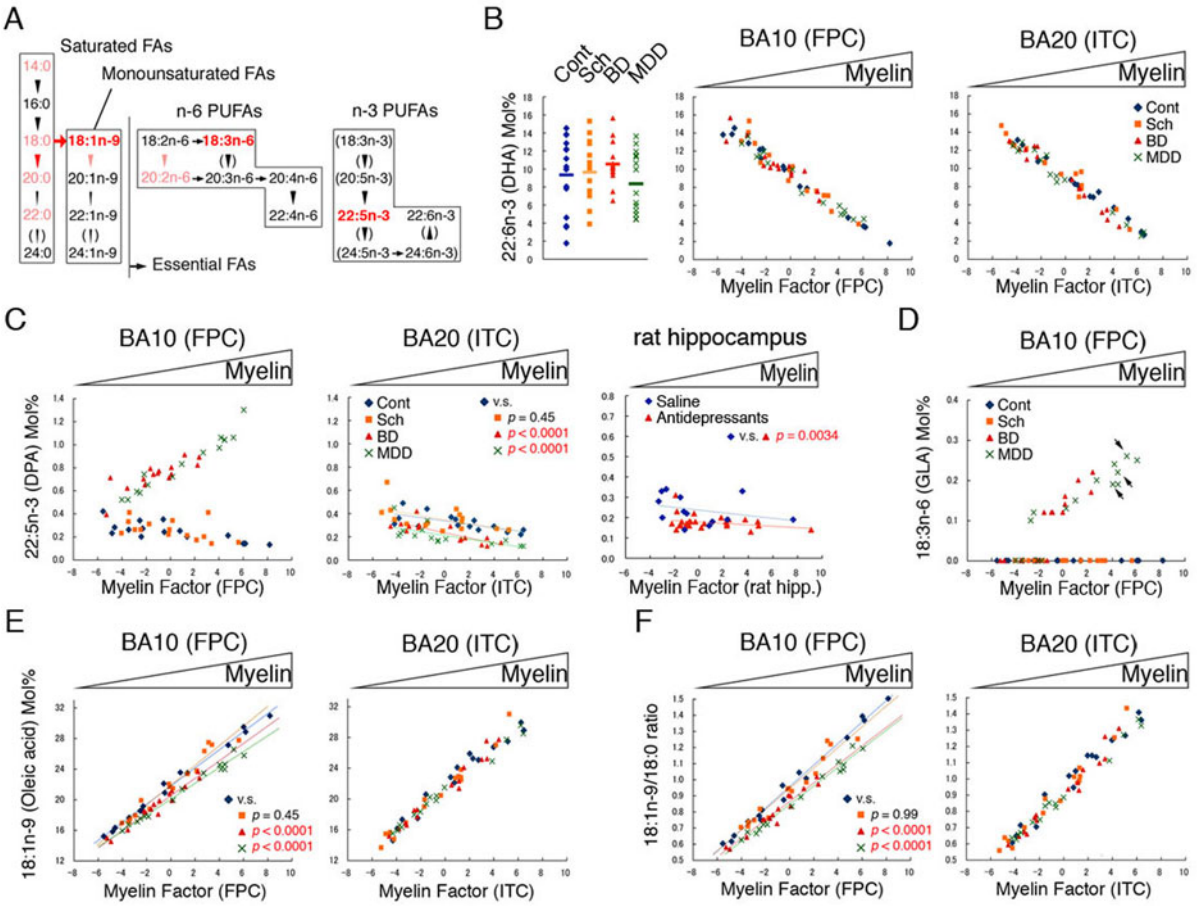
Objective: Conventional neuropathological studies for psychiatric disorders have so far provided some but only limited evidence to implicate for their etiologies. We have tackled these challenges using novel analytic methods developed by ourselves and a well-characterized set of postmortem brains provided by the Stanley Foundation Neuropathological Consortium.

Methods: Frozen unfixed postmortem brains (Brodmann Area (BA)10 & BA20) from patents with schizophrenia, bipolar disorder, or major



depressive disorder or from normal controls were analyzed. Total fatty acid (FA) composition (Fig. A) was analyzed using a novel statistical method. The validity of these methods and the influence of confounding factors were carefully checked by animal and statistical studies.

Results: We found that gamma linoleic (18:3n-6) and docosapentaenoic acids (22:5n-3) abnormally accumulate in the FPC of patients suffering from affective disorders but not from schizophrenia (Fig C, D). No change was found in the levels of docosahexaenoic acid (22:6n-3) (Fig. B). In the affective disorder FPC, the levels of oleic acid (18:1n-9) (Fig. E) and the ratios of oleic to stearic acids (18:1n-9/18:0) (Fig. F), which presumably represent stearoyl-coenzyme A desaturase activities, were also significantly downregulated. These abnormalities were all aggravated in a myelin level-dependent manner, suggesting their close relationship with myelination (Fig. C–F). Animal studies have further revealed that chronic antidepressant treatment induces robust changes in brain FA metabolism (Fig. C), but contributes only part of the abnormalities found in the affective disorder brains.

Conclusion: These findings identify a novel neuropathological hallmark of affective disorders that not only supports biologically Kreapelin#s nosological dichotomy, but which also suggests that the pathogenesis of affective disorders involves a certain lipid-related perturbation in association with cortical myelination in the adult FPC that may serve as a novel diagnostic and therapeutic target.

Policy of full disclosure: None.

Abnormal FA composition in affective disorders:

P-28-002 Cytokine expression in cingulate cortex in major depressive disorder with and without psychosis

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Objective: Mounting evidence suggests that depression is associated with chronic, low-grade inflammation. Furthermore, it has been postulated that changes in the inflammatory system may also be present in other psychiatric disorders, including psychotic disorders. Raised levels of pro-inflammatory cytokines have previously been reported in serum and plasma from patients with major depressive disorder (MDD) and schizophrenia. However, few studies have specifically examined cytokine expression in brain tissue, with inconsistent results. In this study we examined expression of several cytokines in post-mortem cingulate cortex in psychotic and non-psychotic MDD subjects and controls.

Methods: Gene expression levels of the pro-inflammatory cytokines interleukin (IL)-1beta, IL-6, and tissue necrosis factor (TNF)-alpha and the anti-inflammatory cytokines IL-10 and IL-13 were quantified in the cingulate cortex from control subjects (n=12), MDD subjects without psychotic features (n=12), and MDD subjects with psychotic features (n=12), using quantitative PCR.

Results: ANCOVA results indicate that mRNA expression of IL-1beta differed significantly between groups, being lower in MDD subjects with psychosis compared to both control subjects and MDD subjects without psychosis. IL-6, IL-10, IL-13 and TNF-alpha were not significantly altered in MDD subjects with or without psychosis.

Conclusion: Our data are not consistent with with prior reports of increased pro-inflammatory cytokine expression in MDD and psychotic disorders. However, given previous findings that antipsychotics can reduce peripheral IL-1beta expression, we suggest that lower IL-1beta mRNA expression in the cingulate in MDD patients with psychosis may reflect modulation of brain cytokine levels by antipsychotic medications.

Policy of full disclosure: This study was supported by the Michael Smith Foundation for Health Research, the Canadian Institutes of Health Research, and a Coast Capital Savings Depression Research Award. Postmortem brain tissue was donated by the Stanley Medical Research Institute#s brain collection.

P-28-003 Frontal white matter measures are unchanged in adult rats exposed to a 4-day alcohol binge protocol

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Objective: Excessive alcohol consumption is associated with negative short- and long-term health consequences including brain toxicity. Data from human studies indicates that decreased white matter volume, abnormal white matter integrity and lower expression of myelin-associated proteins are present in subjects with chronic alcoholism. In addition, neuronal degeneration, gliosis and neuroinflammation have previously been reported in temporal cortex and hippocampus in adult rodents following short-term binge protocols. Currently, it is not clear whether binge alcohol exposure exerts deleterious effects on white matter. In this study we examined frontal white matter volume, myelin-associated protein levels and markers of gliosis following a 4-day binge alcohol exposure protocol in adult rats.

Methods: Two cohorts of adult female Long-Evans rats were administered ethanol three times/day for four days. Brains were subsequently harvested; in the first cohort tissue was perfused for neuroanatomical examination while in the second cohort frontal white matter was extracted and tissue frozen for biochemical analyses. Frontal white matter volume anterior to the genu of the corpus callosum was measured using stereological techniques. Density of microglial cells and glial fibrillary acidic protein (GFAP) immunoreactivity was quantified by immunocytochemistry and computer assisted image analysis. Expression of myelin-associated proteins was determined using western blotting.

Results: We observed no difference in white matter volume, microglial cell density, GFAP immunoreactivity, or levels of myelin-associated proteins between groups.

Conclusion: Our data indicate that frontal white matter is not significantly affected by short-term binge alcohol exposure in adult rats.

Policy of full disclosure: This study was funded by the Mind Foundation of BC. CB also receives funding from the Michael Smith Foundation for Health Research and the Canadian Institutes of Health Research.

P-28-004 Trace amine-associated receptor, type 1 (TAAR1) as prospective target receptor for neuroleptics: From D-neuron study in postmortem brains of schizophrenia

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Objective: The role of trace amines in the etiology of mental disorders has been underestimated due to paucity of trace amines in mammalian brains. However, recent pharmacological studies have shown the importance of trace amine-associated receptor, type 1 (TAAR1), a subtype of trace amine receptors, as a prospective target receptor for novel neuroleptics. The author shows a novel hypothesis for etiology of schizophrenia, in which TAAR1 and trace amines are involed, and emphasized the importance of TAAR1 ligands as novel neuroleptics.

Methods: Endogenous ligand producing neuron of TAAR1 is the D-neuron, i.e., trace amine neuron, defined as "the aromatic L-amino acid decarboxylase neuron, not containing dopamine (DA) nor serotonin". The author's group found significant reduction of D-neurons (trace amine neurons) in the nucleus accumbens (Acc) of autopsy brains of patients with schizophrenia (Ikemoto et al. 2003). The author reviewed recent relevent publications focued on TAAR1 and D-neurons, and showed involevement of them in etiology of schizophrenia.

Results: Animal model studies have shown that reduced TAAR1 stimulation to DA neurons in the midbrain ventral tegmental area (VTA) increased firing frequency of VTA DA neurons (Wolinsly et al., 2007, Bradaia et al., 2009). Thus, D-neuron reduction and consequent trace amine reduction, causing TAAR1 stimulation decrease on terminals of midbrain VTA DA neurons would be molecular basis of mesolimbic DA hyperactivity of schizophrenia. D-neuron reduction in Acc of postmortem brains is due to neural stem cell (NSC) dysfunction in the subventricular zone of lateral ventricle located in the marginal area of Acc (cf. NSC dysfuction hypothesis of schizophrenia). The new "trace amine hypothesis" ("D-cell hypothesis"), of schizophrenia in which D-neuron and TAAR1 is involved, is in agreement with recent reports showing effectiveness of TAAR1 ligands for schizophrenia model animals (Revel et al., 2013).

Conclusion: The "trace amine hypothesis" ("D-cell hypothesis") links DA hypothesis of schizophrenia with NSC dysfunction hypothesis. D-neuron reduction in Acc, an anatomical area known for antipsychotic acting site, would let us conclude TAAR1 ligand searching study being pivotal in novel neuroleptic discovery.

Policy of full disclosure: "The method for visualizing human D-cells" is under requiring an international patent.

P-28-005 Changes in phospholipase c beta 1 expression in the dorsolateral pre-frontal cortex in schizophrenia and suicide

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Objective: Phospholipase C, beta 1 (PLCB1) is a downstream signalling protein for various receptor systems implicated in schizophrenia (Sz). We recently showed decreased PLCB1 mRNA in Brodmann's Area (BA) 46 from subjects with Sz, while protein levels remained unchanged [1]. PLCB1 protein has been reported to be decreased in BA8 and 9 in adolescent suicides [2], which led us to determine whether PLCB1 mRNA and protein were altered in BA9 from subjects with Sz, a disorder associated with an increased rate of suicide.

Methods: Quantitative PCR was used to measure mRNA for PLCB1 variants a and b, and Western blots were used to measure PLCB1a and b protein, in BA9 from 38 subjects with schizophrenia, of which 12 had died by suicide, and 20 controls with no history of psychiatric illness.

Results: Compared to age/sex matched controls, PLCB1 a and b mRNA were not altered in subjects with schizophrenia. By contrast, PLCB1a, but not b, protein was lower in Sz ($p=0.001$) whereas PLCB1b protein was lower ($p=0.028$) and PLCB1b mRNA was higher ($p=0.018$) in subjects who had died by suicide.

Conclusion: We have shown that PLCB1 variant a protein is lower in BA9 from subjects with schizophrenia whereas that of variant b is lower in those with the disorder who died by suicide. Understanding the potential role of PLCB1 signalling in Sz and suicide risk should be a priority as this signalling pathway is targeted by antipsychotic drugs.

Policy of full disclosure: None.

References

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P-28-006 Gene coexpression analysis in the frontal cortex of bipolar patients and controls

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Objective: Several large scale gene expression analyses addressed the question of genes differentially expressed in bipolar patients. While the list of candidate genes is continuously growing, the reproducibility of the results at gene level, is relatively low. More systemic approach for analysing expression data is based on clustering the genes based on common characteristics e.g. pathways, cellular localization, function etc. While this approach appears to provide more robust results, it is limited to our current knowledge regarding the genes and their products. As such it is biased towards the more studied terms and might neglect important but less examined connections. Coexpression analyses possess the potential to uncover previously unknown interactions and functional connections between proteins, and thus, are not as biased by prior knowledge.

Methods: We performed coexpression analyses of several publicly available gene expression data sets from frontal cortex of bipolar patients and controls. We were specifically interested in the coexpression of subsets of genes previously reported to be related to lithium treatment or to bipolar disorder, but lacking known connections between them.

Results: We show that such genes while not consistently showing differential expression among studies, are highly coexpressed.

Conclusion: Our results suggest existence of yet unknown physical and functional interactions between the genes' products. Such interactions might be relevant to the pathophysiology of bipolar disorder and might relate to the patient's responsiveness to the different treatments.

Policy of full disclosure: None.

P-28-007 Pyruvate dehydrogenase beta subunit expression within the schizophrenia's

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Objective: A recent microarray study by our group showed a significant decreased in the expression of Pyruvate dehydrogenase beta subunit (PDHB) in the dorsolateral prefrontal cortex (BA 9) from people with

schizophrenia (Sz) compared to that in age/sex matched, healthy controls. PDHB is the catalytic component of PDH that plays an essential role in its ability to convert pyruvate to acetyl-CoA, a rate limiting step in the production of energy from glucose. Changes in levels of PDHB in BA 9 could therefore have profound effects on energy utilisation in that CNS region from people with Sz. The potential importance of changes in PDHB in Sz has led us to validate our microarray data.

Methods: Quantitative PCR was used to measure levels of PDHB mRNA whilst Western blotting was used to measure levels of PDHB protein in BA 9 from 30 subjects with Sz and 30 controls.

Results: mRNA for PDHB was significantly increased between people with Sz (0.8796±0.04 units) compared to controls (0.7628±0.04 units; p=0.05). Protein levels were not significantly different between the two groups (Sz=0.708±0.05 vs. Controls=0.6333±0.03; p=0.30).

Conclusion: Our data argues that changes in levels of PDHB expression at the level of mRNA in BA9 from people with Sz do not extend to changes in levels of protein level. However, relatively minor variations in levels of PDHB could impact on PDH activity and therefore functional assays will be employed to investigate the activity of the PDH in this cohort.

Policy of full disclosure: None.

P-28-008 Class II metabotropic glutamate receptors are downregulated in major depressive disorder

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Objective: Major Depressive Disorder (MDD) affects ~10% of the world's population (WHO). Yet, despite high prevalence rates, major aetiological questions remain unanswered, and better therapeutic strategies are urgently needed. Emerging results aimed at identifying the mechanism of action of ketamine, an NMDA receptor antagonist that shows rapid and and effective antidepressant activity, reveal a role for mGlu2/3 in the signaling pathways thought to underlie the antidepressant effects, necessitating further investigations into mGlu2 and 3, and their involvement in MDD. In this study, we investigated the expression of mGlu2/3 receptors in the anterior cingulate cortex (BA24) of people with MDD.

Methods: Saturation binding curves for [3H]LY341495 were established in human cortical tissue. Based on these curves, a concentration of 3nM [3H]LY341495 was chosen for autoradiography. Sections were incubated in 3nM [3H]LY341495, postfixed, and apposed to plates for 3 days prior to being imaged on a BAS system, and analysed using AIS software. BA24 was selected for analysis in MDD, schizophrenia (SCZ), bipolar (BPD) and controls (N=14–15).

Results: mGlu2/3 were found to be expressed across the brain, in regions of relevance to psychiatric disorders. Strong binding was observed in cortical regions (BA9 and BA10), caudate putamen, and hippocampus. Consistent with an important role for mGlu2/3 in MDD, [3H]LY341495 binding was significantly decreased in BA24 of MDD relative to control, but unchanged in the same region in SCZ and BPD.

Conclusion: The emergence of ketamine as a treatment for depression has shifted the focus of affective research programs, underscoring the need for increased insight into glutamate's contribution to the aetiology and treatment of psychiatric disease. We demonstrate dysregulation of mGlu2/3 in MDD, however the dissociation of mGlu2 from mGlu3 is a critical next step in precisely identifying the disruption. Understanding how these receptors are involved in psychopathology will allow for the development of more targeted treatment strategies.

Policy of full disclosure: None.

P-29. Neurophysiology; from ion channels to cortical EEG B

P-29-001 Neurofunctional activation of human visual cortex in amblyopiainduced by S/NRI treatment and sensory stimulation. A case report

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Objective: To demonstrate the neuroplasticity process in the underdeveloped adult brain visual cortex induced by the combination of long term antidepressant administration (S/NRI duloxetine) and sensory stimulation. A model of neuronal restored plasticity has been so far demonstrated only in the visual cortex of amblyopic adults rodents treated with the SSRI fluoxetine.

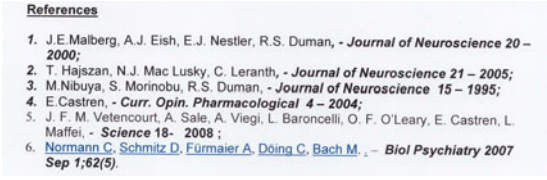
Methods: Measurements at T0 and T1 (respectively 0–18 months) of: – Eyesight: UnCorrected/Best Corrected Visual Acuity (UC/BCVA); – Visual Evoked Potentials (VEPs), with pattern reversal of 15° and 60°. Daily exposure for one/two hour/s of the amblyopic eye to visual stimulation, such as watching TV, for 18 months; Duloxetine intake, 60 mg/die, as prescribed, for 18 months.

Results: Measurements at T1 in the amblyopic left eye, showed: – increase of BC VA from 4/10 to 7/10 (Fig.1); – decrease of VEPs P100 Latency peak time from 117.77 to 111.91 msec in 15°pattern (Fig.2) and from 112.5 to 102.5 in 60°pattern (Fig. 3); – increase of VEPs N75- P100 Amplitude from 0.42 to 4.14 μV in 15°pattern (Fig. 4) and from 3.76 to 5.33 in 60°pattern (Fig. 5).

Conclusion: The clinical and the experimental results (improvement of BCVA, increase of N75-P100 Amplitude, decrease of P100 Latency, remission from dysthymia), seem to confirm other findings and to demonstrate that also the human adults neuronal cortex can be shaped, after proper stimulation, in order to support its natural and specific function, as showed for the contralateral eye (Fig. 6-7-8-9). The functional/structural adaptations observed might be explained through the mechanism of neuroplasticity, likely enhanced simultaneously by the duloxetine related production of BDNF and the active visual-sensory stimulation (watching TV). Since adaptation can occur also in cortical area never properly developed before (as the amblyopic one), a potential clinical application might be investigated in several neurological circumstances, where the neural network/functions has formerly been unexpressed or compromised. References: see attached file.

Policy of full disclosure: None.

Figures 1-2-3-4-5-6-7-8-9-references:



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P-29-002 Modulation of the error-related negativity by emotional interference in obsessive-compulsive disorder

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Objective: Patients with obsessive-compulsive disorder (OCD) typically view perceived inadequacy or error in daily activities and often feel that compensatory action is needed to rid themselves of this perception. Enhanced error monitoring provides evidence for the fronto-striatal model of OCD, typically examined by measuring error-related negativity (ERN). This study examined ERN in OCD patients and compared it with that in healthy subjects through affective modulation induced by task-irrelevant emotional stimuli (fearful faces).

Methods: A modified version of the flanker task with task-irrelevant emotional face stimuli was performed by 22 OCD patients and 22 healthy subjects while EEG signals were recorded from 65 electrodes. To quantify response-locked ERN, a mean amplitude of 20#120 msec post-response was computed.

Results: During trials with fearful face stimuli, the patients with OCD showed more significantly enhanced ERN amplitude(#4.05±4.44) than did the control (#1.03±3.67, t=2.292, p=0.028). The difference between ERN following fearful and neutral face stimuli was larger in the OCD patients than in the control group. Only the OCD patients exhibited significantly increased ERN amplitude under fearful face conditions compared with neutral face conditions (F=11.130, p=0.003). The OCD patients exhibited signficantly larger and correct-related negativity amplitudes than did the controlin both fearful and neutral conditions. Across the entire sample, the ERN amplitude enhancement between fearful and neutral condition was significantly correlated with feeling of incompleteness (r=−0.339, p=0.025).

Conclusion: These data provide further support for the view that performance monitoring is overactive in OCD. These findings also suggest that emotional interference using emotionally valent facial images modulates performance monitoring processes in OCD. On the basis of ERN as a stateaffect-independent property, changes in performance monitoring associated with emotional interference suggest that affective function in the fronto-striatal network be considered in understanding the neural bases of OCD.

Policy of full disclosure: None.

P-29-003 Acute effects of smoked cannabis on brain EEG power, coherence and sLORETA current density – A pilot study

T. Palenicek[1], F. Tyls[1], M. Viktorinova[1], R. Androvicova[1], T. Melicher[1], M. Brunovsky[1], P. Novakova[1], L. Kaderabek[1], J. Horacek[1]. [1]*Prague Psychiatric Center, Prague, Czech Republic*

Objective: The acute effects of cannabis and delta-9-tetrahydrocanabinol (THC) have been reported to induce psychotic symptoms. However, the relation of its psychotropic effects on how acute cannabis changes brain EEG activity during resting is limited. Therefore, we have examined the effects of smoked cannabis on EEG power spectra, coherence and on current density using sLORETA (standardized low resolution brain electromagnetic tomography).

Methods: We used an ecologically valid approach where recreational cannabis users were allowed to smoke their own cannabis in a dose sufficient to produce an appropriate high. We controlled the content and amount of THC in the drug they used and in in the serum. The brief psychiatric rating scale (BPRS) and altered state of consciousness scale (ASCs) were used to evaluate the psychopathology and characterize the high. Data were compared to a group of nonsmokers.

Results: Smokers scaled significantly higher than the controls on both psychometric scales. Cannabis induced a moderate increase of the mean EEG power in the alpha1 band (8–10 Hz), a robust increase of the power in the gamma band (30–40 Hz) and on the contrary a moderate decrease in the alpha2 band (10–12 Hz). EEG coherence was mainly decreased across the whole spectrum, with the most robust changes being present in the beta (12–25 Hz) and high beta (25–30 Hz) bands. sLORETA analysis showed a robust gamma current density increase in the frontal and temporal lobes and a small decrease of alpha2 activity in the middle cingulate and premotor cortex (Brodman area 6 and 24).

Conclusion: Since some parallels can be seen when compared to EEG findings in acutely psychotic patients, our findings have implications for acute THC as a model of psychosis. This work is supported by projects VG20122015080, VG20122015075, NT13897, PCP00023752, ECGA278006 and PRVOUKP34.

Policy of full disclosure: None.

P-29-004 Dread of ego dissolution experience during cannabis intoxication correlated with decrement of activity in default mode network: A LORETA study

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Objective: Cannabis intoxication is known to induce characteristic altered state of consciousness (ASC) (Gouzoulis-Mayfrank, 1998). We wanted to find EEG correlates of different parameters of cannabis-induced changes in the ASC scale (ASCS).

Methods: 45 minutes after smoking the usual amount of cannabis, a group of occasional cannabis users underwent resting state EEG recording. Only those subjects, who had levels higher than 4 ng/ml were included in EEG analysis (N=13). The psychopathology during the experiment was assessed by subjects themselves with ASC scale and by the experimenter with BPRS (Brief Psychiatric Rating Scale) 120 minutes after drug use. Regression analysis was performed using sLORETA to assess whether the activity changes in brain regions interrelate with ASCS and BPRS.

Results: Our main finding was a negative correlation ($r=-0.78$, $p<0.05$) between Dread of ego-dissolution (DED) subscale of ASCS and sLORETA activity in beta 3 frequency band in Cingulate gyrus and Precuneus (BA 7,24,31). Furthermore, we found another negative correlation ($r=-0.72$, $p<0.05$) between anxiety/depression subscale of BPRS and sLORETA activity in similar brain structures in beta 2, beta 3 and gamma frequency bands.

Conclusion: The decrement of brain activity in midline parietal structures in higher frequency bands correlated with subjectively experienced DED (fear, self-disorganization, derealization), as well as with the scores of anxiety/depression rated by the experimenter. These brain structures are thought to be involved in default mode network (DMN) (Raichle, 2001), where deactivations were reported in relation to different ASC (Cavanna and Trimble, 2006). One of the main hub of DMN, the precuneus, is involved in representation of self and external world (Gusnard and Raichle, 2001), therefore its deactivation should result in self-disorganization and changes in representation of external world (as observed by increased scores of DED). These dreadful experiences were shown to correspond to clinically observable anxiety (Gouzoulis-Mayfrank, 1998).

Policy of full disclosure: This work was supported by projects VG20122015080, MHCZ-DRO (PCP, 00023752), PRVOUK P34.

P-29-005 Effects of acute THC intoxication on cognitive functions and vigilance in recreational and chronic cannabis users

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Objective: The aim of the present study was to assess neurocognitive performance in recreational and chronic cannabis users during acute THC intoxication and determine its effects on cognitive performance as well as vigilance.

Methods: Computer-based neuropsychological tests (Trail Making Test – TMT, Continuous performance test – CPT) were administered to a group of 21 recreational, 27 chronic THC users and 19 matched controls 30 and 240 minutes after intoxication by their usually smoked amount of cannabis. To allow for comparison between users, blood levels of THC were measured at regular time intervals and the sample smoked by each individual was subject to genetic analysis. In addition, a 10-minute EEG of a car ride watched from driver's perspective was recorded 60 minutes after intoxication and analyzed by means of spectral analysis (theta/beta ratio; TBR) of 60 consecutive 10 s epochs.

Results: While both groups of THC users performed equally well in terms of their psychomotor speed, the accuracy rates differed significantly between recreational users and controls ($p<0.05$) at 30 minutes after intoxication. Chronic users did not differ from controls in reaction times nor did they differ in accuracy rates. In terms of vigilance, analysis in progress reveals differences in TBR with chronic users showing the fastest vigilance decrement.

Conclusion: In line with previous findings, our data provide support to impairment in visuomotor accuracy in recreational cannabis users after acute THC intoxication. Although we did not find any behaviorally manifested impairment in chronic users, their differences in vigilance have important implications for cannabis use and traffic safety.

Policy of full disclosure: None.

P-30. Sleep disorders

P-30-001 Evaluation of the efficacy and adverse effect (unpleasant taste) of eszopiclone in Japanese patients

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Objective: Eszopiclone is a non-benzodiazepine hypnotic with anti-anxiety, sedative, as well as sleep-promoting actions. Also, as it has no major adverse effects except for an unpleasant taste (primarily bitterness), it is considered to be a hypnotic that can be used safely in patients with all kinds of insomnia, including that associated with physical and psychiatric disorders and old age, as well as primary insomnia. It was approved in Japan about 7 years after approval in the United States, and evidence concerning this novel hypnotic is being accumulated in Japan. In this study, we investigated the efficacy of Eszopiclone and its unpleasant taste, the most common complaint associated with it, in daily clinical use.

Methods: A questionnaire survey concerning the efficacy and adverse effect 2 weeks after the beginning of the administration of Eszopiclone was carried out in 68 patients who were administered Eszopiclone as the initial treatment for insomnia or as a substitute for other hypnotics.

Results: Frequent diagnoses were mood disorder, schizophrenia, and neurotic disorder. As for concomitant medications, other psychotropic drugs were used in 64. The sleep-inducing effect was considered satisfactory by 58.8% of the patients. However, only 36.8% replied that they had a feeling of having slept well, and 63.2% felt lingering sleepiness. Bitterness was reported by 10 patients (14.7%), with 1 of them answering that it was impossible to continue taking the drug.

Conclusion: Eszopiclone was suggested to be effective for the treatment of insomnia, particularly sleep-onset insomnia, associated with psychiatric disorders. The incidence of an unpleasant taste (bitterness) as an adverse effect was observed less frequently in this study (14.7%) than in previous studies (21–36%), but whether or not this low incidence was related to the primary diseases and concomitant medications, the presence of which is a characteristic of this study based on daily clinical practice, is unknown.

Policy of full disclosure: None.

P-30-002 Suppression of limbic neural activity in the sleep apnea model using obese diabetic mice

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Objective: Patients with sleep apnea (SA) exhibit not only sleep disturbances, but also neurocognitive impairments and/or psychoemotional disorders. To explore the changes in neural activities related to SA syndrome, here, we examined the effects of intermittent hypoxia (IH) on brain Fos expression in obese diabetic db/db mice.

Methods: Male db/db mice were exposed to IH stimuli (repetitive 6-min cycles of 1 min with 5% oxygen followed by 5 min with 21% oxygen) for 8 hours (80 cycles) per day or normoxic condition (control group) for 14 days. Fos protein expression was immunohistochemically examined one day after the last IH exposure.

Results: Mapping analysis revealed a significant reduction of Fos expression by IH in the limbic and paralimbic structures, nucleus accumbens and amygdala. In the brain stem regions, Fos expression was region-specifically reduced in the ventral tegmental area while other regions were relatively resistant against IH. In addition, db/db mice exposed to IH showed a trend of sedative and depressive behaviors.

Conclusion: The present results illustrate that SA in the obese diabetic model causes neural suppression preferentially in the limbic and paralimbic regions, which may be related to the neuropsychological disturbances associated with SA.

Policy of full disclosure: None.

P-30-003 Evaluation of efficacy and safety of an occlusal splint vs. gabapentin in the treatment of sleep bruxism

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Objective: The objective of this study was to compare the efficacy and safety of an occlusal splint vs. Gabapentin in the treatment of this problem.

Methods: Twenty subjects with sleep bruxism were divided into occlusal splints and gabapentin treatment groups. Sleep laboratory recordings by polysomnography were made before and 2 months after the interventions to assess the effectiveness of each treatment and in 4 subjects of each group on the third night after two weeks of wash-out, to evaluate the stability of treatment results. Data analysis was done by Harmonie 6.0 software. For statistical analysis, Willcoxon test was used.

Results: Greater reduction in these parameters were found in Gabapentin group. Occlusal splint was effective in reduction of massetter muscle activity (EMG). Moreover, the subjects treated with Gabapentin showed a significant improvement in the total sleep time and sleep efficiency.

Conclusion: Gabapentin showed more improvement in duration of bruxism, whereas occlusal splint showed more reduction of massetter muscle contractions during sleep bruxism so Gabapentin can be an effective treatment modality in sleep bruxism especially in those with poor sleep quality.

Policy of full disclosure: None.

P-30-004 Status of associated factors for the quality of sleep in patients with dementia: An epidemiological assessment

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Objective: Most of the previous studies in patients with dementia explore a combination of behavioral and psychological symptoms, cardiovascular disease, and the impact on the patients and caregivers# quality of life. People with dementia commonly complain of sleep disturbances, therefore, the purpose of this study is to understand the factors in sleep quality that relate to dementia in patients.

Methods: Data was collected from the Sleep Center of Chang Bing Show Chwan Memorial Hospital. One hundred and seven participants with dementia and the four hundred twenty eight participants without dementia were matched by age and gender. Responses to a clinically structured questionnaire contains demographic variables, Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS), Athens Insomnia Scale (AIS), and patients were measured during overnight polysomnography (PSG). Diagnosis of dementia was made by means of DSM-IV criteria. Statistical analysis using SPSS 20.0 software. Differences in percentages were assessed by the chi-squared test. The association between sleep quality and dementia was evaluated using multiple logistic regression models.

Results: Insomnia syndrome was present in 84.1% of subject with dementia and 79.2% of subject without dementia. Participants without dementia has significantly good exercise habits than dementia patients (41.6% [n=178] vs 30.8% [n=33]; odds ratio [OR]=0.63; 95% confidence interval [CI]=0.40–0.99). From the multiple logistic regression analysis, daytime sleepiness (OR=2.13, 95%CI=1.36–3.33) and sleep efficiency (OR=1.90, 95% CI=1.02–3.54) had significantly higher risks of dementia after adjusted for exercise habits. Increased sleep latency was not statistically significant in association with increased risk of dementia. Otherwise, dementia patients had lower arousal index and periodic leg movements index.

Conclusion: Subjects with excessive daytime sleepiness and poor sleep efficiency have a higher likelihood of dementia in population. Insomnia, the most common sleep problem in our study, is not associated with the presence of dementia. Furthermore, good exercise habits may decrease the risk of dementia.

Policy of full disclosure: None.

P-30-005 Risk predictors for hypnosedative-related complex sleep behaviors in adult psychiatric outpatients

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Objective: Previously we reported a higher dose of zolpidem was the most important risk predictors for complex sleep-related behaviors (CSBs) in psychiatric outpatients taking hypnosedative drugs. Here we aimed to validate this finding by using another sample with a larger size.

Methods: A total of 634 subjects using hypnosedatives were enrolled from the adult psychiatric outpatient clinics of a medical center in Taiwan from June 2011 to November 2012. All subjects completed a questionnaire, which included demographic data, current and childhood sleep habits, and CSBs after taking hypnosedatives. CSBs were defined as somnambulism with object manipulation, sleep related eating and other amnestic sleep-related behaviors. A cohabitant was contacted to confirm the existence of CSBs. Demographic and clinical variables were compared in those with CSBs and those without. Then multiple logistic regression analyses were performed in order to identify significant risk predictors for CSBs.

Results: The diagnoses of 634 subjects were as follows: depressive disorder (n=194, 30.6%), schizophrenia (n=166, 26.2%), sleep disorder (n=106, 16.7%), bipolar affective disorder (n=71, 11.2%), anxiety disorder (n=71, 11.2%) and others (n=26, 4.1%). Preliminary analyses showed that, out of the 634 subjects, 49 (7.7%) had CSBs, 207 (33%) took zolpidem and 36 (73.5%) of those having CSBs took zolpidem. Univariate analysis showed that those with CSBs were significantly more likely to be younger ($P=0.023$), to take zolpidem ($P<0.001$), to receive antidepressant treatment ($P=0.007$), to have fewer medical comorbidities ($P=0.002$) and not to go to bed immediately after taking a hypnotic agent ($P=0.013$). Multiple logistic regression analyses revealed that zolpidem was the strongest significant predictor of CSBs (OR=7.6; 95% CI, 3.9–14.9; $P<0.001$), followed by antidepressant use (OR=2.9; 95% CI, 1.5–5.7; $P=0.002$) and having fewer medical comorbidities (OR=1.2; $P=0.045$).

Conclusion: The results of this study validate our previous findings and indicate that zolpidem use is the most important risk predictor for CSBs in adult psychiatric outpatients.

Policy of full disclosure: The study was sponsored by the National Science Council, Taiwan (NSC 101-2314-B-002 -189 and NSC 102-2314-B-002 -157 -MY2).

P-31. Traumatic brain injury and mental health

P-31-001 The effect of cognitive and behavioral therapy on depression among patients with traumatic brain injury

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Objective: Depression is very common following traumatic brain injury (TBI). It is very important to recognize depression after TBI because of the association with poor global and psychosocial outcome and cognitive deficits. The purpose of the study is to explore if cognitive and behavioral therapy (CBT) could reduce depressive symptoms after TBI.

Methods: This randomized, controlled study was conducted in a general hospital setting. We recruited 72 patients with symptoms of depression after a traumatic brain injury. All participants were randomized to the 8-week cognitive and behavioral therapy group or to the control group. The primary outcome measure was symptoms of depression using the Patient Health Questionnair-9items (PHQ-9).

Results: Compared with the control group, the reduction of PHQ-9 was greater in the CBT group ($P<0.05$). The improvement of PHQ-9 scores was maintained at the 8 week follow-up. Most of the patients (80%) preferred this kind of intervention.

Conclusion: CBT is an effective therapy to improve the depressive symptoms after TBI. Also, it is a more preferred treatment for depression among TBI patients.

Policy of full disclosure: Supported by Shanghai health bereau founding of Shanghai, China. The approved number is 20114358.

P-32. Biomarkers (incl. pharmacogenomics and brain imaging) for diagnosis and treatment response B

P-32-001 Altered face inversion effect in schizophrenic patients treated with typical vs atypical antipsychotics

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Objective: There is accumulating evidence that schizophrenics may have deficits in facial recognition, which has been related to disease-specific disturbances in normal social interaction. Neurophysiologically, face inversion results in an amplitude increase of the event-related potential (ERP) component N170. This face inversion effect (FIE) presumably reflects a disruption of face-specific configuration processing. The present study investigated FIE between typical antipsychotics (TAPs)-treated patients and patients treated with other atypical antipsychotics (ATAs).

Methods: The subjects consisted of 20 schizophrenics. Event-related potentials (ERPs) to upright and inverted neutral faces and cars were recorded. We assessed the relationships between typical or atypical antipsychotics and upright or inverted faces or cars in schizophrenics.

Results: ATAs patients exhibited a significant FIE of the N170 amplitude compared to TAPs. In both groupss, no inversion effect was observed for car stimuli. For face stimuli, TAPs patients showed significant bilateral N170 reduction compared to ATAs.

Conclusion: These results indicate face-specific configuration processing deficits in schizophrenia and associations between FIE or face-N170 reduction and TAPs or ATAs.

Policy of full disclosure: None.

P-32-002 Proteomic analysis of the lymphoblastoid cell line derived from Japanese schizophrenic patients

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Objective: Schizophrenia is a chronic and disabling mental disorder with a lifetime prevalence of approximately 1% worldwide. Although a number of studies have shown several convincing candidate genes or molecules, the pathophysiology of schizophrenia has not been completely elucidated. Optimal therapy based on pathophysiology should be performed as early as possible to improve functional outcome and prognosis. Therefore the identification of biomarkers for schizophrenia is necessary to provide timely diagnosis and effective therapy. To explore biomarkers for schizophrenia, we employed the florescence two-dimensional differential gel electrophoresis (2D#DIGE) for proteomic analysis.

Methods: A 2D-DIGE approach was performed to investigate the alteration of protein expression profiles in the lymphoblastoid cell lines (LCLs) (29 schizophrenics and 29 controls). Spot detection and matching were performed using the PDQuest 8.0. Differentially expressed protein spots were sequenced by LC-MS/MS and identified using Mascot program. The identified proteins were confirmed by Western blotting (WB). Receiver operating curve analysis including the area under the curve (AUC) and multivariable logistic regression were investigated to identify an optimal combination of biomarkers to create a diagnostic model.

Results: A total of ~1200 protein spots was identified on a typical LCL gel (schizophrenia mean 1103±11.7; control mean 1103±13.3), and 20 spots were differentially expressed in a 2D-DIGE analysis. These spots were selected for sequencing and 22 unique proteins were identified. Eight out of 22 was confirmed the direction of change by WB. Among the 8 promising biomarkers, the optimal 4-marker model comprised MX1, GART, UROD, and GLRX3. The AUC for the accuracy of predicting schizophrenia by 4-marker model was 0.86, implying good discriminative ability.

Conclusion: As a result, differentially expressed proteins might be associated with molecular mechanisms that contribute to the pathophysiology of schizophrenia. These findings might provide insight into the pathophysiology of schizophrenia and potentially provide diagnostic and prognostic biomarkers.

Policy of full disclosure: This research was supported by the Grant-in-Aid for Young Scientists B (No. 25860999) from Japan Society for the Promotion of Science (JSPS), the Adaptable & Seamless Technology Transfer Program through Target-driven R&D (A-STEP: AS2511400P) from Japan Science and Technology Agency (JST), and the Strategic Research Program for Brain Sciences from Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japan.

P-32-003 Effects of NSI-189, a neurogenic compound, on quantitative electroencephalography (qEEG) in patients with major depressive disorder (MDD) during a phase 1b randomized, double-blind, placebo controlled, multiple ascending dose study

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Objective: NSI-189, a novel molecule (Neuralstem Inc) for the treatment of MDD has been shown to stimulate neurogenesis of human hippocampus-derived neural stem cells in vitro and in mouse hippocampus in vivo. In a Ph1b, double-blind, placebo-controlled, multiple-ascending-dose study, patients with symptomatic MDD were randomized to receive NSI-189 40, 80, 120 mg daily or placebo for 28 days, QEEG was used to characterize pharmacodynamic effects of NSI-189.

Methods: In addition to safety, pharmacokinetic, and behavioral ratings scales, qEEG measurements were obtained 6 hrs post-dose on Day 14 and 28 for 20 minutes at rest. EEGs were recorded using 19-standard International 10/20 System scalp locations plus EMG. and eye movement monitoring. Digital EEGs recorded using Cadwell Laboratories instrumentation, were reviewed to identify the presence of physiological and instrumentation prior to analyses. Artifacts were removed from EEG files manually by an experienced technologist. Epocs of EEG data are submitted to power spectral analyses using Brain Vision Analyzer software.

Results: Safety EEGs recordings pre vs. post dose showed no new findings by visual inspection. Results of qEEG analyses using amplitude and coherence measures, pre vs 6 hrs post-dose on Day 14 and Day 28, show increased HF alpha with active treatment and lower HF alpha with placebo. This effect is particularly prominent in the left posterior temporal and parietal regions in patients receiving NS-189 and is similar when comparing baseline to Day 14 or 28. Significant univariate effects comparing amplitude from baseline to safety are seen only for changes within the active treatment group. Changes within the placebo group for these measures were not significant.

Conclusion: These findings demonstrate a measurable impact of NSI-189 on the qEEG of patients with MDD. The largest effect seen in the active treatment group was HF alpha in the left posterior temporal region. This finding is consistent with improvement in left temporal lobe function and may also reflect changes in activity in left mesial temporal lobe and hippocampus. Neuropsychological correlates of these changes mind include modulating context regulation of affect and clinical response, i.e., fluoxetine, increased alpha activity in posterior regions of the head were associated with clinical response.

Policy of full disclosure: None.

P-32-004 Basal prolactin levels as a predictor of response to antidepressant treatment

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Objective: The relationship between response to antidepressant (ADs) and prolactin (PRL) levels has been studied. It has been shown that baseline cortisol, prolactin and L-tryptophan (TRP) availability may influence response to ADs treatment. Considering mentioned reports we aimed to verify whether the response to antidepressant treatment depends on the endogenous level of PRL in plasma.

Methods: In our study we used the Chronic Mild Stress (CMS) # the animal model of depression. Rats are exposed to CMS procedure for 2 weeks and subsequently to CMS in combination with imipramine (IMI) treatment for 5 consecutive weeks. Behavioral results obtained in CMS experiments showed that after 2 weeks of mild stress, anhedonia in rats is manifested by reduced consumption of sucrose solution. Next 5 weeks of stressful stimuli maintained this effect, and the administration of antidepressant drugs reversed anhedonia. Some animals (ca.30%) did not respond to antidepressant therapy and were considered treatment-resistant. The plasma of animals responding and not responding to therapy was collected from the tail at two time points: before starting the CMS procedure and after seven weeks of stress procedure plus five weeks of IMI administration. Concentrations of peptide in plasma were determined in duplicates using commercially available ELISA kits for rat prolactin (SPIbio, Germany). The inter-assay coefficient of variation was less than 15% for rat plasma samples in the concentration range of 8 to 1000 ng/ml.

Results: We observed significant negative correlation between basal levels of PRL before CMS procedure and behavioral response to IMI administration (difference in the sucrose intake dsucrose intake=after IMI treatment before IMI administration). The Spearman Rank Coefficient, rs is −0.5929, $p<0.0198$, (Statistica, StatSoft, USA).

Conclusion: The obtained results indicate that the basal level of PRL can be a good predictor of response to treatment in depression.

Policy of full disclosure: This work was financially supported by grants from MNiSW nr NN 401 067438, DeMeTer POIG.01.01.02-12-004/09.

P-32-005 Adverse drug reactions and CYP2D6 genotypes in patients with mood disorders

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Objective: The polymorphic gene CYP2D6 encodes for the CYP2D6 enzyme that is involved in the metabolism of a number of drugs. The four genotypes (poor metabolizer, intermediate metabolizer, extensive metabolizer, and ultra-rapid metabolizer) display different metabolic activity. The specific objective of this pilot study was to investigate if the frequency of adverse drug reactions (ADRs) was related to different CYP2D6 genotypes in depressed patients treated with an antidepressant drug.

Methods: Patients with a depressive disorder or bipolar depression were genotyped for CYP2D6, examined and asked to fill in the self-rating version of the UKU Side Effect Rating Scale.

Results: 54 patients were included. The analysis was limited to the two most frequent genotypes: intermediate metabolizer (n=24) and extensive metabolizer (n=27). When only the patients treated with one or more drugs metabolized by CYP2D6 were analyzed (n=41), autonomic and psychological ADRs were significantly more frequent in intermediate metabolizers than in extensive metabolizers.

Conclusion: The results suggest that among patients treated for depression, intermediate metabolizers are more likely to experience autonomic or psychological ADRs than patients who are extensive metabolizers if treated with one or more drugs metabolized by the CYP2D6 enzyme. Genotyping of psychiatric patients who experience ADRs may be of great value, since it could guide the physician to a new antidepressant with a different metabolic pathway. The novel finding of this study was thus that genotyping may help prevent ADRs not only in poor metabolizing patients, as has been suggested earlier, but also in intermediate metabolizers of CYP2D6. However, more and larger studies are needed.

Policy of full disclosure: None.

P-32-006 Investigation of dopaminergic and serotonergic receptors for their association with antipsychotic response in north Indian schizophrenia patients

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Objective: Schizophrenia is a debilitating psychiatric illness with varying degree of symptoms. Understanding of the genetic variation underlying the varying degree of response towards antipsychotic will help towards safe and effective medication and to develop novel diagnostic with improvement in current therapeutics.

Methods: Here, we genotype 331 patients from northern India enrolled as per as DSM-IV criteria. Patients were evaluated by CGI(I) during enrollment and followed up for period of three months and reassessment was performed. The definition of response to treatment was based on rating of 2 or two point reduction of CGI(I) scale from baseline otherwise patients classified as incomplete responders. Following the criteria 159 subject were categorized as complete responders and 158 as incomplete responders. Total 40 single nucleotide polymorphisms (SNPs) from 12 genes of dopaminergic and serotonergic receptors known targets for antipsychotics were investigated using Illumina GoldenGate customized array.

Results: We observed statistical significant difference among complete responders and incomplete responder for polymorphisms of HTR1A (rs878567- OR=2.41, 95% CI=1.33–4.39; rs1423691-2.04,95% CI=1.16–3.58), HTR3B (rs2276307-OR=1.96, 95%CI=1.22–3.17), HTR3B (rs1176744-OR=1.69, 95% CI=1.03–2.79). We identified a significant three marker "GGC" haplotype (rs1423691-rs878567-rs6295) of HTR1A and "CGG" (rs1176744-rs2276307-rs2276308) of HTR3B significantly associated with disease with p-value 0.03 and 0.02 respectively. None of the associations withstands multiple correction. However, the individual role of these genes in antipsychotic response cannot be ignored.

Conclusion: HTR1A haplotype consist SNPs of 5#UTR and 3#UTR region suggesting regulatory potential. Moreover, HTR3B haplotype consist of nonsynonymous variant (rs1176744;Tyr129Ser) which altered protein structure. This study demonstrates the potential of variants from serotonin receptor that could identify drug response predictors that mediate the effect of antipsychotics.

Policy of full disclosure: None.

P-32-007 PAPA – Pharmacokinetics in pregnancy and antidepressant drugs

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Objective: Background. The pregnant woman is unique with regard to the dramatic physiological changes that occur during 40 weeks as well as subsequent pharmacokinetic (PK) changes. Concern for the effects of antidepressant drugs on the fetus is great. Still the mother has to be treated and kept healthy since the impact of psychiatric illness is high on the fetus/child. There is an acute shortage of studies of continuous PK-change in pregnant women not least with respect to antidepressant drugs. Specific objective: The main aim was to elucidate if, how, when and why PK changes of specific antidepressants occur during pregnancy, their metabolites and, if applicable, the enantiomers.

Methods: The study was a hypothesis generating, prospective and naturalistic pharmacokinetic study of 5 antidepressant drugs; citalopram, sertraline, mirtazapine, venlafaxine, and escitalopram. Pregnant women medicated with an antidepressant were identified during their first visit to antenatal care (gestational week 6–10). They were genotyped for genes (CYP2D6, CYP2C19) coding for crucial drug metabolic enzymes. Antidepressant drug serum concentration was taken as well as several blood samples for physiological markers. At gestational week 15, 20, 25, 35 and at partus the procedure was repeated and umbilical cord drug concentration was taken. Concomitant medication, weight changes and smoking habits were observed throughout the pregnancy.

Results: Preliminary results. Seventy-six women were included; antidepressant PK-data were obtained from 39 completed pregnancies. The most common drugs were sertraline and citalopram. The mean ratio for drug concentration umbilical cord/mother was 0.73 for citalopram (n=12); and 0.40 for sertraline (n=20). The mean ratio s-albumin at partus/first visit was 0.7; the orosomukoid ratio 0.9; and the cystatin C ratio 1.9.

Conclusion: In order to optimize antidepressant treatment an increased understanding of the continuous pharmacokinetic changes in the pregnant body is vital. The results of this study fill some of the knowledge gaps.

Policy of full disclosure: None.

P-32-008 A deep sequencing study of circulating microRNA levels in peripheral whole blood following ECT for severe depression

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Objective: A discovery phase study to assess alterations in microRNA expression following treatment with electroconvulsive therapy (ECT).

Methods: 16 patients (8 females; age 63.7 (SD=13.1) with a major depressive episode (DSM-IV) and who showed a good response to ECT were selected from a larger cohort participating in a randomised controlled trial of ECT for depression (ISRCTN23577151). Depression severity was assessed using the Hamilton Depression Rating Scale (HDRS). We also measured: general cognition using the Addenbrooke's Cognitive Examination-Revised (ACE-R); frontal-executive function

using Trail-making (TMT-B) and fluency tests; working memory using Digit Spans; and verbal memory using the Buschke Selective Reminding Test (BSRT). Early morning fasting whole blood samples were taken before and after completing the allocated ECT course using the PaxGene system (Qiagen) and then purified using PaxGene kits. Deep sequencing was performed using the SOLiD platform (Applied Biosystems). Bioinformatic analysis of deep sequencing data was performed to identify differentially expressed miRNAs. With 16 patients we have 80% power to detect a 2-fold change in miRNA levels. Correlation analyses of pre/post-ECT changes in miRNA abundance with clinical data were performed.

Results: Pre and post ECT HDRS scores were 30.4(5.7) and 7.1(4.1). The quality of the miRNA samples was good (RIN>6) for sequencing, which revealed several miRNAs with altered levels post ECT. These data and further bioinformatic analyses of target mRNAs will be presented along with results of clinical association studies.

Conclusion: MicroRNAs may have a role as a biomarker in depression.

Policy of full disclosure: None.

P-33. Psychoneuroimmunology and neuroinflammation B

P-33-001 A cytokine study in children and adolescents with tic disorders and/or OCD

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Objective: Although earlier studies indicated a possible relationship between and the cytokines and tic disorders and/or OCD, it still remains to be determined the expressions of proinflammatory cytokines in the sera of the patients.

Methods: 43 children and adolescents with tic disorders and/or OCD and 17 healthy comparison subjects were enrolled. These samples were analyzed for the concentration of proinflammatory cytokines by enzyme-linked immunosorbent assay (ELISA).

Results: Among these cytokines, little or no expressions of IL-2 and IL-6 were found in both tic patients and healthy subjects. In addition, IL-12, IL-17A, CCL2 and IL-1b were detectable from most samples, but the expressions of these cytokines were comparable between these two groups. On the other hand, the expression of tumor necrosis factor (TNF)-alpha was significantly higher in the sera of the patients compared to the ones of healthy controls.

Conclusion: Findings suggest a role for TNF-alpha in tic disorders and/or OCD. TNF-alpha can be a good target to develop new therapy to treat these patients.

Policy of full disclosure: None.

P-33-002 CCL2 is associated with hippocampal and amygdala volume in females with major depressive disorder

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Objective: Major depressive disorder (MDD) has been associated with altered peripheral concentrations of pro-inflammatory cytokines and chemokines including CC chemokine ligand-2 (CCL2; MCP-1) which is secreted by tissue macrophages and dendritic cells as well as by neurons, astrocytes and microglia. MDD-associated reductions in hippocampal volume that are thought to reflect dendritic atrophy have been reported. Nevertheless, the possibility that morphometric abnormalities of the brain are associated with peripheral immune alterations has not been investigated in the context of MDD.

Methods: Here we tested for an association between plasma concentrations of CCL2 and gray matter (GM) volumes of the hippocampus in unmedicated, moderately-to-severely depressed females with MDD (n=28, age=35.1±9.6, BMI=26.7±4.8) and healthy controls (HC, n=12, age=35.8±10.8, BMI=28.0±5.0). CCL2 was measured using ELISA from plasma samples taken within 3 days of scanning. T1-weighted 3T MRI scans optimized for brain tissue contrast were acquired and GM volumes were segmented using FreeSurfer.

Results: The MDD and HC groups did not differ significantly from each other with respect to CCL2 concentration, total GM volume, and hippocampal volume. Within the MDD group, CCL2 was positively correlated with the Hamilton Depression Rating Scale (Ham-D) score ($rs=0.4$, $p<0.05$) as well as hippocampal volume ($rs=0.4$, $p<0.05$), but not total GM volume. CCL2 showed a similar magnitude of correlation with hippocampal GM volume in the HC although the results were not significant, possibly because of the smaller sample size.

Conclusion: Our preliminary results are consistent with a role for CCL2 in neuroprotection and neuroplasticity and they call for a larger, more systematic study of the relationship between CCL2 and brain morphometry.

Policy of full disclosure: Wayne Drevets is an employee of Janssen Pharmaceuticals. Jonathan Savitz has received funding from Janssen Pharmaceuticals. The other authors have no disclosures to make.

P-33-003 Effects of mood-modulating drugs on lipopolysaccharide-induced hypothermia and elevation in plasma cytokines levels in rats

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Objective: Accumulating evidence suggests that mood-modulating drugs exhibit anti-inflammatory properties. Numerous studies examined the effects of mood-modulating drugs on plasma levels of inflammatory cytokines in bipolar patients, however, these studies revealed various (sometimes antagonizing) findings for specific cytokines, even under treatment with the same drug. This study was undertaken to examine the effects of chronic treatment with lithium (LIT), valproate (VPA), carbamazepine (CBZ), olanzapine (OLZ) and imipramine (IMI) on lipopolysaccharide (LPS)-induced production of tumor necrosis factor (TNF)-alpha, interleukin (IL)-6 and IL-10 in rats.

Methods: Rats were treated with LIT (50 or 100 mg/kg), VPA (50 or 100 mg/kg), CBZ (20 or 40 mg/kg), OLZ (5 or 10 mg/kg) and IMI (5 or 20 mg/kg) for 4 weeks by a single daily intraperitonteal (ip) injection. On day 29, at 2 h post drug treatment, rats were injected (ip) with saline or LPS (1 mg/kg). At 1.5 h post LPS injection, body temperature (BT) was measured and immediately thereafter rats were sacrificed and blood was collected. Plasma levels of TNF-alpha, IL-6 and IL-10 were measured by ELISA.

Results: Treatment with LPS resulted in a significant decreased in BT (hypothermia). All mood-modulating drugs significantly decreased LPS-induced hypothermia. Moreover, treatment with LPS led to a significant increase in plasma levels of TNF-alpha, IL-6 and IL-10. Overall, pretreatment with LIT, CBZ and OLZ significantly reduced LPS-induced elevation in plasma levels of TNF-alpha, IL-6 and IL-10. On the other hand, VPA and IMI did not alter IL-6 and IL-10 while significantly decreasing TNF-alpha levels.

Conclusion: These results suggest that mood-modulating drugs exert different anti-inflammatory properties and that their effects on inflammatory mediators production are not identical. The mechanism underlying the ant-hypothermic effect of the drugs is currently under investigation.

Policy of full disclosure: None.

P-34. Autism spectrum disorders B

P-34-001 Mouse models of tuberous sclerosis complex show autism-related behavioral deficits severer in *Tsc2* than *Tsc1* haploinsufficiency

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Objective: Exaggerated mTOR-mediated signaling is considered as one of the molecular pathomechanisms in autism spectrum disorder (ASD). This underlies human diseases that are highly related to ASD, such as tuberous sclerosis complex (TSC). Haploinsufficiency in the *TSC1* or *TSC2* genes cause TSC and the patients with *TSC2* mutations are likely to have severer neurological complications including ASD. We previously showed the impaired social interaction in mouse models of TSC and the therapeutic efficacy of an mTOR inhibitor rapamycin (Sato *et al*., Nat Commun, 3;1292:2012). We further analyzed these models for ASD-related behavioral deficits, paying special attention to correlation between genotype and phenotype.

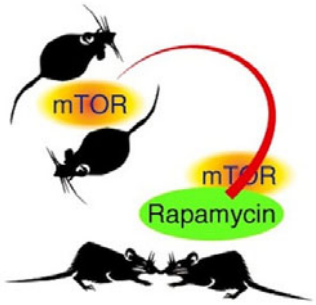
Methods: We crossed $Tsc1^{+/-}$ and $Tsc2^{+/-}$ mice to obtain wild-type (WT), $Tsc1^{+/-}$ (Tsc1HZ), $Tsc2^{+/-}$ (Tsc2HZ) and $Tsc1^{+/-}$;$Tsc2^{+/-}$ (TscD) mice on the same genetic background. These mice were assessed with social interaction test (SIT), 3-chamber social test (3CST) and self-grooming test (SGT). Then rapamycin (5 mg/kg) or vehicle was injected to the mice intraperitoneally for 2 days. The mice were tested using with SIT and 3CST.

Results: Tsc1HZ, Tsc2HZ, and TscD mice showed a reduced interest in a novel mouse in SIT and an intense self-grooming behavior in SGT. In 3CST, the mutant mice as well as WT mice preferred a novel mouse

over an inanimate object. However, when the cagemate was presented instead of the object, WT and Tsc1HZ mice preferred the novel mouse while Tsc2HZ and TscD mice did not. Rapamycin reversed the above abnormalities in Tsc1HZ, Tsc2HZ and TscD mice.

Conclusion: ASD-related abnormal behavior was severer in *Tsc2* than *Tsc1* haploinsufficiency. This finding will contribute to elucidate the molecular mechanism of ASD in TSC and other disorders associated with mTOR dysregulation.

Policy of full disclosure: None.



P-34-002 A higher ratio of omega-6/omega-3 fatty acid remarkably improved the core symptom of autism spectrum disorders via upregulation of signaling: Comparison with risperidone solution

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Objective: The deviant developmental trajectory may lead to the core social and behavioral impairments of autism spectrum disorders (ASD). Impaired signaling due to reduced long-distance functional connectivity may contribute to the pathophysiology of ASD. There is a few drugs for treatment of core social impairment. Polyunsaturated fatty acid (PUFA), docosahexaenoic acid (DHA) and arachidonic acid (ARA) promote neural function. Particularly, omega-6/omega-3 ratio of 4/1 is associated with favorable outcome of neuronal function (Yahuda, 2003). In addition, risperidone solution has been reported to improve social and behavioral impairments.

Methods: We compared the efficacy of supplementation with omega-6/omrga-3 ratio of 4/1 (omega-6 supplementation) (N=10), and risperidone solution (N=9) in 19 individuals with ASD (mean age±SD=12.8±7.5 years) in a 16-week open-label treatment. To investigate the relationship between efficacy of these medical regimens and PUFAs derived signaling, we examined plasma levels of ceruloplasmin which is protecting the brain from various neurodegeneration, and superoxide dismutase and transferrin, both of which are modifier of signaling. The outcome measures were the Aberrant Behavior Checklist (ABC) and the Social Responsiveness Scale (SRS).

Results: Repeated measures ANOVA revealed that the omega-6 supplementation significantly improved the SRS-measured mannerisms compared to the risperidone solution during the treatment. Moreover, the omega-6 supplementation significantly improved four of each five subscales of the ABC and SRS, respectively from the baseline at the end of treatment. Plasma ceruloplasmin levels were significantly increased from the baseline at the end of treatment. Risperidone solution reduced all of the ABC and SRS subscale scores, however, there were no statistical significance in score changes on the ABC and SRS, and on plasma levels of signaling biomarkers from the baseline at the end of treatment. Both treatment regimens did not induce any aversive effects.

Conclusion: Supplementation with omega-6/omega-3 ratio of 4/1 remarkably improved the ASD symptoms and upregulation of signaling.

Policy of full disclosure: None.

P-35. Attention deficit disorders B

P-35-001 Risk factors for Attention-Deficit/Hyperactivity Disorder (ADHD) in Al-Queir City, Red Sea governorate, Egypt

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Objective: To identify the possible risk factors responsible for attention-deficit/hyperactivity disorder.

Methods: In this study, risk factors for ADHD were assessed in 144 patients with ADHD, aged 4- 18 years, in Al- Quseir city- Red Sea governorate. Those patients were diagnosed and assessed for possible risk factors, I.Q, and blood levels of heavy metals using the following tools: Conner's Rating Scales-Revised, The Stanford-Binet Intelligence Scale: Fourth Edition, DSM-IV- TR diagnostic criteria for ADHD, Social scale assessment, and a special questionnaire to assess possible risk factors for ADHD.

Results: 144 patients had been diagnosed as having ADHD. Risk factors for ADHD in this study are: large family size (31.3%, P<0.007), first birth order (15.3%, P<0.003), neonatal jaundice (16%, P<0.01) and separation from one parent where living with divorced mothers was a significant risk factor (4.8%, P<0.006). High blood levels of heavy metals (lead, copper, manganese, cadmium and magnesium) showed significant differences in comparison to the control group for all subtypes of ADHD, (P<0.005).

Conclusion: Large family size, first birth order, neonatal jaundice, separation from one parent and exposure to heavy metals are the most risk factors for ADHD.

Policy of full disclosure: None.

P-35-002 Methylphenidate improves handwriting of children with ADHD; a systematic review of controlled clinical trials

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Objective: While many studies compared handwriting ability of children with ADHD and those children without ADHD, contribution of medications on handwriting in children with attention deficit hyperactivity disorder (ADHD) has been sparse. No systematic review examined the role of stimulants in this regard.

Methods: Literature was searched according to a planned search strategy using the electronic databases PubMed and Google scholar. Inclusion criteria were interventional studies investigating the effects of stimulants on handwriting quality in children and adolescents diagnosed with ADHD. Those articles without the intervention were excluded.

Results: Only nine out of 64 retrieved articles met inclusion criteria. The assessments used for handwriting was very heterogeneous to perform a pooled data analysis. Five articles reported double blind control clinical trials. All the controlled and non-controlled clinical trials administered methylphenidate. These trials reported that methylphenidate improved handwriting quality.

Conclusion: Current evidence supports that the use of methylphenidate is an effective option for the treatment of handwriting in children and adolescents with ADHD. Recommendations for future studies considering current literature limitations are provided.

Policy of full disclosure: None.

P-35-003 The effectiveness of neurofeedback in reducing symptoms of attention deficit and hyperactivity in adults with attention deficit disorder/hyperactivity

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Objective: Attention deficit/hyperactivity disorder, is a common psychological disorder in persons, that begins in childhood and continues into adulthood and leads to problem in various aspects of life, such as personal, social, professional life, and executive function such as working memory and concentration and other aspects of individual performance. The aim of the present research was to investigate the effectiveness of neurofeedback in reducing symptoms of attention deficit/hyperactivity disorder in adults with ADHD.

Methods: Research design was experimental with pre-test and post-test and control group. The population study are formed of adults with attention deficit/hyperactivity disorder that refer to the Atieh clinic in Tehran. Among the statistical population, 8 persons in 2 groups, one experimental group and one control group of patients that referred to the Atieh clinic, based on purposive sampling was selected. The research instruments were the Beck Anxiety Inventory, Beck Depression Inventory, Inventory adult attention deficit/hyperactivity disorder of Barkley, IVA test and CNSVS test. Data analysis, through SPSS software using U Mann-Whitney was performed.

Results: The results showed that neurofeedback led to a significant increase in attention and concentration and significant reduction in impulsivity in experimental group compared with the control group.

Policy of full disclosure: None.

P-36. Foetal-alcohol spectrum disorders

P-36-001 Therapeutic Drug Monitoring (TDM) in maternal serum, amniotic fluid and umbilical cord blood during pregnancy and delivery

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Objective: Treatment of psychiatric diseases during pregnancy is complicated by the concern for the safety of the unborn child because all psychotropic medications more or less cross the placenta. Fetal outcome is influenced by various factors and – among others – the effects of a specific drug itself depend on the concentration in maternal and fetal serum as well as on its concentration in amniotic fluid.

Methods: The present study is a naturalistic prospective investigation of different psychotropic drug concentrations in maternal serum (MS) and amniotic fluid (AF) of 14 women and umbilical cord blood (UC) of nine newborns. The women were treated with different doses of psychotropic drugs such as antidepressants, antipsychotics, anticonvulsants and others.

Results: Patients received thirteen different psychotropic drugs. Results are available for five antidepressants (citalopram, paroxetine, sertraline, fluoxetine and venlafaxine), 3 anticonvulsants (valproic acid, levetiracetam, lamotrigine), 2 benzodiazepines (diazepam, clobazam), as well as for olanzapine, methadone and methylphenidate.

Conclusion: Concentrations of different psychotropic drugs were found in maternal plasma, amniotic fluid an umbilical cord blood in highly variable concentrations suggesting that fetal exposure is continual and may occur through a variety of paths accounting for increased fetal exposure.

Policy of full disclosure: None.

P-37. Neuroimaging B

P-37-001 Neural correlates of antidepressant response to escitalopram in patients with major depressive disorder: A preliminary fMRI study

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Objective: Selective serotonin reuptake inhibitors (SSRIs) are popular medications for major depressive disorder (MDD), and MDD involves deficits in the reward system. However, not much is known about the effects of SSRI on reward system and which biological changes are needed to recover from a major depressive episode. The aim of the present study was to elucidate the underlying mechanism of SSRI treatment and to evaluate the relationship between clinical outcome and changes in brain activation during anticipation of incentives.

Methods: In this preliminary study, twelve patients with MDD underwent functional magnetic resonance imaging (fMRI) during a monetary incentive delay task at baseline and following 6 weeks treatment with escitalopram, an SSRI. Severity of depression was measured with the Hamilton Rating Scale of Depression.

Results: There was no significant main effect of SSRI treatment in any brain area. We noted a significant interaction between treatment response and changes in the brain activation during anticipation of reward. Specifically, improvement in depression ratings was positively correlated with change in the activation of striatum and left lateral prefrontal cortex.

Conclusion: These results suggest that successful treatment with escitalopram may be associated with modulation of brain activity in regions within the reward network.

Policy of full disclosure: None.

P-37-002 Therapeutic window of antipsychotic occupancy at dopamine D2/3 receptors in older patients with schizophrenia: A longitudinal clinical PET study

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Objective: Patients with schizophrenia are aging. Reports suggest that older patients will double by 2030 to equal the population of younger ones. Clinical guidelines for patients with schizophrenia recommend using lower antipsychotic doses. These guidelines are based on limited empirical data that do not take into account mechanistic processes involved in age-associated medication sensitivity. The aim of the current study was to establish a clinically effective therapeutic window of antipsychotic occupancy at striatal dopamine D2/3 receptors in older patients with schizophrenia.

Methods: The current longitudinal and prospective study included 35 clinically stable older patients with schizophrenia (age=60.1±7.0 years) treated with the same dose of oral olanzapine (20.8±6.6 mg/day) or risperidone (4.7±2.9 mg/day) for at least 6 months. Patients were scanned with [11C]-raclopride before and after a 40% reduction of their dose and were monitored clinically for at least three months after reaching the final dose. D2/3R occupancies were estimated using 53 controls to derive an age-and-sex matched non-displaceable binding potential as an antipsychotic free condition.

Results: The relative decrease in striatal D2/3 occupancy was 7%; 85% of the patients remained clinically stable. Clinical deterioration was only observed in patients without extra-pyramidal symptoms (EPS) at baseline. The lowest D2/3 occupancy associated with clinical stability was 45%. EPS were more likely with D2/3 occupancies higher than 60%. EPS and serum prolactin levels decreased following dose reduction. No changes were found in the mean total, positive, negative, and general psychopathology subscale scores of the PANSS; or in the mean total scores of the BPRS and CGI-S over the course of the study.

Conclusion: Antipsychotic dose reduction is feasible in older patients with schizophrenia and improves antipsychotic associated side effects. The therapeutic window for D2/3 antipsychotic occupancy appears lower in older patients with schizophrenia (45%–60%) than previously reported in younger patients (65%–80%).

Policy of full disclosure: Dr. Graff-Guerrero has received research support from the following external funding agencies: CIHR, US NIH, Ontario Mental Health Foundation, Mexico ICyTDF and CONACyT. Other authors have no financial or other relationship relevant to the subject of this manuscript. Dr. Rajji has received research support from Brain and Behavior Research Foundation (previously known as NARSAD), Canadian Foundation for Innovation, Canadian Institutes of Health Research (CIHR), Ontario Ministry of Health and Long-Term Care, Ontario Ministry of Research and Innovation, US National Institute of Health (NIH), and the W. Garfield Weston Foundation. Dr Mulsant currently receives research support from the Canadian Institutes of Health Research, the US National Institute of Health (NIH), Bristol-Myers Squibb (medications for a NIH-funded clinical trial) and Pfizer (medications for a NIH-funded clinical trial). Within the past five years he has received research support from Eli-Lilly (medications for a NIH-funded clinical trial) and some travel support from Roche. He directly own stocks of General Electric (less than $5,000). Dr. Nakajima has received a fellowship grant from the Nakatomi Foundation and Japan Society for the Promotion of Science and manuscript fees from Dainippon Sumitomo Pharma and Kyowa Hakko Kirin. Fernando Caravaggio has not conflict of interest to declare Dr. Suzuki has received manuscript or speaker's fees from Astellas, Dainippon Sumitomo, Eli Lilly, Elsevier Japan, Janssen, Meiji Seika, Novartis, Otsuka, and Weily Japan. Dr. Uchida has received grants from Pfizer, Astellas Pharmaceutical, Eisai, Otsuka Pharmaceutical, GlaxoSmithKline, Shionogi, Dainippon-Sumitomo Pharma, Eli Lilly, Mochida Pharmaceutical, Meiji-Seika Pharma, Janssen Pharmaceutical, and Yoshitomi Yakuhin and speaker's honoraria from Otsuka Pharmaceutical, Eli Lilly, Shionogi, GlaxoSmithKline, Yoshitomi Yakuhin, Dainippon-Sumitomo Pharma, Meiji-Seika Pharma, Abbvie, and Janssen Pharmaceutical within the past two years. Dr. Gerretsen has not conflict of interest to declare Tamara Arenovich has not conflict of interest to declare Dr. Pollock receives research support from the National Institute of Health, Canadian Institutes of Health Research, American Psychiatric Association, and the Foundation of the Centre for Addiction and Mental Health. Within the past five years he has been a member of the advisory board of Lundbeck Canada (final meeting was May 2009). He was also a member of the advisory board of Forest Laboratories (final meeting was March 2008). Dr. Pollock has served one time as a consultant for Wyeth (October 2008) and Takeda (July 2007). He was also a faculty member of the Lundbeck International Neuroscience Foundation (LINF) (final meeting was April 2010). Dr. Mamo has received research support from the following external funding agencies: CIHR, the US NIH, Ontario Ministry of Health and Long Term Care. He has also received grants or consultant fees from the Bristol-Myers Squibb and Pfizer and has received speaker's honoraria from AstraZeneca.

P-37-003 Dopamine transporter gene on prediction of brain dopamine activity and cognitive function in patient with alcohol dependence?

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Objective: Evidence has suggested that the dopamine transporter (DAT) plays a role in the pathogenesis of alcohol dependence (AD) and depression and that polymorphisms of the DAT may influence the brain availability. This study evaluated the differences in DAT availability/cognitive function between healthy controls and AD patients, and evaluated the impact of DAT polymorphisms both on DAT availability and cognitive function.

Methods: Thirty healthy controls and thirty-five patient with AD were recruited. DAT availability was measured in vivo with single photon emission computed tomography and 99mTc-labeled TRODAT-1 in the striatum, caudate, putamen. Cognitive function such as TMT, WCST, Stroop test were investigated before image study. Each subject was genotyped for the DAT polymorphism.

Results: Compared to healthy controls, there was a significantly lower availability of DAT in the striatum, caudate and putamen among patients with AD. Significant disturbances of working memory and executive functions were noted in patients with alcohol dependence. In addition, AD patients had worse results of TMTA,B, Stroop test RIT,NIT,RIC, NIC, WCST total errors. Of patients with anxiety, depression and alcohol dependence (ANX/DEPALC), the carriers of one ten repeat allele showed a significantly higher availability of DAT in the striatum compared to non-ten repeat carriers. After Bonferroni correction, these significances vanished. There were no significant differences in DAT availability between controls and ANX/DEP ALC.

Conclusion: The results suggest that alcoholics may have lower DAT availability in the Striatum; the DAT polymorphism may influence DAT availability in patient with AD. These findings may serve as a springboard for future large-scale studies.

Policy of full disclosure: None.

P-37-004 Dopamine transporter reduction associated the development of heroin dependence and poor cognitive function

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Objective: Much evidence suggests that the Dopamine system may play an important role in the pathophysiology of Heroin dependence (HD) and cognitive function. This study sought to investigate the changes in striatal dopamine transporter density in opioid-dependent individuals and assess their cognitive function.

Methods: Single photon emission computed tomography with 99mTc-TRODAT-1 as ligand measured striatal dopamine transporter levels in 20 opioid-dependent individuals without a history of methadone or methamphetamine exposure and 20 age- and sex-matched healthy controls. Wisconsin Card Sorting Test was performed to assess neurocognitive function.

Results: Opioid-dependent individuals showed significant striatal dopamine transporter reduction, with the greatest severity in left caudate, and poorer performance on the Wisconsin Card Sorting Test, including total amount, total errors, perseverative response, perseverative errors and non-perseverative errors. Striatal dopamine transporter levels correlated with non-perseverative errors in either opioid group or control group.

Conclusion: These results demonstrate that in human repeated opioid exposure may reduce striatal dopamine transporter density that was associated with non-perseverative errors. We suggest that non-perseverative error may be a more sensitive parameter to identify striatal DAT density-associated dysfunction of working memory maintenance.

Policy of full disclosure: None.

P-37-005 Effects of hormone replacement therapy on cerebral serotonin-1A receptor binding in postmenopausal women examined with [carbonyl- 11C]WAY-100635

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Objective: Preclinical research points to a strong modulatory influence of gonadal hormones on the serotonin system. However, human data corroborating this association remains scarce. The aim of this study was to examine the effects of hormone replacement therapy on 5-HT1A receptor binding in postmenopausal women using positron emission tomography (PET) and the radioligand [carbonyl-11C]WAY-100635.

Methods: In this randomized, double-blind, longitudinal study, 30 postmenopausal women underwent treatment with either a combination of oral 17#-estradiol valerate and micronized progesterone (group 1, n=10), oral 17#-estradiol valerate (group 2, n=10), or placebo (group 3, n=10). Two PET measurements were performed, the first on the day before treatment start and the second after at least eight weeks of treatment. Plasma levels of estradiol (E2), progesterone (P4), sex hormone-binding globulin (SHBG), dehydroepiandrosterone sulfate (DHEAS), follicle stimulating hormone (FSH) and luteinizing hormone (LH) were collected prior to PET measurements.

Results: As expected, hormone replacement therapy led to a significant increase in E2 and P4 plasma levels in group 1 and to a significant increase in E2 levels in group 2. The 5-HT1A receptor binding did not change significantly after estrogen, combined estrogen/progesterone treatment or placebo in any of the investigated brain regions. There were no significant correlations between changes in E2 or P4 values and changes in 5-HT1A receptor binding.

Conclusion: Although we were not able to confirm effects of gonadal hormone treatment on 5-HT1A receptor binding, our data do not preclude associations between sex steroid levels and serotonin, the neurotransmitter implicated most strongly in the pathogenesis of affective and anxiety disorders.

Policy of full disclosure: None.

P-38. Others B

P-38-001 Optogenetic activation of dorsal raphe serotonin neurons enhances patience for future rewards

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Objective: The classic theory on serotonin states that it opposes dopamine and inhibits behaviors when aversive events are predicted. However, the therapeutic effects of serotonin signal-enhancing medications have been difficult to reconcile with this theory. Recent recording and pharmacological inhibition studies of serotonin neurons in the dorsal raphe nucleus (DRN) have shown that these neurons play roles in promoting actions for future rewards.

Methods: Here we developed mice that express channelrhodopsin-2 in the serotonin neurons and showed that the selective activation of the serotonin neurons in the DRN enhanced the mice's patience in waiting for both the conditioned reinforcer tone at a tone site and the food reward at a food site.

Results: Optogenetic activation of DRN serotonin neurons while the mice waited for the tone by keep nosepoking at the tone site significantly reduced the number of tone wait errors. When the duration of the tone delay was increased, the reduction in the number of the tone-wait errors was more effective with the longer tone delays. When serotonin neurons were activated during the variable delay periods when the mice waited for the food by keep nosepoking at the food site (3, 6, or 9 sec or infinity, i.e., omission), the reward wait errors were significantly reduced in the 9 sec waiting trials. In the reward omission trials, the waiting time of the mice was significantly longer (17.5 sec; mean) in the serotonin activation trials compared with the trials with no activation (12.0 sec). Prolonged waiting time with optogenetical stimulation would not due to a reinforcing effect induced by serotonin neural activation. Durations of spontaneous nosepoking at the food site were not significantly different between with and without serotonin neural activation.

Conclusion: These results indicate that the temporally precise activation of the serotonin neurons during waiting facilitates patience for delayed rewards.

Policy of full disclosure: None.

P-38-002 Effect of quetiapine on DNA methylation in neuroblastoma cells

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Objective: Epigenetic regulation may be involved in the pathophysiology of mental disorders, such as schizophrenia and bipolar disorder, and in the pharmacological action of treatment drugs. We previously reported the hypermethylation of serotonin transporter, SLC6A4 in patients with bipolar disorder (BD), and the methylation level in the same region was decreased in human neuroblastoma cells treated with three mood stabilizers (lithium, valproate and carbamazepine). Characterizing the epigenetic effects of treatment drugs is an important step to optimal treatment.

Methods: We performed genome-wide DNA methylation analysis of using human neuroblastoma cells treated with quetiapine (QTP) using Infinium HumanMethylation 27 BeadChip. We also examined common methylation changes with other three mood stabilizers by QTP treatment. Furthermore, we performed bisulfite sequencing analysis to examine the effect of QTP on the DNA methylation level of the promoter region of SLC6A4.

Results: A total of 1,173 genes showed altered DNA methylation. Altered DNA methylation dominantly occurred as hypomethylation within the CpG island. Gene ontology analysis revealed that these genes were related to the cellular process of intracellular protein binding. There was no common effect of QTP with other three mood stabilizers. However, common DNA methylation changes in seven genes, including ADRA1A, which encodes alpha 1A-adrenoceptor, were found with quetiapine and lithium treatment. Finally, we detected the decreased DNA methylation level of the promoter region of SLC6A4 by bisulfite-sequencing analysis, which was consistent change with other three mood stabilizers.

Conclusion: QTP altered DNA methylation levels at a subset of CpG sites, preferentially located within CpG islands Although whether these effects are directly related to drug efficacy remain unknown, decreased methylation of the promoter region of SLC6A4 suggests the mood stabilizer-like role of QTP. Future studies such as gene expression analysis and animal model experiments will be required.

Policy of full disclosure: M.B., F.S., and K.I. are employed by the Department of Molecular Psychiatry, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan, which is endowed by Astellas Pharma, Dainippon Sumitomo Pharma, and Yoshitomiyakuhin.

P-38-003 Convulsive liability of cefepime and meropenem in normal and corneally kindled mice

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Objective: We previously reported that the prevalence of convulsions was significantly higher in patients treated with cefepime than in patients treated with meropenem. Additionally, cefepime-associated convulsions occur only in patients with brain disorders, not in those with renal failure. In this study, we examined the convulsive liability of cefepime and meropenem in normal mice and in corneally kindled mice with a low seizure threshold.

Methods: We assessed the proconvulsive liability of cefepime and meropenem in mice using pentylenetetrazol (PTZ) injection, electroconvulsive shock at low stimulus currents and corneal kindled. In addition, we measured electroencephalogram (EEG) activity 1 min after injection of the antibiotics.

Results: Cefepime and meropenem, administered by intravenous injection, at 250 or 500 mg/kg, had no effect on PTZ-induced convulsions in normal mice. In mice with seizures induced by electroconvulsive shock at low stimulus currents, mean seizure duration in animals administered 500 mg/kg cefepime was significantly greater than in animals administered saline. Furthermore, EEG spikes were present in animals injected with 500 mg/kg cefepime. In corneally kindled mice, mean seizure duration in animals given cefepime was significantly greater than in mice given meropenem.

Conclusion: The convulsive liability of cefepime was significantly greater than that of meropenem in normal and corneally kindled mice. These findings suggest that cefepime may have substantial neurotoxicity in patients with a low seizure threshold.

Policy of full disclosure: None.

P-38-004 Psychotropic drug utilization in child and adolescent psychiatry inpatients of a university hospital

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Objective: With a predominantly younger population, psychiatric morbidity in children in India is relatively high. Studies from around the world show an increase in the use of psychotropic medication in children. The patterns of drug utilization vary internationally and within regions. The objective of our study was to determine the psychotropic drug utilization pattern in child and adolescent psychiatry inpatients in a university hospital in India and determine the presence of any gender difference.

Methods: Hospital records of all psychiatry inpatients less than or equal to 18 years of age admitted over a period of one year were studied. Drugs prescribed before hospitalization, during hospital stay and on discharge were recorded. The drug classes were delineated as follows - antidepressants, antipsychotics, mood stabilizers, anxiolytics/hypnotics and stimulants.

Results: Of the 82 patients admitted, 59.8% were males. The mean age was 11.47±5.09 years in males and 13.67±4.09 years in females ($p<0.05$). Adjustment disorder was the commonest psychiatric illness followed by anxiety disorder. 54.88% of the patients did not receive any psychotropic drugs. 18.3% were prescribed antidepressants, 24.4% antipsychotics and 36.6% anxiolytics. Lorazepam was the most commonly prescribed drug followed by olanzapine (22% and 9.8% respectively). Use of antidepressants, antipsychotics and anxiolytics was significantly more in females ($p<0.05$). 26.6% of the patients were prescribed more than one psychotropic drug on discharge.

Conclusion: The age and gender presentation was similar to those reported by other studies. Anxiolytics and antipsychotics were the most commonly prescribed psychotropic drugs. No psychostimulants were prescribed. No significant difference in the drug use was seen on admission and discharge. Polypharmacy seen in our study is less than those reported by other studies among psychiatry inpatients. A gender difference in the use of psychotropic medications was seen which could be due to the difference in the pattern of psychiatric morbidity.

Policy of full disclosure: None.

P-38-005 Treatment of neuroleptic malignant syndrome in child and adolescent: A case report

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Objective: Neuroleptic Malignant Syndrome is a rare clinical syndrome occurring due to idiosyncratic reaction after use of neuroleptics. Recently, the use of antipsychotics has been increasing in the field of child and adolescent psychiatry especially in psychosis, mood disorder, and destructive behavior disorders.

Methods: Case: A 14-year-old male patient, diagnosed with schizophrenia. He was prescribed with 6 mg/day of risperidone in combination with 300 mg/day of quetiapine. The 3 days before the onset of neuroleptic malignant syndrome, all oral medications were stopped along with NPO for treatment due to manifestation of paralytic ileus from worsening of underlying constipation; in addition, IM injection of haloperidol was only allowed for the symptom control. The day before the onset, an IM injection of 15 mg of haloperidol and 10 mg of lorazepam resulted in vomiting, headache, fever of 39°, systemic tremor and stiffness, confusion, tachycardia and sweating. Blood work-up performed on day of admission at ICU indicated CPK 2836 IU/L and myoglobulin 337.2 ng/ml, and CPK, after peaking at 4493 IU/L, continuously decreased and was normalized by the 18th day at ICU. Diazepam, dantrolene, domperidone, L-Dopa/benserazide and cold blanket were applied.

Results: Normalization of hematologic abnormalities were followed by stabilization of tremor, stiffness, and high fever on the 18th day.

Conclusion: Neuroleptic malignant syndrome is an exigent condition which may cause fatal outcomes in the field of psychiatric treatment. Cautious pre-evaluation of risk factors in patients requiring neuroleptics are critical in order to prevent fatal complications.

Policy of full disclosure: None.

P-38-006 Prenatal maternal stress from a natural disaster predicts hippocampal volumes in boys at age 11: Project Ice Storm

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Objective: The hippocampus develops primarily during the fetal period and plays a pivotal role in learning and memory. Non-human primate studies have demonstrated that early and late in utero exposure to maternal stress result in reduced hippocampal volumes. However, no human prospective studies of the effects of prenatal maternal stress (PNMS) on the hippocampal development have been conducted. Our objective was to determine whether in utero exposure to disaster-related PNMS is associated with altered hippocampal volumes in 11½ year-old children. We hypothesized that higher maternal objective or subjective PNMS levels would be related to smaller hippocampal volumes.

Methods: Measures of maternal objective exposure and subjective distress were obtained after the 1998 Quebec Ice Storm. We obtained a 3D, 1×1×1 mm^3, T1-weighted Magnetization Prepared Rapid Gradient Echo sequence (TR/TE/TI=2300/2.98/900 ms) of 33 male and 32 female 11½ year-olds. Hippocampal segmentation from native MRI scans was performed by a collaborator who was blind to all other subject data using the fully automatic SACHA method. The number of obstetric complications was determined by maternal recall at 6 months postpartum and verified using hospital records.

Results: More obstetric complications were related to smaller right hippocampal volumes (RHCV) in both male and females. Higher levels of maternal objective exposure were related to smaller RHCV in males only. Objective exposure and obstetric complications and their interaction, explained 34.6% of variance in males' RHCV: males exposed to high levels of objective exposure or obstetric complication or both had smaller RHCV compared to males exposed to low objective hardship and obstetric complications.

Conclusion: Our results suggest that higher levels of disaster-related objective hardship, but not subjective distress are related to smaller RHCV in male but not female children. It remains to be determined whether this alteration in RHCV of 11.5 years old males is related to observable phenotypes.

Policy of full disclosure: none

P-38-007 Prenatal maternal stress and toddler stress reactivity at 2½ years of age: The Iowa flood study

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Objective: Prenatal maternal stress (PNMS) has been found to affect domains of cognitive, behavioural, emotional, and psychosocial development in offspring. Studies suggest dysregulated activity of the hypothalamic pituitary adrenal (HPA) axis may underlie such manifestations. Given that PNMS is associated with an influx of maternal glucocorticoids, which are transmitted to the fetus via the placenta, researchers are interested in examining how PNMS in turn affects the development of the fetal HPA axis. Moreover, how these effects present themselves throughout postnatal development. While animal and human studies have found PNMS exposure to be associated with dysregulated HPA axis activity in offspring, results are inconsistent and at times contradictory. The objective of this study was to determine the association between the severity of disaster-related prenatal maternal stress (Iowa flood of 2008) and infant stress reactivity.

Methods: Women were recruited shortly after 100-year floods in Iowa, USA in June 2008, and their objective exposure to the floods and subjective distress assessed. A sample of 88 mother-toddler dyads participated in a laboratory assessment that involved a brief maternal-toddler separation to invoke a stress response in the toddler. Salivary cortisol samples were collected four times throughout the assessment. Percent change in cortisol and area under the curve were computed to assess the toddlers# stress response.

Results: Results from regression analyses show that the subjective rating of PNMS was a significant predictor of percent change and area under the curve, but was moderated by infant sex: greater subjective PNMS was associated with hyper-secretion of cortisol in females and a blunted response in males. These results persisted after controlling for time of day of the assessment and baseline cortisol levels.

Conclusion: The results from the present study suggest that in-utero exposure to PNMS can have long-term implications for the functioning of the stress response system, evident throughout early childhood.

Policy of full disclosure: None.

P-38-008 Prenatal maternal exposure to a natural disaster predicts more masculine 2d:4d finger length ratio in girls: Project ice storm

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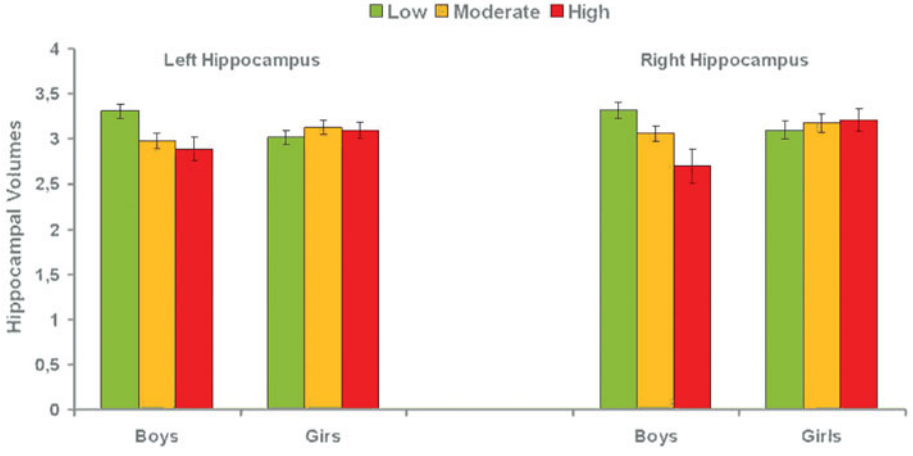
Objective: Prenatal maternal stress appears to have masculinizing effects on some systems and feminizing on others. Most experimental research is conducted in animals. We capitalized on a natural disaster in January 1998 in Quebec, Canada to study the effects of stress exposure in pregnant women on their unborn children. The ratio of the lengths of the 2nd and 4th fingers (2D:4D ratio), a sexually dimorphic trait, reportedly reflects in utero testosterone exposure. Our objective was to determine the extent to which the pregnant women's objective degree of exposure to the 1998 Quebec Ice Storm crisis, and their level of subjective distress about the storm, influenced their children's 2D:4D ratio.

Methods: Subjects were 115 French-Canadian women who were pregnant during the ice storm, or conceived within 3 months of the storm; their children (58 girls, 57 boys) at age 5 ½ years; a matched comparison group of 47 girls and 50 boys; and 111 adult French Canadians (60 women, 51 men). Women were recruited 4-5 months after the ice storm and completed a questionnaire about objective stress exposure (Storm32) and their subjective distress about the storm (Impact of Event Scale # Revised; IES-R). Finger lengths of children and comparison adults were measured with digital calipers.

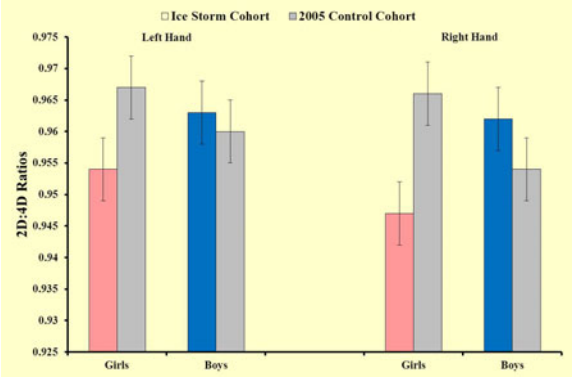


Results: Prenatal ice storm exposed girls had more masculine 2D:4D than their male peers ($p<0.05$) while comparison children and adults had ratios in the expected direction. Ice storm girls had significantly more masculine 2D:4D than comparison girls; ice storm boys had slightly more feminine ratios than comparison boys. Timing in gestation of the stress exposure had effects for both boys and girls.

Conclusion: Prenatal maternal stress exposure, randomly distributed by a natural disaster, influences a sexually dimorphic trait in children, resulting in an overall masculinization of girls. Effects of timing and of objective or subjective stress differed by sex.

Policy of full disclosure: None.

2D:4D Finger lengths in prenatally stressed children and unstressed controls:



P-38-009 COMT genotype moderates effects of prenatal maternal stress due to a natural disaster on birth outcomes: The Iowa flood study

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Objective: Prenatal maternal stress (PNMS) is a risk factor for adverse birth outcomes. These effects vary by timing of exposure and newborn sex, and perhaps by genotype. However, our understanding remains limited because of the challenges of designing human studies of PNMS. We investigate PNMS by studying pregnant women exposed to natural disasters. Disasters provide excellent models of PNMS because the exact timing of the stressor can be identified, and exposure tends to be randomly distributed. Our goal was to determine whether and how the timing and severity of exposure to PNMS due to a natural disaster influences gestational age and growth measures at birth and whether genotype moderates the effect of maternal stress.

Methods: We assessed objective hardship and subjective distress among 144 women exposed to severe flooding in Iowa in June 2008 during pregnancy. The children's DNA provided their COMT genotype. We analyzed associations between objective and subjective PNMS levels and birth outcomes, and PNMSxCOMT interactions.

Results: Earlier timing of flood exposure predicted lighter birth weights. More severe PNMS predicted shorter birth lengths among girls, but longer birth lengths among boys. For babies with the COMT AA (Met/Met homozygous) genotype, greater PNMS predicts larger size at birth, while PNMS predicted smaller size at birth in GG (Val/Val) babies.

Conclusion: Timing of PNMS from a natural disaster during pregnancy affected birth weight, and severity of PNMS affected birth length with variations by infant sex and by genotype. These effects were independent of other maternal characteristics, suggesting that PNMS is an independent predictor of birth outcomes. Differences between boys and girls might reflect sex-specific effects of hormones such as testosterone on fetal growth. More research is necessary to clarify the effects of exposure to moderately stressful events on birth outcomes, and the underlying mechanisms.

Policy of full disclosure: None.

P-38-010 Prenatal maternal stress increases the risk for asthma in 12 year old girls

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Objective: Asthma is a chronic lung disease characterized by the inflammation and tightening of the airways. Affecting 11% of Canadian children, asthma increases physical inactivity, school absences, hospitalizations and premature deaths. Animal and human studies suggest that non-genetic in utero factors may shape the physiological systems involved in the development of asthma in children. Large quantities of cortisol may be released in the blood stream following a highly stressful event, causing alterations in the fetus' stress response system. However, limitations exist in the literature. First, results on animal studies are not directly applicable to humans. Second, stressful events are generally not independent of the mothers' characteristics (e.g. divorce and job loss). Lastly, objective and subjective stress are often not differentiated. This study examined whether higher levels of prenatal maternal stress (PNMS) due to a natural disaster would increase the risk of having asthma in 11 year old offspring.

Methods: In 1998, we assessed severity of objective hardship and subjective distress in women pregnant during the January 1998 Quebec Ice Storm. Data was collected on potential confounding variables (e.g., maternal trait anxiety, life events, obstetric complications, and socioeconomic status). Lifetime asthma symptoms, diagnoses, and corticosteroid utilization were assessed when the children were 12 years old (N=68).

Results: The findings suggest that subjective distress increases the risk of asthma in girls. More specifically, we found that, in girls only, higher levels of prenatal maternal subjective distress predicted greater lifetime risk of wheezing (OR=1.11; 90% CI=1.01–1.23), mother-reported asthma (OR=1.11; 90% CI=1.00–1.23), doctor-diagnosed asthma (OR=1.09; 90% CI=1.00–1.19) and lifetime utilization of corticosteroids (OR=1.12; 90% CI=1.01–1.25).

Conclusion: Further research is required to understand the mechanism by which gender may mediate the relation between PNMS and the development of asthma in children.

Policy of full disclosure: None.

P-38-011 Endocannabinoids in CSF and serum from borderline personality disorder patients

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Objective: The endocannabinoid system plays an important role in the pathophysiology of psychiatric disorders. Due to its neuromodulatory potential, its role in emotion regulation and in extinction of aversive memory, the endocannabinoid system might be another potential candidate system, affecting a broad range of psychopathology in both, posttraumatic stress disorder (PTSD) and/or borderline personality disorder (BPD).

Methods: We addressed this question by analyzing serum and cerebrospinal fluid (CSF) levels of the endocannabinoids anandamide and 2-arachidonoyl-sn-glycerol (2-AG) and related endogenous lipids oleoylethanolamide and palmitoyletnanolamide. Based on our previous approach we developed and validated a specific and sensitive method using high performance liquid chromatography coupled with tandem mass spectroscopy (HPLC-MS/MS). We analyzed human serum samples from patients suffering from BPD (n=23) or PTSD (n=21) as well as matched healthy controls (n=34). In addition, we measured these and the neuropeptides oxytocin (OXT) and vasopression (VPA) in CSF and serum samples in an independent cohort of 27 BPD patients and 26 matched controls.

Results: Serum levels of anandamide and 2-AG were significantly elevated in BPD, while oleoylethanolamide was significantly elevated in PTSD when compared to controls. In CSF, levels of anandamide as well as oleoylethanolamide and palmitoyletnanolamide were significantly decreased in BPD, while 2-AG was not affected.

Conclusion: Our data rise evidence that the endocannabinoid system may play an independent functional role in the pathophysiology of BPD and warrant further investigation of this contribution.

Policy of full disclosure: None.

P-38-012 Structure of psychotropic drugs prescribed by therapists of primary care (territorial polyclinics)

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Objective: Of the study was to determine how often and what kind of drugs are prescribed therapists in primary health care (territorial polyclinics).

Methods: Study was conducted on the basis of the territorial polyclinic of Moscow. The study involved 12 doctors. The average age was 46,1±12,7 years, average service record was 22,7±12,9 years. Were analyzed 679 prescription forms. In the month subscribed about 48,5 titles of psychotropic drugs, per physician accounted for about 4 recipes. Frequency of assignments by different specialists ranged from 0,7 to 9,8 drugs per month.

Results: Most commonly prescribed psychotropic drugs were benzodiazepine tranquilizers 57,7% (n=392). There were fenazepam 39,5% (n=155), clonazepam – 24,5% (n=96), alprazolam – 13% (n=51), diazepam – 9,2% (n=36) nozepam – 6,1% (n=24), tazepam – 5,6% (n=22), mezapam – 2% (n=8), lorazepam – 0,5% (n=2). Sedatives other groups (ataraxia, grandaxinum) were discharged in 1,5% of cases (n=10). Widely prescribed drugs containing phenobarbital. A second group of frequency assignments became hypnotics – 23,1% (n=157), zopiclone is prescribed in 64,3% (n=101), zolpidem in 35,7% (n=56). Preparations of other groups discharged significantly less: neuroleptics – 2,5% (n=17), antidepressants – 2,4% (n=16), nootropics – 1,3% (n=9), mood stabilizers / anticonvulsants - 0 3% (n=2) of the total prescriptions.

Conclusion: Therapists do not always correctly and efficiently discharged psychotropic drugs. They preferred tranquilizers and hypnotics. However, general practitioners (primarily therapists) have high potential and wide range of opportunities for providing pharmacological assistance to patients with mental disorders.

Policy of full disclosure: None.

Wednesday 25 June 2014

P-39. Addictive disorders C

P-39-001 D- and l-govadine block d-amphetamine conditioned place preference

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Objective: Tetrahydroprotoberberines (THPB) derived from traditional Chinese medicine have been extensively evaluated for targeting dopamine D1 and D2 receptors and have potential as novel treatments for drug addiction. Govadine is a THPB derivative and recent findings have identified both similarities and differences in the neuropsychopharmacological properties of d- and l-stereoisomers (Lapish et al., 2014).The present study assessed the effects of d- and l-Govadine on the acquisition of amphetamine-induced conditioned place preference (CPP).

Methods: CPP was established in rats by pairing d-amphetamine (d-AMPH, 1.5 mg/kg, i.p.) or saline with a specific environmental context. The rats received d-Govadine (1 mg/kg, s.c.) or vehicle 5 min prior to d-AMPH administration during the acquisition phase. CPP was assessed as time spent in the d-AMPH- and the saline-paired contexts. We also evaluated the effect of l-Govadine on d-AMPH-induced CPP using the same protocol.

Results: Preliminary results show that both d- and l-Govadine inhibit the induction of d-AMPH CPP.

Conclusion: It appears that both stereoisomers block the rewarding effects of d-AMPH suggesting therapeutic potential for drug addiction. Investigations into the effect of d-Govadine on the expression, extinction and reinstatement of d-AMPH-induced CPP are ongoing.

Reference

Lapish CC, et al.(2014). Selective effects of d- and l- Govadine in preclinical tests of positive, negative, and cognitive symptoms of schizophrenia. Neuropsychopharmacology. Advance online publication. Retrieved 30 January 2014. doi:10.1038/npp.2014.23.

Policy of full disclosure: None.

P-39-002 Tolerance to different types of frustration in alcohol dependent patients and healthy controls as related to anxiety and impulsivity

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Objective: Since anxiety has been found to be related to susceptibility to punishment and impulsivity to susceptibility to reward (J.A.Gray, 1981), it was investigated, if these associations are also valid with respect to frustration by application of negative stimuli (neg+) versus by withdrawal of rewards, (pos-), and if this relationship equally applies to alcohol dependent persons and healthy controls according to their differences in anxiety and impulsivity.

Methods: 60 male alcohol dependent patients and matched healthy controls, each divided according to high and low anxiety and impulsivity scores were compared for their questionnaire scores on sensitivity to punishment and reward and for their depressive and aggressive responses to questionnaire items representing the two types of frustrations (QDF, Baars et al., 2011).

Results: All participants were more frustrated by neg+ than by pos-conditions, and both types of frustration correlated more clearly with sensitivity to reward than with sensitivity to punishment. No general difference in tolerance to either type of frustration emerged between alcohol dependent patients and controls, but in controls high scorers on anxiety exhibited significantly higher levels of predominantly depressive responses in particular to neg+ items than low scorers (interaction p=0.018) confirming expectations, whereas impulsivity did not predict tolerance to frustration. In alcohol dependent patients, on the other hand, impulsivity was a better predictor of intolerance to both types of frustration than anxiety, in particular when comparing aggressive responses.

Conclusion: Frustration from withdrawal of rewards does not reflect sensitivity to reward and is not more pronounced in alcohol dependent patients than in controls, but in alcohol dependent patients frustration in general is more determined by impulsivity as a personality trait than in controls leading to predominantly aggressive responses. This suggests to consider trait impulsivity for the prognosis of a successful therapy of alcoholics.

Policy of full disclosure: None.

P-39-003 Nicotine replacement therapy in our patients: Are they getting the right nicotine dose?

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Objective: This trial evaluated the impact of optimizing nicotine replacement therapy on agitation levels in subjects admitted to the inpatient psychiatric unit of a university affiliated hospital. A pre-post quasi-experimental design was used.

Methods: All consenting patient admitted to the psychiatry ward were eligible to participate. Agitation levels were assessed with the PANSS-EC rating scale. Pharmacy residents were scoring patients with direct interview and with chart review. Group 1 patients were only allowed a nicotine transdermal patch; group 2 subjects could also use nicotine gums and inhalers in addition to the patch.

Results: Most patients were suffering from psychotic disorders (56%). In the first 48 hours post-admission, the scores on the PANSS-EC were 16.9 in group 1 (n=18) and 13.6 in group 2 (n=19). The between group difference in evolution from baseline was 5.4 points (p=0.0002). This difference is very clinically significant. Sensitivity analysis did not show any confounding factors.

Conclusion: Some studies show that such an effect is stronger than what is observed when a patient receives the usual antipsychotic+benzodiazepine combo for agitation.The addition of nicotine gums and inhalers to the nicotine transdermal patch greatly reduced agitation levels in psychiatric inpatients and should be considered in the treatment plan.

Policy of full disclosure: None.

P-39-004 An open-label naturalistic study: Mirtazapine orally disintegrating tablets treatment for depression in heroin-addicts

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Objective: Heroin dependence is often complicated by depression requiring antidepressant treatment. Mirtazapine is an established antidepressant

with well-documented efficacy. The objective of the present study is to investigate the efficacy and tolerability of the new formulation of mirtazapine, Orally Disintegrating Tablets (ODT) for depression among heroin-addicts.

Methods: This prospective, open-label, naturalistic study was conducted in the Outpatients Department of a general hospital. 24 depressed heroin-addicts were recruited, of whom 22 were followed up for 17 weeks. All patients initially received mirtazapine ODT 15 mg/day and the dose was titrated to 30 mg or 45 mg when response was not significant and in the absence of obvious adverse effects. Efficacy was the primary measure using the total score of the Hamilton Depression Rating Scale-17(HAMD-17). Tolerability was mainly assessed by the incidence of treatment-emergent adverse events. Patients were evaluated at baseline, at weeks 1, 5, 9, 13 and 17.

Results: among the 22 patients (14 female and 8 male) who finished the study, the mean total (SD) HAMD-17 score decreased significantly from 29.2(4.1) to 7.2(4.1) ($P<0.05$). At each visit, the mean HAMD-17 score was significantly lower than that at the preceding visit. At the endpoint (week 17), remission (HAMD-17 score<or=7) was achieved in 12(55%) patients. Among those patients, four reported at least one adverse effect during Treatment, but those adverse effects were described as mild to moderate and lasted just several days. The most majority of the patients preferred the new formulation of mirtazapine.

Conclusion: Mirtazapine ODT was an effective, well-tolerated and preferable formulation for the treatment among heroin-addicts with depression.

Policy of full disclosure: Supported by National Natural Science Foundation in China. The number of approved is 81201033.

P-39-005 Benzodiazepine receptor system of the human and rat's brain under chronic influence of alcohol

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Objective: Alcohol abuse induces neuroadaptive alterations of benzodiazepine receptors (BDR), that modulate GABAAR, and GABA mediation in brain regions, associated with reward function in the brain, that serve alcohol addictions. Properties of BDR in synaptosomal and mitochondrial membranes from different brain areas (prefrontal cortex, n.caudatus and cerebella cortex) of alcohol abused patients and brain cortex of male rats with different preference to alcohol were studied.

Methods: Properties of BDR "synaptosomal" (CBR) and "mitochondrial" (MBR) types were examined in respective membrane fractions obtained from different brain areas of alcohol abused patients and non-alcoholic persons (early postmortem material) by radioreceptor assay (RRA) with [3H]flunitrazepam and [3H]PK-11195. Properties of BDR in rat brain cortex were examined in such as membrane fractions by RRA with [3H]flunitrazepam and [3H]Ro5–4864.

Results: Comparative study of kinetic parameters (Kd and Bmax) of [3H]flunitrazepam and [3H]PK-11195 binding with synaptosomal and mitochondrial membranes obtained from autopsy samples has shown, that affinity of BDR was decreased and capacity was increased in different areas of human brain under influence of alcohol abuse. More alterations of BDR appeared in prefrontal cortex, less - in n.caudatus and cerebella cortex. Finding results showed that alcohol addiction induces more alterations in MBR than CBR, that agree with physiological and maintaining function of MBR in CNS under influence of toxic factors.

Conclusion: Affinity of [3H]flunitrazepam and [3H]Ro5–4864 binding with membranes from rats brain was decreased, but capacity of receptors was increased in brain cortex of "heavy drink" and "non-heavy drink" male rats compared with "non-prefer" alcohol rats. Administration of anticonvulsant meta-chloro-benzhydryl-urea (m-chBHU) increased affinity of BDR in brain cortex of "heavy drink" rats. So, m-chBHU has a normalizing effect on GABA - receptor function.

Policy of full disclosure: None.

P-39-009 Opioid dependence disrupts cocaine reward by disrupting GABAergic chloride homeostasis mediated by activated microglia

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Objective: Opioid dependent states are associated with adaptations within the mesocorticolimbic dopaminergic system that contribute to the negative affective state when the drug is absent (withdrawal). Here, we analyze molecular adaptations in the ventral tegmental area (VTA) and their effect on drug reward.

Methods: C57Bl/6 mice were made opioid dependent with increasing injections of morphine (10–40 mg/kg, i.p) twice daily for 4 days.

Results: Opioid dependent animals displayed significant microglial activation in the VTA and blocking microglial activation decreased BDNF expression. Chronic morphine exposure decreased expression of the potassium/chloride (Cl-) co-transporter, KCC2, within VTA GABAergic neurons, which resulted in a loss of Cl- extrusion as measured by fluorescent lifetime imaging. Interfering with BDNF signaling recovered Cl- extrusion in morphine-dependent GABAergic neurons. Loss of Cl- extrusion is known to undermine GABAergic inhibitory potential, which translates into an increased inhibition in dopaminergic VTA neurons. In support of this, cocaine reinforcement (as measured using the conditioned place preference paradigm) was diminished in opioid dependent animals. Cocaine place preference was restored in opioid dependent animals by cotreatment with microglial inhibitors.

Conclusion: This study provides evidence for disrupted reward circuitry in opioid dependent animals that is driven by microglial activation within the VTA. Reactive microglia release BDNF that precipitates a shift in EGABA within VTA GABAergic inhibitory interneurons leading to dysregulation of dopaminergic circuitry.

Policy of full disclosure: None.

P-39-010 Repeated amphetamine sensitizes dopaminergic modulation of the basolateral amygdala neurons: Physiological, behavioural, and molecular analyses

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Objective: Chronic abuse of psychostimulants such as amphetamine (AMPH) impairs cognitive processes associated with the limbic system. Rodent studies showed that repeated AMPH causes behavioural, neurochemical, and physiological changes in mesolimbic dopamine (DA) modulation on various regions of the limbic circuit (e.g., prefrontal cortex, nucleus accumbens). However, relatively little is investigated in the basolateral amygdala (BLA). We therefore examined how repeated AMPH (2 mg/kg i.p. every 48hr, 5 injections, two-week washout) may alter behavioural, neurophysiological, and molecular properties of the BLA.

Methods: We conditioned rats to pair previously neutral stimuli to delivery of sugar pellets (15-day training), followed by AMPH injection regimen described above. Rats subsequently were trained to acquire a novel instrumental response for conditioned stimuli paired with food. In a separate experiment, we extracellularly recorded changes in BLA neuron activity in response to DA manipulation in anesthetized rats, as well as western blot analysis to assess DA-related proteins within the BLA.

Results: Rats received repeated AMPH showed reduced instrumental respond to stimuli previously paired with food reward. In addition, BLA neurons demonstrated increased sensitivity to the inhibitory effects of endogenous phasic DA. Burst stimulation of the ventral midbrain causes reliable suppression of putative BLA principle neuron firing. This DA hypersensitivity appeared to be dependent on increased D2 receptor sensitivty, as low dose (0.02 mg/kg, i.v.) of D2 agonist quinpirole can suppress BLA neurons firing in AMPH-treated rats but not in control. These results were complemented by a western blot experiment, where AMPH-treated rats showed increased D2 and DARPP-32 expression in the BLA.

Conclusion: Collectively, these findings provide behavioural, physiological, and molecular evidence suggesting repeated AMPH increases D2 receptor and downstream DA effector protein, DARPP-32, expression, causing an enhanced inhibitory tone within the BLA. Furthermore, they suggest that impairments in reward-related functions observed in psychostimulant abusers may be at least in part due to D2 receptor hyperactivity of the BLA.

Policy of full disclosure: None.

P-39-011 Recovery of substance-induced psychotic disorder following an olanzapine treatment in patients with cannabis addictive disorder and the emergence of panic disorder, after stabilization of the psychosis

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Objective: To show the development of Panic Disorder symptoms after the stabilization of substance induced psychosis, especially the anticipatory anxiety related to reappearance of psychosis.

Methods: In our drug rehab program we registered which patients had psychosis. Those that developed psychosis continued treatment with olanzapine. Once stabilized, we found panic disorder with strong anticipatory anxiety. We used the EASE scale (Examination of Anomalous Self Experience) to measure the psychotic compromise when the Panic symptoms appeared (measured by the scale ESAP). The measurements were presented in graphics.

Results: After the improvement of psychosis, the ESAP scale shows development of Panic Disorder symptoms. We characterized those symptoms by using the patients' narrative and by applying the ESAP measurement.

Conclusion: The psychotic experience is very traumatic. Although the recovery of hallucinations and delusions is decisive, the memory of the psychosis may condition a panic response. Use of clonazepam allows psychotherapy to work and create enough insight; it permits the critique of psychosis and of the panic symptoms. These patients were able to continue occupational therapy without the symptoms reappearance.

Policy of full disclosure: None.

P-40. Anxiety disorders C

P-40-001 Prediction error demarcates the transition from retrieval, to reconsolidation, to new learning

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Objective: Retrieval-induced plasticity (reconsolidation) does not necessarily occur when a memory is reactivated. Recently, we demonstrated that reconsolidation depends on prediction error (PE) - a discrepancy between what is expected and what actually occurs on a given learning trial. It may however be questioned whether PE is a sufficient condition for reconsolidation, given that PE can also give rise to new learning instead (e.g. extinction learning). It has indeed been demonstrated that extinction training puts a constraint on reconsolidation. During extinction training, repeated or prolonged unreinforced exposure generates multiple PEs. We tested whether the transition from reconsolidation to the formation of a new memory trace occurs long before the expression of the inhibitory extinction memory can be observed.

Methods: In a human differential fear conditioning paradigm, we created three groups in which fear acquisition was partially reinforced (50%; reinforcement on all even trials). One day later the memory was reactivated with one (no PE, n=18), two (single PE group, n=18) or four unreinforced reminder trials (multiple PEs group, n=16), followed by administration of the noradrenergic beta-blocker propranolol (40 mg). Expression of the fear memory was measured with the fear potentiated startle, while declarative US-expectancy ratings served to index PE. On day 3, all groups underwent an extinction and reinstatement procedure to test the absence of fear memory expression.

Results: The beta-adrenergic receptor antagonist propranolol erased the startle fear response 24 h after reactivation only when memory retrieval induced a single PE but not when there was no PE or multiple PEs, as indicated by post-retrieval changes in US-expectancy.

Conclusion: 1) PE is a necessary but not a sufficient condition for memory reconsolidation. 2) Too little and too much PE mark a boundary condition of memory reconsolidation. 3) Reconsolidation is prevented long before fear extinction can be observed.

Policy of full disclosure: None.

P-40-002 Psychotropic effects profiles of benzodiazepines and atypical anxiolytics in the treatment of uncomplicated generalized anxiety disorder

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Objective: Generalized anxiety disorder (GAD) is the prevalent chronic disorder often complicated by comorbid conditions worsening outcomes. It is crucial to treat GAD on early, uncomplicated stages of disorder. To achieve symptomatic remission and improve long-term outcomes it is important to address treatment to full set of therapeutic targets. Atypical anxiolytics (AA) and benzodiazepines (BDZ) are options for GAD treatment and most effective in uncomplicated cases. The aim of this study is to compare effectiveness and psychotropic effects profiles of AA and BDZ in the treatment of uncomplicated GAD to assess how it comply the therapeutic needs of these patients.

Methods: GAD patients without comorbity and with duration of illness less than 2 years were included. The study utilized Hamilton Anxiety Rating Scale (HARS), Clinical Global Impression (CGI) scale and Scale for Evaluation of Severity of Symptoms (SESS) that allows assessing changes in severity of psychopathological symptoms reflecting anxiolytics clinical effects. After 7-day placebo lead-in period to eleminate placebo-responders 65 patients received AA (mercaptobenzimidazole derivate Afobazole or peptide anxiolytic Selank derivate of tuftsin) and 32 patients received BDZ (phenazepam or medazepam).

Results: Patients treated with BDZ and AA had comparable background characteristics. Treatments didn't differed on either HARS or CGI-Severity score changes after 2 weeks. Though CGI therapeutic effect was greater in AA group. Both BDZ and AA significantly reduced anxiety, insomnia and autonomic symptoms domains of SESS. Hypnotic effect was more evident with BDZ. Despite similarities BDZ and AA differed in terms of action on asthenia symptoms domain. AA improved asthenia while BDZ showed undesirable sedative and muscle relaxant properties.

Conclusion: Improved therapeutic effect of AA in uncomplicated GAD despite more robust anxiolytic action of BDZ may be due to that fact that their psychotropic effects profile is closer to match full set of therapeutic needs of GAD patients.

Policy of full disclosure: None.

P-40-003 Augmentation strategies in treatment resistant anxiety disorders: Meta-analysis and systematic review

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Objective: Anxiety disorders are associated with high rates of non or partial response to first-line treatment with selective serotonin reuptake inhibitors. The primary objective was to examine the potential benefits of using medication augmentation strategies compared to control treatments in patients who have had a partial or non-response to initial treatment for generalized anxiety disorder(GAD), social anxiety disorder(SAD) and panic disorder(PD) by meta-analysis of a pooled dataset.

Methods: Double-blind, controlled (placebo or active comparator) trials of medication augmentation in treatment resistant anxiety disorders were systematically reviewed by independent raters for inclusion, quality and risk of bias. MEDLINE, EMBASE, PsycINFO, The Cochrane Library and conference proceedings were searched to identify trials. Effect estimates were calculated using random effects modeling; heterogeneity and sensitivity analyses were completed.

Results: Six studies(3 in GAD, 1 in SAD, 2 in PD) were included in the meta-analysis. Five studies had small samples; a study of pregabalin in treatment resistant GAD had a largest sample and was given the greatest weight in the analyses. Augmentation was not associated with an increased risk of response, (CGI-I # 2) versus placebo RR=1.08, 95% CI 0.94 to 1.24. A small, significant effect was found in reduction in symptom severity: Standard Mean Difference −0.32, 95% CI −.56 to −0.08. No significant differences were found between augmentation with medication versus placebo in functional impairment and drop-outs due to adverse events.

Conclusion: Augmentation does not appear to be beneficial in treatment resistant anxiety disorders. These results may be limited by small study samples, and a small number of overall studies in the analysis.

Policy of full disclosure: Dr. Van Ameringen has received grant/research support from personal fees from Canadian Foundation for Innovation (CFI), Forest Laboratories, Janssen-Ortho Inc., National Institutes of Health, Pfizer Inc., Servier, and Wyeth-Ayerst . He is on the speaker#s bureau for Biovail, GlaxoSmithKine, Janssen-Ortho Inc., Lundbeck, Pfizer Inc., and Shire. He has received consultant frees from and is on advisory boards of Astra Zeneca, Biovail, Eli Lilly, Forest Laboratories , Janssen-Ortho Inc., Labo Pharm, Lundbeck, Pfizer Inc., and Shire. Beth Patterson has nothing to disclose.

P-40-004 Technology-based communication in individuals with social phobia

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Objective: There is emerging literature examining the effects of increased internet use on social behavior, however the results have been equivocal with some studies indicating benefit and some indicating harm. Social phobia is an anxiety disorder which has a profound impact on communication. In addition, Social phobics (SPs) have been found to be high internet users. The impact of internet use on the social functioning of SPs was examined via an internet survey.

Methods: A survey was posted on the website of an anxiety research centre about the reasons for and time spent on the internet during leisure time. Participants also completed an anxiety and depression screener, measures of severity and impairment.

Results: The survey was completed by 513 participants; 62% had social phobia (SP) 54% had major depressive disorder and only 18% of the sample did not meet criteria for a mental disorder. Over 1/3 spent less than 2 hours/day online and 34% had met friends online. Those with SP were compared to those without social phobia (NoSP) and to those without any diagnosis (controls). SPs reported higher rates of functional impairment compared to NoSPs or Controls. Compared to NoSP and Controls, SPs were significantly more likely to send a text message or use the computer to avoid face to face (FTF) ($p<0.001$) or telephone($p<0.001$) contact. SPs vs. NoSPs and Controls reported significantly higher rates of avoiding making friends, shopping, banking, obtaining information and ordering food FTF due to the ability to access information and services online. SPs reported feeling significantly less close to the people they socialize with compared to NoSPs and Controls. If available online, 67% would be motivated to obtain treatment.

Conclusion: Given the high use of the internet by SPs for social interaction, technology based treatments may improve access to treatment and improve social functioning.

Policy of full disclosure: Dr. Van Ameringen has received grant/research support from personal fees from Canadian Foundation for Innovation (CFI), Forest Laboratories, Janssen-Ortho Inc., National Institutes of Health, Pfizer Inc., Servier, and Wyeth-Ayerst. He is on the speaker's bureau for Biovail, GlaxoSmithKine, Janssen-Ortho Inc., Lundbeck, Pfizer Inc., and Shire. He has received consultant frees from and is on advisory boards of Astra Zeneca, Biovail, Eli Lilly, Forest Laboratories , Janssen-Ortho Inc., Labo Pharm, Lundbeck, Pfizer Inc., and Shire. Beth Patterson has nothing to disclose William Simpson has nothing to disclose Jasmine Turna has nothing to disclose.

P-40-005 Generalized anxiety disorder and ACTH plasmatic concentrations

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Objective: ACTH plasmatic concentrations in MDD are frequently increased, however how is it in the most prevalent group of anxiety disorders - GAD?

Methods: 24 patients high level of anxiety in general anxiety disorder participated in the study. Age 21 – 25 years. ACTH and cortisol plasma concentrations were followed in regular intervals (week 10,12,14,16) in patients who did not respond to 8 weeks of antidepressant treatment. All pacients were switched from various SSRI and SNRI antidepressants to paroxetine 40 mg. In addition to the clinical interview, the HAMA Rating Scale was used to assess general anxiety symptomology and the Hamilton Depression Rating Scale a standard measure of depressive symptoms, was also administered. Study participants underwent an initial evaluation, which included collection of demographic information, self-reported current and past medical history and medication use, and the Structured Clinical Interview for DSM-IV Axis I Disorders. GAD subjects with a secondary diagnosis of comorbid depression, panic disorder, social phobia, or specific phobia were not included. All subjects were excluded from this analysis if had a history of psychosis, unstable medical illness, or alcohol or substance abuse. Participants were also excluded if they were currently using corticosteroids and female participants were excluded if they were on hormone replacement therapy.

Results: We did not find correlation between ACTH plasmatic concentration and severity of symptomatology measured by HAM-A ACTH plasmatic concentrations in women and men remained unchanged despite of improvement in HAM-A score or introducing the treamtment. Our findings show that highly anxious females exhibited higher cortisol release than highly anxious males, however in the range of normal values. Cortisol plasmatic concentrations in women decreased with the improvement of HAM-A score and did not change with improvement of HAM-A score in men, they remained low.

Conclusion: GAD does not seem to be connected with increased ACTH plasmatic concentrations during acute state.

Policy of full disclosure: None.

P-40-007 Selected G alpha proteins are involved in morphine-induced impairment of fear memory

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Objective: Fear conditioning (FC) is an animal model of anxiety disorders, where the ability to learn and remember an association between aversive experience and environmental cues is measured. It has been shown that the hippocampus mediates contextual fear conditioning and opioid receptors (OR) become involved in this process. However, the molecular mechanism mediating fear memory by OR remains unknown. The aim of this study was twofold. Firstly we wanted to assess whether morphine, administered immediately after FC, influences mice fear behavior (freezing) induced by exposure to conditioned context (CTX) or cues (CUE) applied 23 hr after a footshock. Secondly, we assessed the influence of FC training and CTX/CUE retrieval on mRNA expression of alpha subunits of G(i/o), G(s), G(q), G(11) and G(12) proteins in the mouse hippocampus.

Methods: C57BL/6J mice were subject to 1-day FC procedure, morphine (1 mg/kg/ip) was injected immediately after learning. Freezing behavior was measured during FC training and during CTX/CUE test. mRNA expression was assessed 24 hr after footshock and 1 hr after CTX/CUE test using RealTime PCR with TaqMan probes.

Results: Behavioral results showed that the immediate post-training administration of morphine prevented CTX- and CUE-triggered freezing. Biochemical analysis revealed the increase in Galpha(11) as a FC consequence. Galpha(11) was also elevated after exposure to CTX and CUE. However, morphine treatment prevented the increase in Galpha(11) triggered by FC and CTX. Morphine also prevented the CTX induced increase in Galpha(12). Galpha(s) was differently regulated, as its mRNA decreased after FC. This was still observed after CTX but only in mice treated with morphine.

Conclusion: Our data demonstrate the involvement of G11-, Gs- and G12- dependent signaling pathways in murine hippocampus in the development of fear memories. Moreover OR stimulation with morphine immediately after fear exposure can prevent the fear-triggered neuroadaptations responsible for fear memory.

Policy of full disclosure: Study originated in the frame of cooperation between the Italian National Research Council and the Polish Academy of Sciences and supported by statutory funds of the Institute of Pharmacology PAS.

P-41. Bipolar disorders C

P-41-003 Combined treatment: Impact of optimal psychotherapy and medication in bipolar disorder

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Objective: To investigate the longitudinal course of symptoms in bipolar disorder among individuals receiving optimal treatment combining pharmacotherapy and psychotherapy, as well as predictors of the course of illness.

Methods: One hundred and sixty participants with bipolar disorder (BD-I: n=115, BD-II: n=45) received regular pharmacological treatment, complemented by a manualized, evidence-based cognitive-behavioral therapy or psychoeducation. Participants were assessed at baseline and prospectively for 72 weeks using the Longitudinal Interval Follow-up Evaluation (LIFE) scale scores for mania/hypomania and depression, as well as comparison measures (clinicaltrials.gov identifier: NCT00188838).

Results: Over a 72-week period, patients spent, on average, about two-thirds of the time well. Symptoms were experienced more than 50% of the time for about a quarter of the sample. Depressive symptoms strongly dominated over (hypo)manic symptoms, while subsyndromal symptoms were more common than full diagnosable episodes for both polarities. Mixed symptoms were rare, but present for a minority of participants. Participants who had fewer depressive symptoms at intake, a later age of onset and no history of psychotic symptoms spent more weeks well over the course of the study.

Conclusion: Combined pharmacological and adjunctive psychosocial treatments appear to provide an improved course of illness compared to previous studies. Efforts to further improve the course of illness beyond that provided by current optimal treatment regimens will require a substantial focus on both subsyndromal and syndromal depressive symptoms.

Policy of full disclosure: None.

P-41-004 Bipolar disorder is more virulent in the United States than many European countries

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Objective: Controlled and naturalistic studies reveal a high degree of treatment resistance in patients with bipolar disorder from the US. We examined factors that might be associated with this adverse course of illness.

Methods: 968 outpatients with bipolar disorder average age 41 gave informed consent for participation in a treatment outcome network and provided detailed demographic, family history, and course of illness information on a questionnaire. Data from 676 patients from 4 sites in the US were compared with 292 from 3 sites in the Netherlands and Germany (abbreviated Europe).

Results: Virtually every aspect of bipolar disorder was more frequent or severe in those from the US compared to Europe. This included: genetic vulnerability (more parents and other relatives with bipolar disorder and a range of other psychiatric illnesses); psychosocial vulnerability (childhood verbal, physical, and sexual abuse, as well as more stressors accumulating over the course of illness); 31.1% vs 5.6% with childhood onset (< 12 yrs.); greater time delay to first treatment; more anxiety disorder comorbidity; rapid cycling; 20 or more episodes; medical comorbidities (including obesity); and twice the percent with a history of alcohol abuse and of drug abuse.

Conclusion: Almost all of these characteristics that are worse in the US vs Europe are associated with a poor long-term outcome, and we found a greater incidence of non-response to prospective naturalistic treatment in those from the US. The greater accumulation of 1) stressors, 2) episodes, and 3) substance use contributes to illness progression as each is associated with sensitization effects (increasing behavioral responsivity upon repetition) and cross-sensitization to the others. A paradigm shift toward earlier and more consistent treatment may help prevent these progressive processes, likely based on epigenetic mechanisms, and lessen the associated great illness burden, disability, and early demise associated with bipolar disorder in the US.

Policy of full disclosure: None.

P-41-005 Biochemical and genetic correlates of homocysteine in bipolar disorder

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Objective: An increased level of homocysteine (HCY) has been observed in bipolar mood disorder and an association of the polymorphisms of methylene-tetrahydrofolate reductase (MTHFR) gene with bipolar disorder was postulated. We studied clinical and biochemical factors in relation to hyperhomocysteinemia in patients with bipolar disorder during depressive episode and also investigated a possible association between 5 polymorphisms of four genes coding enzymes of HCY metabolism.

Methods: One-hundred and twelve patients (24 male, 88 female), aged 20 to 78 (mean 51±14 years) with bipolar disorder were included. The assays of serum concentrations of HCY, vitamin B12, folic acid as well as markers of endothelial function such as E-selectin and intracellular adhesion molecule-1 (ICAM-1) were made during depressive episode. Genotyping was performed for C677 T (rs1801133) and A1978C (rs1801131) polymorphisms of MTHFR gene, T833C polymorphism (rs5742905) of cystationine beta-synthase (CBS) gene, A2756 G polymorphism (rs1805087) of homocysteine methyltransferase (MTR) gene and A66 G polymorphism (rs1801394) of methionine reductase synthase (MTRR) gene, and compared with 167 healthy control subjects (81 male, 86 female).

Results: During depressive episode, hyperhomocysteinemia (>15 mM/l) was found in 50 patients (45%), significantly more frequently in male (67%) than in female subjects (39%). A significant inverse correlation between HCY and concentration of folic acid and vitamin B12 as well as with E-selectin and ICAM-1 was observed. An association with bipolar disorder was found for the T833C polymorphism (rs5742905) of CBS gene. No relationship with bipolar disorder was obtained for the remaining polymorphisms studied.

Conclusion: The results show a significant prevalence of hyperhomocysteinemia in bipolar depressed patients during acute episode and corroborate the correlation between increased concentration of HCY and lower level of vitamin B12 and folic acid. They are also pointing to a possible association between T833C polymorphism (rs5742905) of cystationine beta-synthase gene and bipolar disorder.

Policy of full disclosure: None.

P-41-006 Phosphoinositols accumulation following lithium treatment is mimicked by IMPA1 knockout and intracerebroventricularly IP3 administration results in lithium-like behavior

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Objective: In agreement with the inositol depletion hypothesis of lithium (Li)'s mechanism of action IMPA1 (coding for inositol monophosphatase1) knockout (KO) mice exhibit Li-like behavior in the forced-swim test (FST) and in the pilocarpine-induced seizures paradigm. We hypothesized that similarly to Li's effect bi-allelic IMPA1 knockout results in brain phosphoinositols accumulation and that this accumulation mediates Li's behavioral effects.

Methods: 3H-inositol was administered intracerebroventricularly (icv) to determine its conversion into phosphoinositols (separated by anion exchange chromatography) and phosphoinositides (extracted by chloroform:methanol:HCl 100:200:1). IP3/IP1 was administered icv in lyposomes.

Results: Chronic Li treatment and ablation of IMPA1 resulted in several fold increased frontal cortex and hippocampal radiolabeled phosphoinositols; acute Li treatment led to a trend of increased 3H-phosphoinositols levels. icv administration of 150 ug IP3 in liposomes decreased immobility in the forced-swim test (FST) and attenuated the hyperlocomotion response to amphetamine without affecting motor behavior. Administration of the same amount of IP1 had no effect. Administration of 500 µg IP1 induced sickness. Intriguingly, chronic Li treatment combined with administration of IP3 receptor antagonist (IP3Ra) induced a synergistic effect in the FST.

Conclusion: Li has been reported to downregulate IP3Rs. A possible interpretation of the behavioral results is that IP3 administration induced IP3Rs desensitization and that IP3Ra blocked the remaining IP3Rs following Li treatment. Overall, our results support the notion that Li's therapeutic effect is mediated by its intervention in inositol metabolism.

Policy of full disclosure: None.

P-41-007 Behavioural characterisation of ebselen; a potential lithium-mimetic

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Objective: To characterise the behavioural effects of ebselen, a potential lithium-mimetic in animal models and healthy volunteers.

Methods: Ebselen was tested in animal models in which lithium has an established phenotypic effect. Ebselen was injected intra-peritoneally (i.p.) into male, C57Bl/6 mice that were then tested for behavioural effects in the open-field test, the amphetamine-induced hyperactivity test, the forced swim test, and the dimethoxy-4-iodoamphetamine (DOI) induced head twitch. In a randomised, double-blind, parallel group, placebo-controlled healthy volunteer (n=40) study, we administered 3×600 mg ebselen over two days and tested the effects on tasks of emotional processing. Additionally, we assessed the ebselen effects on brain myo-inositol levels using magnetic resonance spectroscopy and on the architecture of the sleep polysomnogram in a double-blind, randomised, cross-over study.

Results: In mice, ebselen caused a reduction in exploratory behaviour in the open field, as well as in the hyperactivity that followed administration of amphetamine. In the DOI head twitch model, ebselen caused an attenuation of the head-twitches. These effects are consistent with effects previously reported with lithium. In the forced swim test, a sub-cutaneous injection of ebselen caused a reduction in immobility, also consistent with literature on both ebselen and lithium. In healthy volunteers, some antidepressants have been shown to bias emotional processing in positively. Lithium has been shown to increase slow-wave sleep in the polysomnogram although its effects on brain myo-inositol levels are inconsistent. At present, we are near completion of the studies, but are still blind to the treatment. The data analysis will be complete by April

and will be presented. Ebselen has been found to be well-tolerated and safe at the doses that we are administering.

Conclusion: Ebselen shows various behavioural effects in mice that are consistent with it being a novel mood-stabiliser and a potentially safer alternative to lithium.

Policy of full disclosure: None.

P-41-008 A pilot, open-label, 8-week study evaluating the efficacy of adjunctive minocycline for the treatment of bipolar I/II depression

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Objective: To evaluate if 8 weeks of adjunctive minocycline treatment will reduce the severity of depressive symptoms in individuals with bipolar I/II disorder.

Methods: A total of 29 individuals between the ages of 18 and 65 who met DSM-IV-TR criteria for a major depressive episode as part of bipolar I or II disorder were enrolled in an 8-week, open-label study with adjunctive minocycline (100 mg b.i.d). A total of 27 subjects were included in the intent to treat sample. Efficacy was evaluated with the mixed-effects model for repeated measures (MMRM).

Results: Adjunctive minocycline treatment was associated with significant change from baseline to week 8 on the Montgomery Asberg Depression Rating Scale (MADRS), Hamilton Depression Rating Scale 17 item (HAMD-17), and Clinical Global Impression Severity (CGI-S) ($p=0.002$, <0.001 and $p=0.002$, respectively). Significant improvement was observed as early as week 1 on the MADRS and HAMD-17 and week 2 on the CGI-S ($p=0.017$, $p=0.007$ and $p=0.006$, respectively).

Conclusion: This pilot study suggests that adjunctive minocycline may be an efficacious antidepressant for individuals with bipolar depression. These results provide a rationale for testing minocycline's efficacy in a larger randomized, placebo-controlled trial.

Policy of full disclosure: Joanna K. Soczynska is a recipient of the Eli Lilly Canada Fellowship, Ontario Graduate Scholarship, and Joseph Bazylewicz Fellowship. Sidney H. Kennedy has received research support from Bristol-Meyers Squibb, Brain Cells Inc., Clera Inc., Eli Lilly, Lundbeck, Pfizer, Servier, St Jude Medical Inc, and Canadian Institutes of Health Research. Roger S. McIntyre Eli Lilly has received research support from Janssen-Ortho, Shire, Astra-Zeneca, Pfizer and Lundbeck.

P-41-009 Lurasidone treatment for bipolar I depression: Effect on core depression symptoms

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Objective: To evaluate the antidepressant effect of lurasidone using the 6-item MADRS subscale which has been shown to be a unidimensional measure of "core" depressive symptoms (Bech et al., Psychopharm 2002;163:20–25).

Methods: Patients with bipolar I depression were randomized to 6 weeks of double-blind treatment with lurasidone in a monotherapy study with fixed-flexible doses of 20-60 mg/d and 80–120 mg/d vs. placebo (total N=485); and in an adjunctive therapy study of lurasidone (20–120 mg/d) with either lithium or valproate vs. placebo (total N=664). The criterion for severe depression: baseline MADRS score $\geqslant 30$.

Results: Lurasidone monotherapy resulted in significantly greater Week 6 improvement on the MADRS-6 for the 20–60 mg and 80–120 mg dose groups vs. placebo (−10.4 and −10.4 vs. −6.9; $P<0.001$ for both comparisons). In the severe depression group, lurasidone therapy (combined doses vs. placebo) was associated with significantly greater Week 6 improvement on the MADRS (−17.3 vs. −11.8; $P<0.001$) and on the MADRS-6 (−11.7 vs. −7.5; $P<0.001$). Week 6 effect size was larger for the severe (vs. less severe) depression group on the MADRS (0.56 vs. 0.44), and the MADRS-6 (0.62 vs. 0.44). Treatment with adjunctive lurasidone was associated with significant improvement on the MADRS-6 ($P=0.003$), but effect sizes were smaller for the severe depression group (0.25 vs. 0.49).

Conclusion: Treatment of bipolar I depression with lurasidone was associated with significant improvement in core depressive symptoms. In patients with severe depression, treatment with lurasidone was associated with larger effect sizes in the monotherapy study.

Policy of full disclosure: During the past 3 years, Dr. Thase has been an advisor or consultant to Adolor Corp; Alkermes; AstraZeneca; Bristol-Myers Squibb; Eli Lilly and Company; Forest Pharmaceuticals, Inc; GlaxoSmithKline; Johnson & Johnson (including Janssen Pharmaceuticals, Inc and Ortho-McNeil); Lundbeck; MedAvante, Inc; Merck (formerly Organon and Schering- Plough); Neuronetics, Inc; Novartis Pharmaceuticals Corporation; Otsuka America Pharmaceutical, Inc; Pamlab; Pfizer Inc (formerly Wyeth Research); PGx; Rexahn Pharmaceuticals; Shire; Supernus Pharmaceuticals; Takeda Pharmaceutical Company Ltd; and Transcept Pharmaceuticals, Inc. During the same time frame, he has received grant support from the Agency for Healthcare Research and Quality; Eli Lilly and Company; Forest Pharmaceuticals, Inc; GlaxoSmithKline; the National Institute of Mental Health; Otsuka America Pharmaceutical, Inc; and Sunovion Pharmaceuticals Inc (formerly Sepracor Inc). During the past 3 years, Dr. Thase has been on the speakers' bureaus of AstraZeneca, Bristol-Myers Squibb, Eli Lilly and Company, GlaxoSmithKline, and Pfizer Inc (formerly Wyeth), and holds equity in MedAvante, Inc. Dr. Thase has received royalties from American Psychiatric Publishing, Guilford Publications, Herald Publishing House, and W.W. Norton & Company. Drs. Tsai, Kroger, Pikalov, Cucchiaro, and Loebel are full-time employees of Sunovion Pharmaceuticals, Inc.

P-41-011 Safety and tolerability of cariprazine in patients with acute bipolar mania: Pooled analysis of 3 phase II/III pivotal studies

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Objective: The efficacy and tolerability of cariprazine, a D3-perferring dopamine D3 and D2 receptor partial agonist, was assessed in 3 randomized, double-blind, placebo-controlled, 3-week, Phase II/III studies in patients with bipolar mania (NCT00488618, NCT01058096, NCT01058668). Here we report an integrated summary of safety and tolerability data from these studies.

Methods: Cariprazine doses from 3 studies were pooled (3–12 mg/d); additional analyses evaluated the 3–6 and 9–12 mg/d groups. Safety assessments included adverse events (AEs), laboratory values, vital signs, weight, electrocardiograms (ECGs), Columbia-Suicide Severity Rating Scale, and extrapyramidal symptom scales.

Results: The pooled safety population comprised 1065 patients (placebo, n=442; cariprazine, n=623); approximately 70% of patients completed the study. The most frequently reported treatment-emergent AEs (TEAEs) (>=5% and twice placebo) were akathisia (placebo, 5%; cariprazine, 20%), extrapyramidal disorder (5%; 13%), restlessness (2%; 6%) and vomiting (4%; 9%). The incidence of serious AEs was similar between groups. AEs leading to discontinuation occurred in (7% of placebo and 12% of cariprazine patients. There was 1 death in the cariprazine group (pulmonary embolism; considered unrelated to treatment). TEAEs of suicidal ideation were infrequent (placebo, 4; cariprazine, 2); there were no suicide attempts. Mean changes in weight were small (placebo, 0.17; cariprazine, 0.54 kg); the proportion of patients with >=7% increase in weight were similar between groups (both 2%). Mean changes in blood pressure and pulse were slightly greater with cariprazine and indicative of a dose-relationship. Cariprazine was not associated with mean increases in ECG parameters except for a slight increase in ventricular heart rate vs placebo (5.0 and 0.9 bpm, respectively). Mean changes in metabolic parameters (eg., lipids, glucose) were generally small and similar between groups. Prolactin levels decreased in both groups.

Conclusion: In this pooled analysis, treatment with cariprazine for up to 3 weeks was generally safe and well-tolerated.

Policy of full disclosure: Supported by funding from Forest Laboratories, Inc. and Gedeon Richter Plc. Lakshmi Yatham has received research grants from Forest, Otsuka, Roche, Shire; is a consultant to: Genentech, Janssen, Merck, Teva Novartis, Sunovion, Gruenthal, Boehringer- Ingelheim, Lundbeck; and is a speakers bureau member for Janssen, Merck, Novartis, Sunovion.

P-42. Depression C

P-42-001 The effect of group therapy on the depression, quality of life, stress hormone, immunity and heart rate variability in Korean patients with breast cancer

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Objective: The aim of this study was to examine the effect of group therapy on the depression, quality of life, stress hormone, immunity and heart rate variability.

Methods: The subjects were 52 patients with breast cancer who completed surgery and adjuvant therapy more than 2 years ago at the Department of Surgery from at Wonkwang University Hospital. The Beck depression inventory (BDI), Spielberger State-Trait Anxiety Inventory (STAI), Visual analogue scale for pain (VAS), Somatic Symptoms Inventory(SSI), Cancer coping questionnaire(CCQ), Social support rating Scale (SSRS) and Short Form Health Survey-36-Korean (SF-36-K) were used. Venous blood from patients were collected for assessing immunity and stress hormones at the same time before and after group therapy. Heart rate variability (HRV) were measured by SA-6000 (Medicore, Korea) for assessing adapation for stressful situation. Seventeens of subjects among 52 patients were selected according to the patients' informed consent of participation in group therapy. The patients completed 14 weeks treatment program which was compose of 90 minutes session per week. Psychological parameters and biological parameters were compared before and after group therapy.

Results: 1) The prevalence of depression in patients with breast cancer was 36.4%. 2) The group therapy for Korean patients with breast cancer decreased depression and increased role physical and general health perception of SF-36-K. 3) The group therapy increased level of T cell and T helper cell, and significantly decreased norepinephrine level. 4) The group therapy increased Standard Deviation NN interval(SDNN) and Total Power(TF) in HRV.

Conclusion: These results suggest that group therapy for Korean patients with breast cancer could decrease depression and increase quality of life as well as increase immune function and HRV. Group therapy will be a treatment program for patients with breast cancer in Korea.

Policy of full disclosure: None.

P-42-002 The antidepressant vortioxetine does not disrupt sleep-wake rhythms during sub-chronic treatment with clinically-equivalent doses - an electroencephalographic polysomnography study in rats

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Objective: With few exceptions, antidepressants are reported to disrupt sleep architecture. Vortioxetine is an antidepressant that acts through 5-HT3, 5-HT7 and 5-HT1D receptor antagonism, 5-HT1B receptor partial agonism, 5-HT1A receptor agonism and inhibition of the 5-HT transporter (SERT). In depressed patients treated with vortioxetine, the incidence of sleep-related adverse events was 2.0–5.1% compared to 4.4% in patients who received placebo (Baldwin et al., IJPCP, 2013). A sleep-EEG study of vortioxetine and paroxetine in healthy subjects indicated that at a given SERT occupancy, vortioxetine affected rapid eye movement (REM) sleep to a lesser degree than paroxetine (Wilson et al., Eur Neuropsychopharmacol, 2013). Here we investigated clinically equivalent doses of vortioxetine on sleep-EEG in rats.

Methods: Cortical EEG, neck EMG, and locomotor activity were recorded in male Sprague Dawley rats in home cages using telemetric implants. Recordings were made 90 minutes before and 4 hours after a 10 a.m. acute dose and continued for 2 weeks in rats receiving normal chow or chow containing vortioxetine 0.6 g/kg food, which corresponds to 80–90% SERT occupancy in the brain. Sleep stages were manually scored into Active Wake, Quiet Wake, and Non-REM and Paradoxical (REM) sleep.

Results: Acute vortioxetine, 1, 3, 5, 10 mg/kg, increased latency to the first REM episode and 10 mg/kg also increased non-REM sleep latency. Sub-chronic administration of vortioxetine resulted in a normal sleep-wake rhythm comparable to that of rats receiving normal chow (measured on days 3, 7, 10, 14).

Conclusion: Our data appears consistent with clinical findings that vortioxetine does not greatly alter sleep-wake patterns during treatment. Based on literature showing 5-HT1A agonism promotes wakefulness while 5-HT3 and 5-HT7 antagonism regulates REM sleep, it seems vortioxetine's overall modest effect on sleep architecture is due to its multimodality. Further work is needed to substantiate this.

Policy of full disclosure: All authors were full time employees or consultants of Lundbeck at the time of the study.

P-42-003 Effects of chronic social instability stress during adolescence on social and cognitive functions

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Objective: Adolescence is a critical developmental period. The neurodevelopmental plasticity during this period may make it particularly vulnerable to perturbations from adverse life events such as chronic stress, which may cause behavioral abnormalities and eventually contribute to the onset of psychiatric disorders. Considering the stressors involved in human stress-associated disorders are mostly of social nature, in this study, we used a chronic stress model of social instability to investigate the effects of chronic social stress during adolescence on social and cognitive functions.

Methods: The chronic stress procedure was performed with adolescent male C57BL/6 mice. Starting at postnatal day 28, the group composition in each cage was changed twice per week for seven weeks, so that each time four mice from different cages were put together in a new cage. Control mice remained with the same cage mates throughout the experiment. At the end of treatment, all mice were single housed for seven days before subject to a series of behavioral testing, including open field, social approach, social preference, social recognition and Y-maze spontaneous alternation tests.

Results: We first replicated previous findings by showing that stressed animals displayed anxiety-related behaviors in the open field test. For social behaviors, we found that chronic social stress did not alter animals' latency to approach a novel mouse, but induced greater sociability in the social preference test and a defect in a preference for social novelty in the social recognition test. Besides, stressed animals showed poorer performance in the spontaneous alternation test, indicating a deficit in spatial working memory.

Conclusion: These findings suggest that chronic social instability stress during adolescence results in increased anxiety and impaired social and cognitive behaviors. Further studies are needed to investigate biochemical changes to obtain a better understanding of the mechanisms underlying such deficits.

Policy of full disclosure: None.

P-42-004 Recovery of age-related memory impairment in mice by vortioxetine is associated with activation of genes related to the neurotrophic factor signaling

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Objective: Changes in intracellular signal transduction may be involved in memory decline during aging. Antidepressants have been shown to modulate signal transduction in rodent disease models, but it is not clear if this also occurs in otherwise healthy old mice. Furthermore, antidepressants with different mechanisms of action have not been systematically examined in old mice regarding cognitive function and signal transduction. We compared the effects of aging and two different antidepressants (the SSRI fluoxetine and the multimodal-acting antidepressant vortioxetine) on visuospatial memory and expression levels of genes related to signal transduction in old mice. Vortioxetine is a 5-HT3, 5-HT7 and 5-HT1D receptor antagonist, 5-HT1B receptor partial agonist, 5-HT1A receptor agonist and inhibitor of the serotonin transporter.

Methods: Female C57BL/6 mice at 11 months of age received the following treatments for 1 month: vortioxetine (10 mg/kg/day in food), fluoxetine (16 mg/kg/day in drinking water) or vehicle (plain tap water and normal rodent chow). Vehicle treated three-month old female mice were included as age control. Visuospatial memory was evaluated by object placement test. Expression levels of genes were measured in hippocampus using quantitative PCR. Results were compared to vehicle treated old mice and $p<0.05$ was considered significant.

Results: Visuospatial memory deficit in old mice was significantly improved by vortioxetine, whereas fluoxetine was ineffective. In hippocampus, expression of TrkB, NF-kB1, JAK2, mTOR, CaMK2A, Arc, CREB1, and c-FOS was significantly decreased in old versus young mice. Vortioxetine, but not fluoxetine, significantly increased the expression of TrkB, NF-kB1, RELA, CaMK2A, Arc and c-FOS in old mice.

Conclusion: In otherwise healthy old female mice, deficits in visuospatial memory were accompanied by decreased expression of genes involved in signal transduction. Vortioxetine improved age-related deficits in visuospatial memory, which was associated with increased expression levels of genes related to neurotropic factor signaling.

Policy of full disclosure: This study was supported by H. Lundbeck A/S.

P-42-005 Vortioxetine restores memory function and reverses depression-like behavior in ovariectomized rats

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Objective: Ovariectomy (OVX) causes spatial memory deficits and depression-like behavior in rodents (Kiss et al., 2012). However, it is unclear if other cognitive domains are affected. Estrogen has been shown to alleviate these symptoms and modulation of the serotonergic system has been proposed as a possible underlying mechanism (Kiss et al., 2012; Osterlund 2010). However, it is not known if antidepressants with direct serotonergic receptor modulating properties are also efficacious in this model. We used a battery of behavioral tests to characterize the OVX rat model and to test the effects of vortioxetine in the behavioral domains in which OVX rats displayed deficits. Vortioxetine is an antidepressant with multimodal activities: a 5-HT3, 5-HT7 and 5-HT1D receptor antagonist, 5-HT1B receptor partial agonist, 5-HT1A receptor agonist, and inhibitor of the serotonin transporter.

Methods: Female Sprague-Dawley rats underwent ovariectomy at 10 weeks of age. Gonadally intact age-matched female rats were included for determining the behavioral consequences of OVX. To test effects of vortioxetine, OVX rats were fed with vortioxetine-containing chow (doses equivalent to 10 mg/kg/day) for 4 weeks and were compared to OVX rats fed with plain chow. The behavioral test battery included the object placement test (for visuospatial memory), social preference test, social memory test and forced swim test (for depression-like behavior).

Results: OVX rats exhibited deficits in visuospatial memory and increased immobility in the forced swim test, while social preference and social memory were not affected. Chronic vortioxetine treatment significantly ($p<0.05$) improved visuospatial memory performance and decreased immobility in the forced swim test comparing to the vehicle-treated OVX group.

Conclusion: Ovariectomy induces specific memory deficits and depression-like behavior in rats and may be valuable as an animal model of cognitive dysfunction comorbid with depression. Vortioxetine reversed memory deficits and exhibited antidepressant-like efficacy in this model.

Policy of full disclosure: This study was supported by H. Lundbeck A/S.

P-42-006 Pontine microbleeds and depression in stroke

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Objective: This study was designed to determine the relationship between cerebral microbleeds (CMBs) and poststroke depression (PSD).

Methods: A cohort of 229 patients with acute ischemic stroke admitted to the Acute Stroke Unit of the Prince of Wales Hospital between June 2004 and Oct 2010 was recruited. Depressive symptoms were assessed using the Geriatric Depression Scale (GDS).PSD was defined as a GDS score of 7 or above at three months following the subjects' index stroke. The presence and location of CMBs were evaluated with magnetic resonance imaging (MRI).

Results: Compared with the non-PSD group, PSD patients were more likely to have pontine CMBs (32.0% versus 18.2%; $p=0.019$). Pontine CMBs remained an independent predictor of PSD in the multivariate analysis, with an odds ratio of 2.24 ($p=0.015$).

Conclusion: The results suggest that pontine CMBs may play a role in the development of PSD. The importance of CMBs in the pathogenesis of PSD in stroke survivors as well as general elderly population warrants further investigation.

Policy of full disclosure: None.

P-42-007 Syndrome of inappropriate antidiuretic hormone secretion secondary to antidepressants: Fact or fiction?

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Objective: Analyze incidence of SIADH secondary to antidepressants in hospitalized patients.

Methods: Retrospective review of all consultants to psychiatric service between 2012 and 2013 (n=1393). Repeated consultations were removed (n=458). From the resulting, patients who initiated antidepressant treatment before admission were analyzed and, in these, if they had signs of hyponatremia suggestives of SIADH, having ruled out other possible causes.

Results: 30,38% (n=74) of patients received antidepressants. Of them, 10,81% (n=8) had hyponatremia suggestive of SIADH. 57% (n=4) were female. The average age was 74,85 years. Antidepressant were SSRIs in 68% (n=5); dual-action antidepressants in 26% (n=2); and, 1 patient (13%) was taking risperidone (see Table).

Conclusion: According to literature, most cases described were older people with diuretic treatment. Our incidence was 11%. Unfortunately, the actual incidence cannot be calculated because of a significant bias, we only could analyzed people hospitalized. Increase awareness of this disorder is necessary, especially due to the aging of population and increasing use of antidepressants. We believe appropriate to do analytical monitoring in patients over 65 years that begin antidepressant treatment and have other risk factors for developing SIADH. The relative risk of hyponatremia associated with each SSRIs drug needs to be determined, for that, more research is needed.

Policy of full disclosure: None.

P-42-008 Phenelzine increases rat brain levels of L-tyrosine, an effect apparently mediated by its active metabolite beta-phenylethylidenehydrazine

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Objective: Phenelzine is a monoamine oxidase inhibitor (MAOI) with antidepressant, anxiolytic and neuroprotective properties. In addition to increasing the concentrations of biogenic amine neurotransmitters by inhibiting MAO, phenelzine has additional effects on brain amino acids, including increases in GABA, alanine and ornithine and decreases in glutamine levels, which may contribute to its therapeutic effects. Phenelzine is a unique MAOI in that it is also a substrate for the enzyme, with beta-phenylethylidenehydrazine (PEH) being one of the metabolites formed. While PEH itself is a weak MAOI, it produces alterations in rat brain levels of the aforementioned amino acids that are comparable to those of phenelzine. These effects on amino acids are reversed for

Patient	Sex	Age	Psychotropic Drug	Dose (mg/day)	[Na+] (mmol/L)	Possible somatic causes
1	Male	72	Duloxetine	60	118	Diuretics
2	Female	86	Sertraline	50	116	Old TB lesion, diuretics
3	Male	61	Escitalopram	15	128	Active tumor
4	Female	80	Citalopram	20	128	Diuretics
5	Female	65	Risperidone	2	115	Diuretics
6	Male	87	Venlafaxine	225	130	Not listed
7	Male	73	Paroxetine	20	118	Congestive heart failure
			Fluoxetine	20	129	

Table 2. Summary of patients with hyponatremia suggestive of SIADH.
Note that patient 7 had hyponatraemia with two antidepressants

phenelzine, but not for PEH, when the animals were pre-treated with another MAOI, suggesting that they are dependent on the MAO-catalyzed formation of PEH. We now report that phenelzine and the E- and Z- geometric isomers of PEH also increase rat whole brain concentrations of L-tyrosine.

Methods: Rat whole brain L-tyrosine levels were measured by HPLC with electrochemical detection following a 30 mg/kg intraperitoneal administration of phenelzine, E-PEH and Z-PEH. To investigate whether this effect on L-tyrosine was MAO-dependent, animals were pre-treated with a 1 mg/kg intraperitoneal dose of the MAOI tranylcypromine prior to administration of phenelzine or racemic PEH.

Results: Phenelzine, E-PEH and Z-PEH increased rat whole brain L-tyrosine levels at 3 and 6 hours, reaching maximum levels of 265-305% of vehicle-treated controls at 3 hours. MAO inhibition with tranylcypromine abolished the increase in L-tyrosine for phenelzine, but not for PEH, suggesting that PEH is responsible for the tyrosine-elevating property of phenelzine.

Conclusion: Since L-tyrosine is a precursor for dopamine and noradrenaline, these results suggest that PEH may be a useful adjunctive drug to consider in a number of neurological and psychiatric disorders. Funded by CIHR(MOP:86712).

Policy of full disclosure: None.

P-42-009 The efficacy of vortioxetine in adult patients with a recurrent major depressive episode (MDE): A randomized, double-blind, placebo-controlled study

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Objective: To present secondary analyses of depressive efficacy endpoints after acute treatment of vortioxetine 10 mg/day and 20 mg/day versus placebo in patients with a recurrent MDE.

Methods: Patients (18–65 years) with a current MDE ⩾3 months, and a MADRS ⩾26 were eligible for this randomized, double-blind, placebo-controlled, multi-national, 8-week study (FOCUS: NCT01422213). Pre-defined secondary efficacy outcomes assessing depressive symptom severity included change from baseline to Weeks 1, 4, and 8 in MADRS total score and Clinical Global Impression CGI scores using MMRM.

Results: Patients had a mean baseline MADRS total score of 31.6±3.7 and a CGI-S score of 4.6±0.6. After 8 weeks, the mean MADRS decreased (improved) by 10.9 (placebo), 15.6 (vortioxetine 10 mg) and 17.6 (vortioxetine 20 mg) points. The difference to placebo (n=194) in mean change from baseline to Week 8 in the MADRS total score (FAS, MMRM) was −4.7 (n=193, p<0.001) for vortioxetine 10 mg and −6.7 (n=204, p<0.001) for vortioxetine 20 mg. The clinical relevance of these outcomes was supported by the CGI results, with separation from placebo for the CGI-S of −0.08 at Week 1 (p=0.077), −0.27 at Week 4 (p=0.004) and −0.65 at Week 8 (p<0.001) for vortioxetine 10 mg and −0.18 at Week 1, −0.43 at Week 4 and −0.85 at Week 8 (p<0.001 for all) for vortioxetine 20 mg. Separation from placebo for the CGI-I for vortioxetine 10 mg was −0.15 at Week 1 (p=0.020), −0.41 at Week 4 (p<0.001) and −0.61 at Week 8 (p<0.001) and for vortioxetine 20 mg was −0.28 at Week 1 (p<0.001), −0.54 at Week 4 (p<0.001) and −0.86 at Week 8 (p<0.001).

Conclusion: In this study, both vortioxetine doses separated from placebo with respect to depressive symptom severity and clinical global assessments. The difference to placebo in the MADRS total score was greater for the 20 mg dose than the 10 mg dose.

Policy of full disclosure: Dr. McIntyre does not have any financial conflicts of interests to disclose. This study was funded by H. Lundbeck A/S and Takeda Pharmaceutical Company, Ltd.

P-42-010 Neurohormonal response to psychosocial stress and food consumption in depression: The association of cortisol, leptin and ghrelin

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Objective: Obesity is frequently co-morbid with depression and can complicate treatment and prognosis. Altered stress perceptions and eating behaviours (particularly emotional eating, or increased food consumption in response to stress or negative affect), as well as neurohormonal mediation, had been suggested as shared pathophysiologies. The aim of this investigation was to examine the association of stress and appetite hormones with stress response and eating behaviour in individuals with depression.

Methods: Patients with major depression and matched healthy controls (18–65 years) underwent two physiological challenges, i.e., psychosocial stress (the Trier Social Stress Test), and food ingestion. Serial plasma samples were collected with both challenges to assess secretion of cortisol (associated with stress) and ghrelin and leptin (associated with hunger and satiety processes, respectively). Eating behavior and stress perception were also measured.

Results: 18 depressed patients and 17 matched healthy controls were recruited. In response to both physiological challenges, lepin levels were higher in depressed participants compared to controls, with greater elevation associated with longer duration of illness. There were no group differences in cortisol or ghrelin response to either challenge. Emotional eaters in the combined sample (patients and controls) exhibited significantly lower levels of ghrelin in response to food than non-emotional eaters. Elevated leptin levels, negative affect and emotional eating were also significantly noted.

Conclusion: The results of this study indicate that depression is associated with abnormal leptin concentrations, and that this may be partly due to the influence of stress. The association of depressive chronicity and higher leptin levels is also notable, as it may indicate a vulnerability to obesity for those with chronic depression. Similarly, emotional eating may also increase risk of weight gain for individuals with this tendency.

Policy of full disclosure:

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P-42-011 Broader conceptualization of remission assessed by the remission from depression questionnaire and its association with symptomatic remission

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Objective: The primary objective of this prospective, multicenter, observational study was to evaluate the association between a broader conceptualization of remission in Major Depressive Disorder (MDD), based on the Remission from Depression Questionnaire (RDQ) score at baseline, and being in symptomatic remission, based on the Hamilton Rating Scale for Depression (HAM-D17) score at study end following 6 months of observation.

Methods: Patients #18 years of age who previously experienced an acute period (12±2 weeks ago) for the current MDD episode but were in symptomatic remission at baseline were included. In addition to baseline RDQ total score, further factors potentially influencing remission status (HAM-D17) at 6 months were considered: baseline severity of depression (determined by HAM-D17), age, gender, employment status, years since diagnosis, family history of depression, history of MDD, treatment duration for current episode, and somatic comorbidities. A backwards selection strategy was used to statistically model remission status and determine factors with the strongest association.

Results: The study included 613 patients with a mean age of 46.6±13.48 years (years±standard deviation). Most subjects (77.3% at baseline and 66.3% at 6 months) were still treated for their episode of MDD. Of 575 patients completing the study, 54 were no longer in symptomatic remission at 6 months. Statistical modeling indicated that an increase in baseline HAM-D17 score of 1 unit decreased the odds of being in remission by 18% (odds ratio 0.82, p=0.017, 95% confidence interval (CI) 0.70#0.96). Increasing RDQ by 1 unit did not change the odds of being in remission at 6 months (odds ratio 1.00, 95% CI 0.98#1.02).

Conclusion: After adjustment for baseline severity of depression measured by HAM-D17, there was no association between baseline RDQ score and remission status, ie HAM-D17, at 6 months.

Policy of full disclosure: Alonso Montoya, Jeremie Lebrec, Karen Mary Keane, Irene Fregenal, and Antonio Ciudad are employees of Eli Lilly and Company.

P-42-012 Changes in alpha(1)-adrenergic receptor subtypes in the prefrontal cortex of rats subjected to chronic mild stress and imipramine treatment

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Objective: The alpha(1)-adrenergic receptor (alpha(1)-AR) is important target of many psychoactive substances, including antidepressants. Three subtypes of alpha1-AR (alpha1A, alpha1B, alpha1D) are widely expressed in brain, though the functional difference among individual subtypes is still not well understood. We investigated alterations in the alpha(1)-ARs subtypes at their mRNA and protein levels in the prefrontal cortex of male Wistar rats subjected to the chronic mild stress (CMS) procedure followed by treatment with antidepressant drug, imipramine (IMI).

Methods: Five groups of animals were studied: sham-saline; stress-saline; sham-IMI; stress-IMI-responders and stress-IMI-nonresponders, i.e., the stressed animals resistant to IMI treatment as indicated by anhedonia test. The receptors mRNA level was measured using RT-qPCR and SybrGreen dye, and the protein level was assessed by Western blotting.

Results: The changes found at mRNA level concerned mainly the alpha (1B) expression. The CMS procedure decreased the alpha(1B) expression (by 39 % vs. sham-saline group). Surprisingly, a similar effect was observed in stressed animals that responded behaviourally to IMI treatment, but not in the IMI-nonresponders group. However, these mRNA changes were not followed by alterations in the alpha(1B) receptor protein level. Whereas the alpha(1A)-AR mRNA was not influenced by any procedure, the alpha(1D) was increased in stressed rats that did not respond to IMI (by 28 % vs. saline-sham group). In the latter group, an opposite change was seen in the alpha(1D) protein level which was decreased in comparison to the stress-IMI-responders (by 20 % vs. saline-sham). Moreover, IMI alone caused the decrease in protein expression levels of alpha(1A)- and alpha(1B)-AR.

Conclusion: Our results indicate that though all three alpha(1)-ARs seem to be involved in mechanism of IMI action, the individual alpha (1)-AR subtype may differ in its vulnerability to stress in CMS model of depression.

Policy of full disclosure: None.

P-42-013 Levomilnacipran inhibits both norepinephrine and serotonin reuptake across the clinical dose range

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Objective: Levomilnacipran extended-release (ER) is a potent and selective SNRI approved for the treatment of major depressive disorder (MDD) in adults. In vitro, levomilnacipran ER shows greater potency for inhibition of NE relative to 5-HT reuptake. The objective of this analysis was to characterize the pharmacokinetic (PK) profile of levomilnacipran ER 40, 80, and 120 mg/d and to use the PK data to estimate 5-HT and NE reuptake inhibition over the levomilnacipran ER dose range.

Methods: PK data were collected from approximately 15% of adult patients with MDD who participated in an 8-week placebo-controlled, fixed-dosed trial of levomilnacipran ER 40, 80, and 120 mg/day. Blood samples were collected predose, and at 2, 4, 6, 8, 12, and 24 hours postdose. Plasma samples were analyzed using a validated LC-MS/MS method. To evaluate 5-HT and NE inhibition over the levomilnacipran ER clinical dose range, unbound levomilnacipran ER plasma concentrations obtained over a 24-hour period were plotted against previously determined in vitro 5-HT and NE reuptake inhibition profiles, which had been generated using human recombinant transporters expressed in HEK cells.

Results: Levomilnacipran steady state PK profiles were linear and dose proportional following oral administration. The Cmax was 92.8 ng/mL, 180.4 ng/mL, and 297.2 ng/mL, for the 40, 80, and 120-mg doses. The average plasma concentrations at steady state for levomilnacipran ER were 63.3 ng/mL for 40 mg/day, 122.3 ng/mL for 80 mg/day, and 199.9 ng/mL for 120 mg/day. The average unbound plasma concentrations for levomilnacipran that were reached in MDD patients treated with levomilnacipran ER 40, 80, or 120 mg/day exceeded the concentration which showed 90% and 80% inhibition of NE and of 5-HT reuptake, respectively, in vitro.

Conclusion: These data suggest that levomilnacipran ER strongly inhibits both NE and 5-HT across the clinically effective dose range.

Policy of full disclosure: This study was funded by Forest Laboratories, Inc.

P-42-014 Serotonin 5-HT4 receptor agonist is able to promote erythropoietin expression and cell proliferation in hippocampal neural progenitor cells

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Objective: Serotonin (5-hydroxytryptamine, 5-HT), a monoamine neurotransmitter, plays important roles in in the regulation of various functions, such as emotional status, sleep, feeding, sexuality and pain. There are numerous evidences that 5-HT and its receptors are involved in the action of antidepressants. Our previous study showed that fluoxetine (selective serotonin reuptake inhibitor) recovers the down-regulation of EPO in the hippocampus of chronic unpredictable stress-induced depression model rats.

Methods: The present study was undertaken to investigate the effect of 5-HT and 5-HT receptor agonists (8-OH-DPAT, 5-HT1A receptor agonist; RS67333, 5-HT4 receptor agonist) on EPO expression and cell proliferation in cultured hippocampal neural progenitor cells (NPCs).

Results: EPO expression was increased time dependent manner being significant at 3, 4 and 5 days after 5-HT treatment as determined by reverse transcription-polymerase chain reaction (RT-PCR) and Western blotting ($P<0.05$). Four days treatment of 5-HT and 5-HT receptor agonists on NPCs significantly increased EPO expression and the fraction of bromodeoxyuridine (BrdU, proliferation marker)-positive cells co-labeled with microtubule-associated protein 2 (MAP2, neuronal marker) compared with those in the control groups ($P<0.05$). The most prominent effect was demonstrated by RS67333.

Conclusion: In summary, these results provide evidences that 5-HT and 5-HT receptor agonists promote EPO expression and hippocampal cell proliferation. These suggest that 5-HT4 receptor agonist could be a good candidate for treating mental illness such as depression and anxiety associated with neuronal atrophy and reduced hippocampal neurogenesis.

Policy of full disclosure: None.

P-42-015 The role of the vagus nerve in the anti-inflammatory action of antidepressants in rats

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Objective: Signalization by the vagus nerve influences different processes, including both peripheral and central inflammation. The decreased vagal activity was found in depressed individuals. We suggest that some antidepressants may exert their antiinflammatory effect at least partially by activation of antiinflammatory pathway of the vagus nerve. In our study this concept has been evaluated in animal model.

Methods: Sprague-Dawley rats were assigned to subdiaphragmatic vagotomy (SV; n=30) or sham operation (SHAM; n=29). After 4 weeks of recovery period, the effect of acute fluoxetine (Fx) treatment on LPS-induced plasma cytokine and corticosterone secretion, splenic cytokine expression, c-fos mRNA, and cytokine (TNFa, IL1b) gene expression in brain areas was studied. Rats were injected intraperitoneally (i.p.) with saline or Fx (10 mg/kg) 30 minutes before i.p. injection of lipopolysaccharide (LPS; 50 μg/kg) or saline. After three hours rats were sacrificed and samples were collected.

Results: Acute injection of Fx significantly attenuated LPS-induced increase of plasma cytokine and corticosterone levels and caused a marked reduction in TNFa, IL1b and IL6 mRNA expression in the spleen in SHAM rats. Vagotomy restricted this inhibitory effect on the periphery. Centrally, immune challenge with LPS induced significant changes of c-fos and cytokine gene expression in brain areas (Paraventricular Nucleus; PVN, Nucleus Tractus Solitarii; NTS) with mean c-fos mRNA levels 2.0 and 5.5fold higher in LPS-treated SHAM rats than in saline-treated controls. TNFa and IL1b mRNA levels were also significantly higher in the PVN and NTS of LPS-treated SHAM rats. In vagotomized rats, LPS produced a slight increase in the expression of c-fos, and cytokine mRNA, which was not influenced by the Fx treatment.

Conclusion: We found that fluoxetine blocked systemic LPS-induced increase in peripheral cytokines and this effect was reduced by subdiaphragmatic vagotomy. These data indicate that peripheral antiinflammatory effect of fluoxetine is mediated also via the vagus nerve.

Policy of full disclosure: None.

P-42-016 Vortioxetine does not affect sexual behavior in a male rat model for sexual dysfunction

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Objective: Antidepressants acting via inhibition of the serotonin (5-HT) transporter (SERT) inhibit sexual behavior. Vortioxetine, an antidepressant with a multimodal mechanism of action, is an inhibitor of the SERT, a 5-HT3A, 5-HT7 and 5-HT1D receptor antagonist, a 5-HT1A receptor agonist and a 5-HT1B receptor partial agonist. Since modulating 5-HT receptor subtypes (e.g., 5-HT1A, 5-HT1B receptors) and transporter may affect sexual function differently, we compared the effects of vortioxetine and a selective serotonin reuptake inhibitor (SSRI), paroxetine, on the sexual behavior of male rats.

Methods: The effects of vortioxetine (1 and 10 mg/kg/day), paroxetine (10 mg/kg/day) and vehicle were compared acutely and after 1 and 2 weeks of dosing on various measures of male rat sexual behavior, i.e., latency and number of ejaculations, mounts and intromissions. Since the affinity of vortioxetine for the rat 5-HT1A receptor is approximately10-fold lower than for the human 5-HT1A receptor, vortioxetine was also tested in the presence of flesinoxan (2.5 mg/kg) to mimic the human level of 5-HT1A receptor activation. Vortioxetine was dosed via the food, paroxetine and flesinoxan were administered as s.c. injections. Antidepressant exposures were determined as SERT occupancy using ex vivo autoradiography.

Results: Neither vortioxetine nor vortioxetine plus flesinoxan affected sexual behavior, whereas 2-weeks paroxetine dosing impaired sexual behavior significantly ($P<0.05$) in several measures. Vortioxetine, 1 and 10 mg/kg, corresponded to 50 and 88% SERT occupancy, which matched occupancies seen at clinical doses (5–20 mg/day) as shown in human PET studies. Paroxetine produced approximately 90% SERT occupancy. Flesinoxan alone increased sexual performances acutely and after 1 week, but not after 2 weeks of treatment.

Conclusion: Vortioxetine at clinically relevant levels of SERT occupancy did not affect male rat sexual performance. Thus, it appears that one or more of vortioxetine's receptor activities counteract the serotonin-mediated inhibition of sexual performance produced SERT inhibition.

Policy of full disclosure: The research was funded by Lundbeck USA.

P-42-017 Aripiprazole augmentation, antidepressant combination or switching therapy in patients with major depressive disorder who are partial- or non-responsive to current antidepressants: A multi-center, naturalistic study

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Objective: There has been no studies comparing the clinical benefits of aripiprazole augmentation (AT), antidepressant combination (AC), and switching to a different antidepressant (SW) in patients with major depressive disorder (MDD) patients partially or not responding to an initial antidepressant. AT, AC, or SW was chosen by patients.

Methods: The primary efficacy measure was the proportion of patients showing an improvement in the Clinical Global Impression-Clinical Benefit (CGI-CB) score at week 8. Secondary efficacy measures included changes in CGI-CB, CGI-Severity (S) and subjective satisfaction scores. Remission and responder analysis were also employed.

Results: A total of 295 patients were enrolled. The most preferred strategy was AT (n=156, 52.9%), followed by AC (n=93, 31.5%) and SW (n=46, 15.6%). The improver was significantly higher in AT (74.1%) compared with AC (48.1%; $p<0.001$) and similar to SW (73.5%, $p=0.948$), whereas no significant difference was found between AC and SW. Similar results were also found in the most secondary endpoint measures proving a superiority of AT over AC without differences between AT and SW. Tolerability profiles were similar across the three groups; however, the mean weight gain for SW (−0.1 kg) was significantly less than that for AC (1.3 kg, $p<0.05$). Patients preferred AT to AC or SW when an antidepressant was ineffective in treating their depression.

Conclusion: Among the three treatment strategies, overall AT yielded greater clinical benefit than did AC and SW. Adequately powered, well-controlled clinical trials are strongly warranted to confirm our findings due to methodological shortcomings.

Policy of full disclosure: None.

P-42-018 Agomelatine treatement in outpatient depressives: A short effectiveness study

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Objective: Assessment of efficacy and safety of agomelatine alone or in combination in outpatients with DSM-IV major depressive episode of variable duration.

Methods: To 40 outpatients (18 males, 22 females) with DSM-IV major depression, agomelatine 25 mgs omni nocte was prescribed, with a possible increase to 50 mgs omni niocte after two weeks. Efficacy was assesed with the dministration of 17-item HAM-D in 0, 2,4,8 and 12 weeks. Side effects were assessed through clinical observation or self reports.There was a separate analysis of efficacy for both monotherapy (25or 50 mgs of agomelatine) and polypharmacy patiens and also for older (>65 years of age) and younger patients. A liver biochemistry profile was administerd in week 0 and week 12 to 33 patients.

Results: After 12 weeks a mean reduction of 10,2 points in HAM-D for both groups was observed. A greater reduction (11, 6 points) was found in the group under 50 mgs/day but the difference was marginally statistically significant. Another interesting finding was that a better outcome was observed in monotherapy patients (− 11 units) compared with polypharmacy patients (−8,4)), a non-significant finding. . The most common reported adverse event was headache (14,6 %). Two patients had a non significant rise of ALT (16 and 23 units at the end of the study).

Conclusion: Agomelatine proved to be an effective treatment choice for outpatients with major depression.

Policy of full disclosure: None.

P-42-019 The effects of 3 weeks repetitive transcranial magnetic stimulation on the P200 amplitude in patients with medication-resistant major depression

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Objective: Previous studies have reported that the repetitive transcranial magnetic stimulation (rTMS) would be able to induce neuronal plasticity in the brain. Although event-related potential (ERP) is an expecting tool for exploring, a study of rTMS effects on ERPs in patients with major depression has not been fully explored. The aim of this study is to prove that rTMS treatment induces changes in brain function of patients with medication-resistant major depression using ERP.

Methods: Eighteen patients with medication-resistant major depression (five males and thirteen females) participated in this study. The patients received rTMS treatment for three weeks. All patients completed clinical scales including Hamilton Depression Rating Scale (HAM-D), Hamilton Anxiety Scale (HAM-A), Beck Depression Inventory (BDI), State-Trait Anxiety Inventory (SAI, TAI), Ruminative Response Scale (RRS), Emotion Regulation Questionnaire (ERQ), and Cognitive Emotion Regulation Questionnaire (CERQ), and EEG assessment including ERP auditory oddball task, at their first visit (baseline) and second visit (3-weeks).

Results: In rating scales, HAM-D, HAM-A, BDI, SAI, and 'blaming others' scale of CERQ decrease significantly after rTMS treatment. In ERP auditory oddball task, when FP1, FP2, FZ, FCZ, CZ, and PZ channels were analyzed, P200 amplitudes showed a main effect for time of measure and increased after 3-weeks rTMS treatment. Standardized low-resolution brain electromagnetic tomography (sLOREA) showed significant activation in left middle frontal gyrus.

Conclusion: This study suggests that long-term rTMS treatment induces changes of brain function in patients with medication-resistant major depression, which can be identified using ERP.

Policy of full disclosure: None.

P-42-020 The association between serum lipid levels, suicide ideation, and central serotonergic activity in patients with major depressive disorder

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Objective: There is some evidence that low lipid levels cause suicide in depressed patients. The purpose of this study was to identify whether low serum lipid levels are associated with suicide ideation or are correlated with central serotonin function.

Methods: Auditory processing for the loudness dependence of auditory evoked potentials (LDAEP) was measured in 73 outpatients with major depressive disorder. The Hamilton Depression Rating Scale (HAMD) and Beck Depression Inventory (BDI) were administered on the same

day as measurement of the LDAEP. In addition, serum levels of total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglyceride (TG) levels were measured. All subjects had received antidepressant monotherapy.

Results: The depressed subjects were divided into those with and without suicide ideation according to the score for HAMD item 3 or BDI item 9. TG levels differed significantly between the two groups, whereas body mass index (BMI), total cholesterol, LDL, HDL, and LDAEP did not. The scores for HAMD item 3 and BDI item 9 were negatively correlated with TG levels ($p=0.049$ and 0.027, respectively). The LDAEP was negatively correlated with TG levels ($p=0.012$). Although there was tendency toward a negative correlation between the LDAEP and serum LDL, it did not reach statistical significance ($p=0.068$).

Conclusion: The findings of this study revealed a relationship between TG and suicide ideation that is independent of both BMI and body weight. Furthermore, serum lipid levels were associated with central serotonergic activity, as assessed using the LDAEP.

Policy of full disclosure: This study was supported by a grant from National Research Foundation of Korea (NRF), funded by Ministry of Education and Science Technology (MEST) (NRF-2011-0010562). They support authors in financial aspect.

P-42-021 Concentrations of different antidepressants in plasma and cerebrospinal fluid under naturalistic conditions

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Objective: Aim of this study was to investigate whether drug concentrations of different antidepressants in plasma can be considered as a surrogate marker of concentrations in brain/cerebrospinal fluid (CSF).

Methods: The present study is a naturalistic prospective investigation of 48 depressive patients treated daily doses of venlafaxine (16), citalopram (16) and mirtazapine (16). Patients underwent lumbar puncture (LP) for medical reasons and not for the purpose of this study. Blood was collected in at the same time as lumbar puncture was done. LP was done as part of the clinical routine without placing a special emphasis on trough levels of the ingested drug.

Results: The correlation between venlafaxine, O-desmethylvenlafaxine and AM in plasma and CSF was highly significant ($p<0.001$). Mirtazapine in plasma and CSF were just trend-wise correlated ($r=0.441$, $p=0.088$) and no relation of daily dose and CSF levels of mirtazapine could be observed ($r=0.313$, $p=0.238$). Citalopram-levels showed a high correlation between plasma and CSF _$r=0.890$, $p<0.001$,

Conclusion: 3 different antidepressants show highly variable penetration ratios into CSF. The poor correlation of dose to concentrations in body fluids and the highly significant correlation of plasma to CSF concentrations indicate that plasma concentration is a much better marker of drug concentration in brain than the dose.

Policy of full disclosure: None.

P-42-022 Vortioxetine treatment reverses cognitive impairment induced by long-term dysregulation of glutamate neurotransmission in rats

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Objective: Vortioxetine is a multimodal-acting antidepressant that indirectly modulates glutamate neurotransmission via serotonergic mechanisms. Preclinical evidence suggests that vortioxetine ameliorates impairments in memory and cognitive flexibility. However, there is little evidence directly tying vortioxetine's cognitive effects to glutamate modulation. Our objective was to assess whether vortioxetine ameliorates cognitive deficits induced by long-term glutamate dysregulation using a glutamatergic NMDA receptor antagonist.

Methods: Subchronic phencyclidine (SubPCP): Male rats were treated with saline or PCP (5 mg/kg ip bid) for 7 days followed by a 7 day washout. After washout, rats were assessed in the attentional set-shifting task (AST) 1 h after vortioxetine (0, 1, 3, 10 mg/kg sc) or 30 min after modafinil (64 mg/kg po). A separate cohort was assessed in the novel object recognition (NOR) task 1 h after vehicle or 10 mg/kg vortioxetine. A third cohort had free access to vehicle or vortioxetine-infused food (0.22 or 1.8 *g* vortioxetine/kg food) during the 14-day SubPCP administration/washout period. On day 15, rats were assessed in the AST. Frontal cortex tissue was analysed for altered GABA- and glutamate-related protein expression using western blots.

Results: SubPCP impaired AST performance in the extradimensional shift and extradimensional reversal subtests ($F(30,383)=1.519$, $p<0.05$). The SubPCP-induced extradimensional shift deficit was reversed by modafinil, and all vortioxetine doses. The extradimensional reversal deficits were normalized by 10 mg/kg vortioxetine. SubPCP also impaired NOR performance ($F(2,31)=5.46$, $p<0.01$), and 10 mg/kg vortioxetine reversed this deficit. Subchronic vortioxetine blocked SubPCP-induced impairment in AST performance at both concentrations ($F(30,417)=2.29$, $p<0.001$). Rats in the high subchronic vortioxetine group had significant increases in GAD67 ($F(2,32)=4.91$, $p<0.05$) and NR2B ($F(2,32)=5.06$, $p<0.05$) expression vs controls.

Conclusion: Vortioxetine administration reversed subchronic PCP-induced deficits in memory and executive function, suggesting that vortioxetine may be able to normalize dysregulated glutamate neurotransmission.

Policy of full disclosure: Alan Pehrson, Jessica Waller, and Connie Sanchez are employees of Lundbeck Research USA, Inc. Niels Plath is an employee of H. Lundbeck A/S.

P-42-023 Synaptic and neuroplastic mechanisms of chronic lurasidone treatment in the chronic mild stress model

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Objective: It is well-established that major depression is associated with impaired synaptic function and reduced neuronal plasticity in selected brain structures, and that such changes represent an important target of pharmacological intervention. In the present study we have investigated the ability of the second-generation antipsychotic drug lurasidone to modulate neuroplastic alterations in the chronic mild stress (CMS) model of depression.

Methods: Male Wistar rats were exposed to CMS for 2 weeks and sucrose consumption was used to distinguish between susceptible and non-susceptible animals in order to identify the molecular alterations that are relevant for stress susceptibility. Control and CMS-susceptible rats were then randomized to receive chronic vehicle or the novel antipsychotic drug lurasidone for 5 more weeks, while continuing the stress procedure, in order to evaluate the antidepressant properties and molecular changes set in motion by chronic drug treatment.

Results: After 2 weeks of CMS, we found reduced expression of the pool of BDNF transcripts with long 3#UTR that may be targeted to the synaptic compartment, suggesting the contribution of the neurotrophin to the behavioral dysfunction produced by CMS. The down-regulation of BDNF expression persisted until the end of the stress procedure in vehicle-treated rats, whereas chronic lurasidone treatment was able to revert the depressive-like behavior and normalized the BDNF mRNA levels in the prefrontal cortex of CMS rats. Moreover, we found that stressed rats display significant defects in the post-synaptic compartment, as shown by the reduced expression of PSD-95 but not of synapsin I, and that these changes were also normalized by chronic lurasidone treatment.

Conclusion: Our results demonstrate that lurasidone show antidepressant properties in the CMS model through the modulation synaptic and neuroplastic proteins. The adaptive changes produced by sub-chronic treatment with lurasidone may contribute to the amelioration of functional capacities, which are deteriorated in patients with major depression and stress-related disorders.

Policy of full disclosure: M.A. Riva has received honoraria or research support from Bristol-Myers Squibb, Dainippon Sumitomo Pharma, Eli Lilly, Servier and Sunovion. All the other authors have no financial conflicts to declare.

P-42-024 Neurobiological correlates of anhedonia: Findings based on the dimensional anhedonia rating scale

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Objective: To identify the brain regions and dopamine receptor binding associated with anhedonia in treatment resistant depression patients.

Methods: Patients with treatment resistant depression (n=15) underwent two positron emission tomography (PET) scans at baseline as part of a Deep Brain Stimulation trial: glucose metabolism using 18F-fluorodeoxyglucose and extrastriatal dopamine D2/D3 binding using 11C-FLB 457. On the day of the D2 scanning, patients completed the Dimensional Anhedonia Rating Scale (DARS), a novel questionnaire to measure anhedonia (maximum possible score: 68, where a high score reflects less anhedonia), and the Snaith Hamilton Pleasure Scale (SHAPS; maximum possible score: 14, where a high score reflects more anhedonia). Patients also completed measures of depressive symptoms

and physical activity. A group of healthy controls completed the scales but not the PET imaging (n=99).

Results: There was a statistically significant difference between depressed patients and healthy controls on the DARS (15.4+/−6.6 vs. 51.8+/−11.6, t=11.5, p<0.0001). There was a similar group difference based on the SHAPS (9.9+/−2.6 vs. 1.6+/−2.8, t=−10.6, p<0.0001). Neuroimaging correlates based on glucose metabolism and dopamine binding potential will be discussed.

Conclusion: Anhedonia is prominent in treatment resistant depression. Further research should aim to identify this symptom as a potential diagnostic and treatment biomarker.

Policy of full disclosure: The PET scan data used in this study were from a Deep Brain Stimulation clinical trial sponsored by St. Jude Medical. SJR has received travel funding from Eli Lilly and St. Jude Medical. SHK has received honoraria/research funding from AstraZeneca, Bristol Myers Squibb, Boehringer-Ingelheim, Canadian Institute of Health Research, Lundbeck, Ontario Brain Institute, Pfizer, Servier, and St. Jude Medical. AC, APS and BAS declare no conflicts.

P-42-025 Clinical depression predicts paranoia in high-risk patients

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Objective: Since the nineteenth century, causal connection between affective disorders and paranoid thinking has been one of the most interesting questions in psychiatric psychopathology. Patients with affective disorders or symptoms may have non-psychotic or psychotic paranoid symptoms. On the other hand, paranoid patients often reveal depressive or anxiety symptoms. In cross-sectional studies, causal direction between affective disorders and paranoia can not been evaluated. In a prospective follow-up study, we aimed to study whether clinical depressive or anxiety disorders predict occurrence of paranoid-like symptoms in clinical high-risk (CHR) patients.

Methods: In the EPOS project, 245 young help-seeking CHR patients were examined and prospectively followed for 18 months. At baseline, patients' current clinical SCID diagnoses, depressive and anxiety symptoms, premorbid adjustment and childhood and adolescence traumatic and distress experiences were assessed. Persecutory/paranoid symptoms were assessed by the Structured Interview for Prodromal Syndromes at baseline and at the 9 and 18 months follow-up. Baseline paranoid symptoms were subtracted from follow-up paranoid symptoms (follow-up paranoia). The association between premorbid and baseline factors and follow-up paranoia were analysed with hierarchical linear model.

Results: From clinical diagnoses, depressive, anxiety and somatisation disorders, as well as depressive and anxiety symptoms associated significantly with follow-up paranoia. Likewise, poor premorbid adjustment, and emotional and sexual abuse had a significant association with follow-up paranoia. In multivariate hierarchical modelling, clinical depressive and somatisation disorder, premorbid adjustment and sexual abuse predicted significantly follow-up paranoia. In post hoc analyses, also anxiety symptoms were entered into the predictive model.

Conclusion: From clinical disorders, depression and somatisation are the major predictors of paranoid symptomatology in CHR subjects. Also anxiety symptoms, especially excessive social anxiety, play a significant and independent role in occurrence of paranoid symptoms. From early developmental factors, poor premorbid social adjustment and childhood/adolescence sexual abuse may increase vulnerability to paranoid experiences.

Policy of full disclosure: None.

P-42-026 Vortioxetine, a multimodal-acting antidepressant with distinct pharmacological properties - A comparative preclinical study vs. SRIs

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Objective: The antidepressant vortioxetine is a 5-HT3, 5-HT7 and 5-HT1D receptor antagonist, 5-HT1B receptor partial agonist, 5-HT1A receptor agonist and inhibitor of the 5-HT transporter (SERT). The aim of this investigation was to compare vortioxetine with SSRIs or SNRIs in rat assays predictive of anxiolytic and antidepressant activity and cognitive enhancement.

Methods: Effects on 5-HT-induced spontaneous inhibitory postsynaptic currents (sIPSCs) were recorded in CA1 pyramidal cells of hippocampus slices using whole cell patch recordings. Since theta rhythms are involved in memory formation and 5-HT3 receptor-expressing interneurons regulate the strength of theta rhythms by controlling the output of pyramidal cells, theta rhythms were recorded in vivo using electroencephalographic recordings. Acute anxiolytic activity was measured as reduction of conditioned fear-induced ultrasonic vocalization and increase of social interaction time under unfamiliar aversive light conditions. Antidepressant activity was measured by means of the forced swim test in female rats during a progesterone withdrawal (PWD) phase.

Results: Vortioxetine blocked 5-HT-induced sIPSCs, likely through blockade of 5-HT3 receptors on interneurons; escitalopram was inactive. Vortioxetine increased theta power during the active wake state; escitalopram and duloxetine were inactive. Vortioxetine showed acute anxiolytic activity in both assays; duloxetine and paroxetine were inactive in the conditioned fear and social interaction tests, respectively. Chronic dosing with vortioxetine, but not fluoxetine or duloxetine, produced an antidepressant-like effect during PWD. Furthermore, in rats chronically treated with fluoxetine and subsequently exposed to PWD, addition of a 5HT1A receptor agonist or a 5-HT3- or 5-HT7-receptor antagonist failed to produce antidepressant-like activity. The latter suggests that a complex interaction between SERT inhibition and > 1 receptor activity is involved in the antidepressant-like activity of vortioxetine in this model.

Conclusion: Vortioxetine differs from SSRIs and SNRIs in preclinical assays of anxiolytic and antidepressant activity and cognitive enhancement. This supports a crucial role for vortioxetine's receptor activities.

Policy of full disclosure: CS, ED, YL, SCL are fulltime employee at Lundbeck Research. MG is a consultant to Lundbeck Research.

P-42-027 Cognitive impairment in depression

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Objective: To study cognitive function in depressed patients, between 18 to 45 year old.

Methods: It were studied 28 patients with depression and 10 healthy controls during six months, using MINI, MADRS and Cognitive test to determine cognitive level, visual memory and executive function, as well as problems related at work and concentration to read and do homework.

Results: Eighty percent of patients with depression (minor, mild and major depression had cognitive impairment, and 20 percent of healthy people had it too. Statistical analysis was done with SPSS.

Conclusion: Most of the patients with depressed mood had cognitive impairment (visual attention and executive function) with a correlation with social problems at home and work. It would neccessary to sensibilize mental health professionals to explore cognitive function in depressed patients, asking about it or using appropiate scales of measure. To know about the degree of cognitive impairment will be usefull to determine psychopharmaology and psychotherapy treatment.

Policy of full disclosure: None.

P-42-028 Having difficulty concentrating or making decisions is a useful clinical cue for depression

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Objective: To determine which symptoms within the DSM criteria for a Major Depressive Episode (MDE) might have the most utility for clinical decision making among practitioners.

Methods: Interview data were collected by telephone from randomly selected working adults in Alberta, Canada, in 2009. Step-wise regression models were built from those reporting depressed mood or loss of interest. The independent variables are the seven remaining depressive symptoms. The following dependent variables were considered relevant to clinical decision making: (1) a sufficient number of symptoms for an MDE, (2) significant distress or impaired ability to function, (3) hopelessness, and (4) previous help-seeking for a mental health problem.

Results: Of the sample, 26% (N=743 of 2817) reported a period of depressed mood or loss of interest. A single symptom, "Difficulty concentrating or making decisions", captured 52% of the variance in modeling a sufficient number of symptoms for an MDE. As expected, this model improved incrementally with each additional depressive symptom (67%, 76%, 83%, 92%), since these define the threshold. "Difficulty concentrating or making decisions" captured 27% of the variance in modeling distress or impairment (33%, 38%, 39%, incrementally). "Feelings of worthlessness or guilt" captured 20% of the variance in modeling hopelessness (29%, 31%, 32%, incrementally). Help-seeking for a mental health problem could not be modeled (8%, with 1 symptom, 13% with 4).

Conclusion: In working adults, the use of a single depressive item was most useful in modeling a sufficient number of symptoms for an MDE, was somewhat useful in modeling distress/impairment and hopelessness, but was not useful in modeling help-seeking. Most of the utility of the step-wise models was captured with the first depressive item. "Difficulty concentrating or making decisions" yielded the most information and may be a worthwhile clinical cue for practitioners presented with a working adult.

Policy of full disclosure: Noam Ship is a full time employee of Lundbeck Canada Inc.

P-42-029 Resilience and vulnerability are dose-dependently related to corticosterone treatment in adult but not adolescent rats

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Objective: Adolescence is a key developmental transition period characterized by highly plasticity, which renders heightened risks for stress-related disorders. Little is known about the effect of different severity of adolescent stress on the development of vulnerability and resilience.

Methods: Both adolescent (postnatal days (PND) 30) and adult (PND 70) male rats were allocated into three treatment regimens, receiving daily injections of either high (40 mg/kg) or low (5 mg/kg) doses of CORT or vehicle consecutively for 21 days. Both short-term and long-term effects of treatment regimens on behaviors, cognition and HPA axis activity were assessed.

Results: Adulthood 40 mg/kg, but not 5 mg/kg CORT treatment significantly decreased sucrose preference/intakes, heightened startle reflexes, decreased central exploration, impaired spatial learning, caused adrenal atrophy and decreased endogenous plasma CORT within 1-week of CORT cessation. After 4-week recovery, 5 mg/kg CORT pretreatment significantly increased central exploration and spatial learning, 40 mg/kg CORT impaired reversal learning in adult rats. Although adolescent 40 mg/kg CORT also caused adrenal atrophy and reduced plasma CORT, no deficit in behaviors were found in short-term and long-term. Both 5 mg/kg and 40 mg/kg CORT significantly increased short-term sucrose intakes/preference, reduced startle reflexes and enhanced pre-pulse inhibition in adolescent rats. After 4-week recovery, while adolescent 5 mg/kg CORT pretreatment significantly enhanced reversal learning, 40 mg/kg pretreatment significantly enhanced pre-pulse inhibition and spatial learning.

Conclusion: CORT exert an inverted U-shape effect on adult rats. 40 mg/kg CORT induced depressive-like behaviors, anxiety-like behaviors, and deficits in cognitive ability in short-term while 5 mg/kg CORT enhanced spatial learning in long-term. However, this dose-effect relationship did not exist in adolescent rats. Both adolescent 5 mg/kg and 40 mg/kg CORT treatment appeared to favor behavioral functioning. This study opened the possibility of using stress inoculation effects to promote building resilience in adolescence.

Policy of full disclosure: None.

P-42-030 Alterations of the cortisol and dehydroepiandrosterone (DHEA) in perinatal depression

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Objective: The purpose of this study is to investigate the alterations of the hypothalamic–pituitary–adrenal (HPA) axis hormones, especially salivary cortisol and dehydroepiandrosterone (DHEA) in perinatal depression.

Methods: 44 patients with depression and 217 normal subjects in perinatal period were included in this study. Edinburgh Postnatal Depression Scale (EPDS) and Beck Depression Inventory II (BDI-II) were performed. The subjects below 10 points of EPDS score or below 13 points of BDI-II score were classified to normal subjects. Among the subjects more than 11 points of EPDS score or more than 14 points of BDI-II score were diagnosed depression by DSM-IV TR by psychiatrists. All subjects were to collect their saliva in each 4 collecting tubes, immediately upon awakening (IA), 30 minutes after awakening (30A), 60 minutes after awakening (60A) and before bedtime (BB).

Results: The number of subjects in antenatal period were 103, and antenatal depression (AD) patients were 21, antenatal normal (AN) subjects were 82. The number of subjects in postnatal period were 114, and postnatal depression (PD) patients were 23, postnatal normal (PN) subjects were 91. Salivary cortisol levels in subjects with AD collected IA, 30A and 60A were lower than with AN subjects significantly except BB. Salivary cortisol levels in subjects with PD collected 60A only were lower than with PN subjects significantly. Salivary DHEA levels in subjects with both AD and PD were lower than with normal subjects significantly. Also cortisol/DHEA ratio (F/D ratio) in subjects with both AD and PD were much higher than with normal subjects significantly.

Conclusion: These results suggest that the blunted response was shown in AD, and the characteristics between AD and PD are different. Also the differences of salivary DHEA levels and F/D ratio between subjects with PD and normal subjects are suggested the one of the key points of difference among both groups.

Policy of full disclosure: None.

P-42-031 A clinical case of velaxin therapy in a teenager

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Objective: To briefly characterize the state of mental health in a teenager with a revealed mild depressive episode and assess antidepressant Velaxin in the therapy used for the treatment.

Methods: The clinical-psychopathological and pathopsychological methods.

Results: After the first administration of the medication the patient in conversation complained about the frequent and pronounced effect of "déjà vu" that lasted for 10–15 seconds and manifested itself 3–4 times a week. Also he complained about low spirits, apathy, loss of appetite and deterioration of memory. Doctor prescribed him antidepressant Velaxin (the dosage of 300 mg per day divided into two doses), Nootropil (the dosage of 1600 mg per day divided into two doses) and Mexidol (the dosage of 125 mg once a day in the evening). During the third week of the Velaxin therapy the patient showed some improvements in his condition: the spirits improved, apathy disappeared. The effect of "déjà vu" manifested itself 1–2 times a week and became less pronounced. At the same time the decision was made to leave the same dosage of the main medication, Velaxin. During the sixth week of the therapy the mental health of the teenager remained good. After the next talk, in order to avoid the withdrawal syndrome it was decided to gradually decrease the Velaxin dosage by 50 mg in the next week of the therapy. When the dosage of the antidepressant was reduced to 37.5 mg per day the withdrawal syndrome was not revealed. During the twelfth week of the therapy the patient stopped taking the antidepressant, the effect of "déjà vu" did not occur anymore.

Conclusion: Velaxin can be applied in the therapy of such a mental disorder as mild depressive episode in the teenage patients. The treatment should start with a dosage of 300 mg per day with its gradual reduction to 37.5 mg per day against the background of a good mental health.

Policy of full disclosure: None.

P-42-032 The cognitive effects of vortioxetine are associated with increased expression of neuroplasticity markers

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Objective: The antidepressant vortioxetine acts as an antagonist at 5-HT3 and 5-HT7 receptors, partial agonist at 5-HT1B receptors, agonist at 5-HT1A receptors, and a SERT inhibitor. In contrast to typical SSRIs, vortioxetine enhances long-term potentiation, the cellular basis of memory, in hippocampal slices and improves cognitive performance in preclinical studies [1,2]. In addition, recent clinical studies reveal a role for vortioxetine in alleviating cognitive dysfunction in depressed subjects [3]. However, the underlying molecular mechanism by which vortioxetine augments memory performance remains unknown. We examined the effect of vortioxetine and the putative antidepressant ketamine on mRNA and protein expression of various synaptic markers that play a central role in protein synthesis and plasticity.

Methods: Transcription of neuroplasticity-related genes was measured by quantitative PCR and protein levels assessed by western blot analysis in frontal cortex and hippocampus at various time points following acute vortioxetine (10 mg/kg, i.p.) or ketamine (10 mg/kg, i.p.) treatment in adult male rats.

Results: Vortioxetine and ketamine treatment increased mRNA levels of mTOR, spinophilin, mGluR1, and HOMER3 in the frontal cortex 8 h post-injection. Levels of phospho-mTOR at Ser2448, a marker of mTOR activation, were elevated in the frontal cortex 24 h following acute vortioxetine treatment. Moreover, protein levels of some glutamate markers, including phospho-Tyr1472 of the GluN2B subunit of the NMDA receptor, a site implicated in stabilization of receptors at the synaptic membrane, were increased in the frontal cortex relative to vehicle-injected animals.

Conclusion: Together, these results suggest that vortioxetine affects pathways involved in protein translation and glutamatergic signaling at the synapse. The direct activity of vortioxetine at multiple 5-HT receptors may trigger activation of these signaling cascades, leading to improvement of cognitive dysfunction [1].

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Policy of full disclosure: Employee of Lundbeck Research USA.

P-42-033 Randomised, double-blind study of vortioxetine versus venlafaxine in adults with major depressive disorder (MDD)

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Objective: This randomised, double-blind 8-week comparator study compared efficacy and tolerability of fixed-dose treatment with multimodal-acting antidepressant vortioxetine 10 mg/day and venlafaxine XR 150 mg/day (SNRI) in MDD patients from Asia (China, South Korea, Taiwan and Thailand).

Methods: Eligible patients aged 18–65 years with a diagnosis of MDD and a Montgomery-Åsberg Depression Rating Scale (MADRS) total score >=26 were randomised (1:1). The primary endpoint was change from baseline to Week 8 in MADRS total score analysed by ANCOVA (FAS, LOCF), using a non-inferiority test margin of ±2.5 MADRS points. Pre-defined secondary endpoints included MADRS response and remission rates, anxiety symptoms (HAM-A), global clinical judgment (CGI), overall functioning (SDS), and health-related quality of life (Q-LES-Q).

Results: On the primary efficacy endpoint at Week 8, non-inferiority was established with a difference between vortioxetine (n=211) and venlafaxine (n=226) of −1.2 MADRS points in favour of vortioxetine (95% CI: -3.0 to 0.6; p=0.1989). The MADRS total score decreased (improved) from 32.3±4.6 at baseline to 13.6±9.6 (vortioxetine) and from 32.3±4.5 to 14.8±10.4 (venlafaxine) (FAS, LOCF). At Week 8, the HAM-A and SDS total scores, CGI and Q-LES-Q scores, and response and remission rates demonstrated similar improvement for vortioxetine and venlafaxine, with MADRS response rates of 66.5% (vortioxetine) vs 61.4% (venlafaxine) and remission rates of 43.1% (vortioxetine) vs 41.4% (venlafaxine) (LOCF). Fewer vortioxetine than venlafaxine patients withdrew for any reason (18.0% versus 27.4%) or for adverse events (6.6% vs 13.7%). The most frequent adverse events were nausea, dizziness, dry mouth, and decreased appetite.

Conclusion: Vortioxetine was at least as efficacious as venlafaxine in this MDD study and was safe and better tolerated than venlafaxine.

Policy of full disclosure: This study was sponsored by H. Lundbeck A/S.

P-42-034 Effects of levomilnacipran er on measures of attention in a phase III trial of major depressive disorder

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Objective: To evaluate changes in cognitive measures in patients with major depressive disorder (MDD) treated with levomilnacipran ER (LVM) versus placebo (PBO), and assess relationships between cognitive changes and depression symptoms.

Methods: In an 8-week study of LVM 40–120 mg versus PBO in adult patients with MDD (NCT00969709), cognitive assessments included change from baseline on the Bond-Lader Visual Analog Scales (VAS) of Mood and Alertness and the Cognitive Drug Research (CDR) System. The CDR tests speed and accuracy on 3 computerized tasks (Simple Reaction Time, Digit Vigilance, and Choice Reaction Time); test results are used to derive 4 composite scores: Power of Attention (PoA), Continuity of Attention (CoA), Cognitive Reaction Time (CogRT), and Reaction Time Variability (RTV). Post hoc analyses evaluated relationships between changes in cognitive measures and baseline depressive symptoms (as measured by MADRS Total and Item 6 [Difficulty Concentrating] scores). Relationships between MADRS response (⩾50% improvement) and changes in cognitive measures were assessed.

Results: Of 429 ITT patients, 187 PBO and 182 LVM patients had valid Week 8 cognitive assessments and were included in the analyses. Greater improvement for LVM versus PBO in depressive symptoms was accompanied by greater improvement over PBO in all measures of attention (CoA, P=0.0016; PoA, P=0.0382; RTV, P=0.0237;) except CogRT (P=0.3409). There was no significant correlation between change in attention measures and baseline (or change in) MADRS scores. However, LVM MADRS responders experienced significant improvements from baseline in PoA, CoA, and RTV; in contrast, LVM non-responders and PBO patients did not show significant improvements in cognitive measures (except for significant improvement in PoA for PBO responders).

Conclusion: LVM treatment was associated with significant improvement over PBO in depressive symptoms and cognitive measures. MADRS response in LVM-treated patients was associated with significant improvement on most cognitive measures.

Policy of full disclosure: This study was funded by Forest Laboratories, Inc.

P-42-035 An international study of the grid-hamd: Has it fulfilled its promise?

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Objective: An international group developed the GRID-HAMD to address many critiques of the HAM-D and improve its administration. The GRID-HAMD provides novel grid scoring, structured interview guide and scoring conventions on the same page as each item, and revised anchor points for problematic or inconsistently rated items. The purpose of this study was to assess the success of this effort.

Methods: A survey distributed to 74 experienced clinical trial raters included 20 questions about the usability and ease of use of the GRID-HAMD, rated from strongly disagree to strongly agree. Raters were also asked to compare the GRID-HAMD with the SIGH-D by responding to four statements with answers ranging from 1=GRID-HAMD to 7=SIGH-D.

Results: Sixty questionnaires were completed (81%). Most raters agreed that wording of GRID-HAMD questions made it easy to administer (80%), the conventions were clear (85%) and helpful (90%), and guidelines for rating symptom intensity were clear (82%). Fewer rated it "easy to decide on a frequency level" (65%). A large majority (87%) thought "having the scoring conventions integrated into the interview guide has made scoring easier." More than half (57%) of 46 raters who had used both preferred the graphical layout. However, slightly more preferred the SIGH-D for its "ease of use" (52% vs. 41%) and "efficiency" (40% vs. 34%), and expressed "overall preference for the SIGH-D" (47% vs. 40%).

Conclusion: The raters evaluated the clarity and ease of use of the GRID-HAMD positively. They prefer the graphical layout that places each item with its interview questions and conventions all on the same page. Surprisingly, the raters did not indicate overall preference for the GRID-HAMD versus the SIGH-D. The respondents indicated several areas of improvement and highlighted the #most difficult# items for both instruments.

Policy of full disclosure: Authors are affiliated with MedAvante.

P-42-036 Correlation analysis of hair cortisol levels in female depressions

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Objective: To detect the hair cortisol level and the cumulative and retrospective hypothalamic-pituitary- adrenal (HPA) axis function in the first-episode and recurrent female patients with depression.

Methods: We used the Hamilton Depression Scale (HAMD), Hamilton Anxiety Scale (HAMA) to evaluate the clinical symptoms of 35 female depressions (22 cases of first-episode, 13 cases of recurrent) and 30 healthy controls. We collected the hair samples by scissoring hair as close as possible to the scalp of the particepates. Since the hair grows approximately 1 centimeter per month, we used the 1 centimeter length interception of hair close to the scalp as the representation of cortisol level of patients during the episode duration and baseline in controls. We selected 1 centimeter length after the episode of disease and scissored 1centimeter length interception to represent the hormone levels of patients before the disease episode. Electrochemiluminescence immunoassay was used to measure the hair cortisol hormone levels. And we compared the differences of hair cortisol levels among first-episode and recurrent patients with depression and control subjects.

Results: Before the disease episode, the hair cortisol levels in first-episode patients are lower than that in control subjects (t=2.280,

p=0.027).No significant differences were found between the hair cortisol levels of recurrent patients compared to the control subjects and first-episode patients(t1=−1.332,p1=0.190; t2=0.678 ,p=0.503). During the illness, the hair cortisol levels in first-episode patients are higher than that in control subjects (t=3.284,p=0.002). No significant differences were found between the hair cortisol levels of recurrent patients compared to the control subjects (t=0.830,p=0.412). Moreover, the hair cortisol levels in first-episode patients was significant higher than that in recurrent patients in the duration (t=2.209,p=0.034). We found no correlation between the hair cortisol levels and the HAMD/HAMA scale scores (HAMD: r=−0.203,p=0.319;HAMA:r=−0.002,p=0.991).

Conclusion: The function of adrenal gland has changed in female patients with depression which might be different between the first-episode and recurrent patients. These findings suggest that measurement of cortisol in hair could serve as a retrospective biomarker of hypothalamic-pituitary-adrenal (HPA) axis function in female depression.

Policy of full disclosure: None.

P-42-037 Herbal medicine for hospitalized patients with severe depressive episode: A non-randomized controlled study

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Objective: The purpose of this retrospective study was to evaluate the effectiveness and safety of herbal medicine used in hospitalized patients with severe depressive episode.

Methods: In this retrospective, nonrandomized controlled study, 146 patients with severe depressive episode were hospitalized between September 2009 and November 2013. While all of them were treated with conventional psychotherapeutic agents, 78 received additional herbal medicine. The severity of depressive symptoms was measured using 24-item Hamilton Rating Scale for Depression (HAMD-24) on a weekly basis. Clinical response, remission rate and incidence of adverse events were compared between patients treated with (n=78) and without (n=68) herbal medicine.

Results: The two groups had similar average length of hospital stay with approximately 28 days and were not different in the use of psychotherapeutic agents during hospitalization. However, survival analysis revealed that patients with herbal medicine exhibited significantly higher clinical response (RR=2.179, P<0.001) and remission rate (RR=5.866, P<0.001) compared to those without herbal medicine. Herbal medicine-treated patients experienced remarkably lower incidences of physical tiredness, headache, palpitation, dry mouth and constipation, but had a significantly higher incidence of digestive discomfort compared to patients without herbal medicine.

Conclusion: Additional herbal medicine is capable of enhancing antidepressant response and reducing certain adverse effects associated with psychotherapeutic agents. Herbal medicine can be considered as an effective and relatively safe therapy for severe depressive episode (Trial Registration: ChiCTR-OCH-13003864).

Policy of full disclosure: None.

P-43. Schizophrenia C

P-43-001 White matter alterations in first-episode deficit and non-deficit schizophrenia patients and their first-degree relatives - a combining TBSS and VBM study

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Objective: Clinically and genetically heterogeneity has been greatly contributed to the lack of progress in our understanding of schizophrenia. The categorization of deficit schizophrenia (DS), differ from the nodeficit schizophrenia (NDS), is regarded as one of the most promising attempts to reduce the heterogeneity within schizophrenia. Present study aimed to investigate the differences in white matter (WM) alterations between first-episode DS and NDS patients and explore the potential endophenotype of subgroups.

Methods: Structural MRI and diffusion tensor imaging data of first-episode DS (n=44) and NDS (n=44) patients, their unaffected first degree relatives (n=67), and age-and sex matched health controls (n=84) were collected (table 1). Both the WM integrity measures and WM volume (WMV) were examined using tract-based spatial statistics (TBSS) and voxel-based morphometry (VBM) analysis.

Results: 1) Both DS and NDS patients showed WMV reduction in cerebellum posterior lobe and WMV enlargement in bilateral frontoparietal regions, while 2) DS patient showing selective WMV reduction in bilateral posterior limb of internal capsule (PLIC), when compared with both healthy controls and NDS patients(figure 1,2). Moreover, 3) the first degree relatives of DS patients shared the WMV deficit in right insula (part of right PLIC cluster) with probands, representing an endophenotype in DS(figure 3). In addition to volumetric alterations, 4) DS patients also showing more sever white matter integrity deficit, indexed by fractional anisotropy(FA) reduction, in bilateral sub_gyral of parietal lobe and left precuneus than NDS patients do(figure 4). 5) The WMV of bilateral PLIC and right insula, as well as the FA value in left precuneus were inversely correlated with negative symptoms in patients.

Conclusion: These results suggested that significant WM disruption, especially volume deficit in PLIC, may represent a neurobiological marker of DS.

Policy of full disclosure: None.

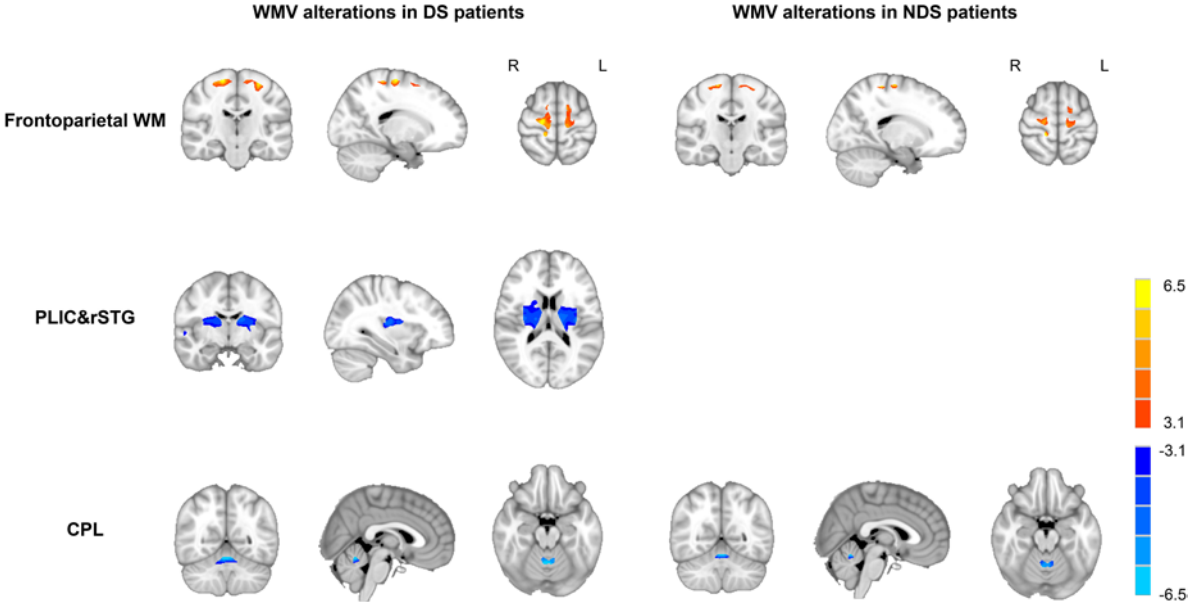

Figure 1. WMV alterations in first-episodic DS (left panel) and NDS (right panel) patients when compare with sex- and age-matched healthy controls:

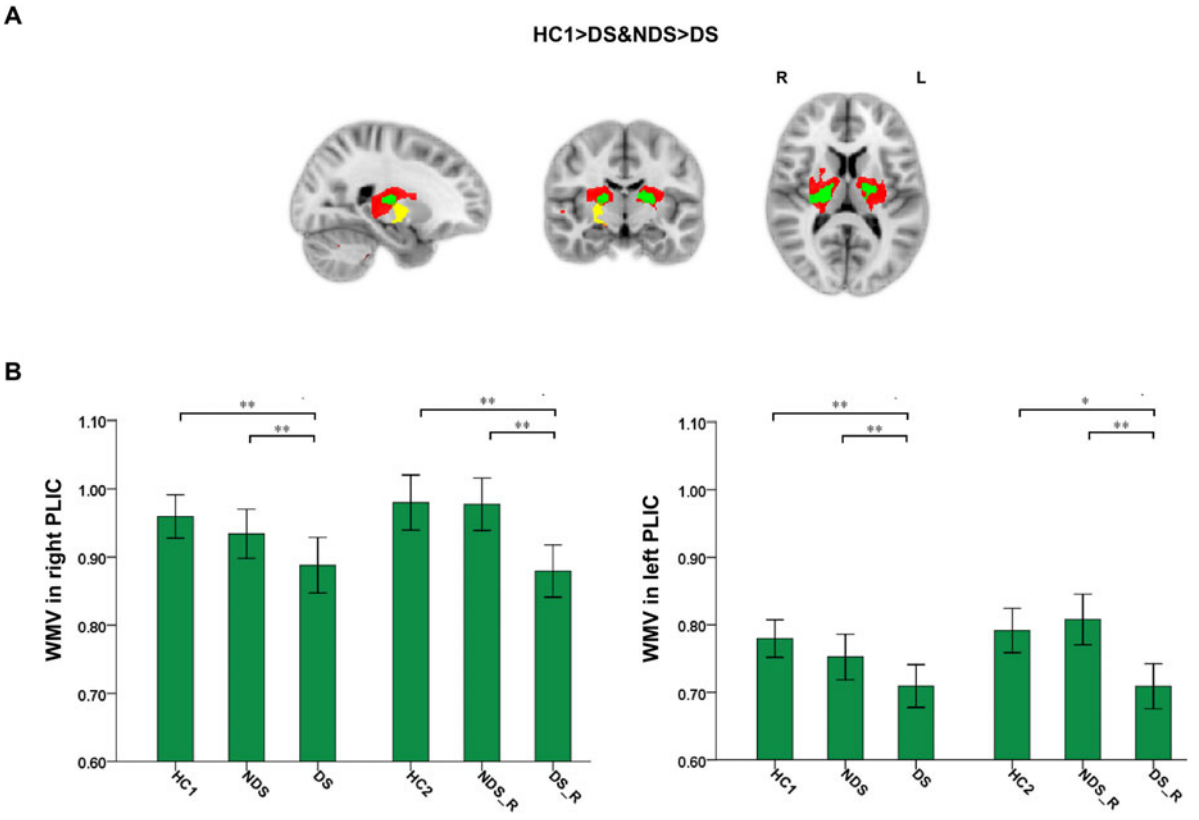

Figure 2. DS patients showing selective WMV reduction in bilateral PLIC (defined as the overlapped regions of HC1>DS and NDS>DS) when compare with NDS patients (yellow) and HC1 (red):

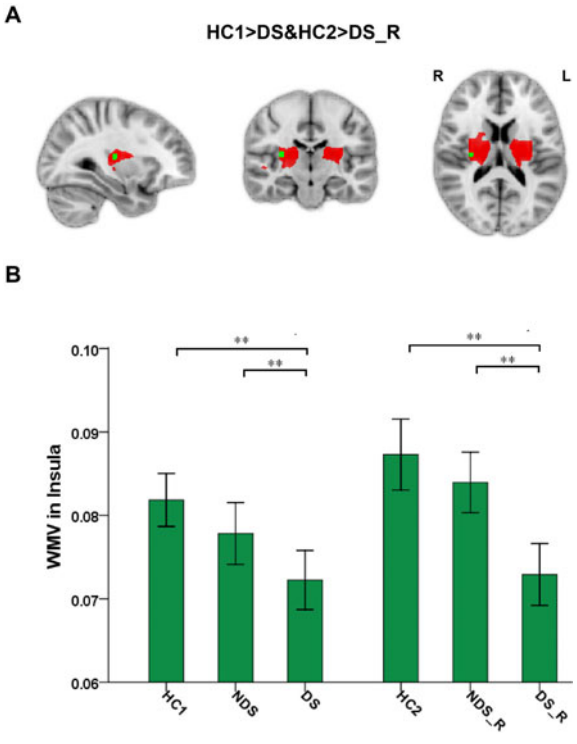

Figure 3. Endophenotype of DS:

P-43-002 **Gray matter alterations in first-episode patients with deficit or non-deficit schizophrenia and their first-degree relatives**

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Objective: Different patterns of gray matter (GM) abnormalities in deficit schizophrenia (DS) and non-deficit schizophrenia (NDS) have been reported. The aim of the present study was to examine the structural brain alterations in first-episode DS/NDS patients and to explore the potential difference in genetic risk of DS and NDS.

Methods: The structural magnetic resonance imaging (sMRI) was performed in 132 first-episode patients with schizophrenia (44 DS and 88 NDS), 67 of their first-degree relatives and 84 healthy controls (44 and 40 matched with patients and relatives, respectively). GM volume (GMV) was assessed by using Voxel-based Morphometry (VBM) and compared between groups. Correlation analysis was also carried out between GMV and clinical symptoms in patients.

Results: DS patients displayed more severe GMV reduction in the cerebellar culmen than NDS patients. The GMV reduction in cerebellar culmen was also observed in the first-degree relatives of DS patients but not in the relatives of NDS patients, suggesting possible different genetic risk in DS and NDS. Moreover the right supramarginal gyrus (rSMG) was significantly smaller in DS patients than both NDS patients and healthy controls, while NDS patients did not show any significant GMV difference compared to health controls in this area. In addition, The GMV of rSMG was inversely correlated with negative symptoms.

Conclusion: The present study revealed distinct spatial patterns of gray matter alterations and possible different genetic risks in DS and NDS.

Policy of full disclosure: None.

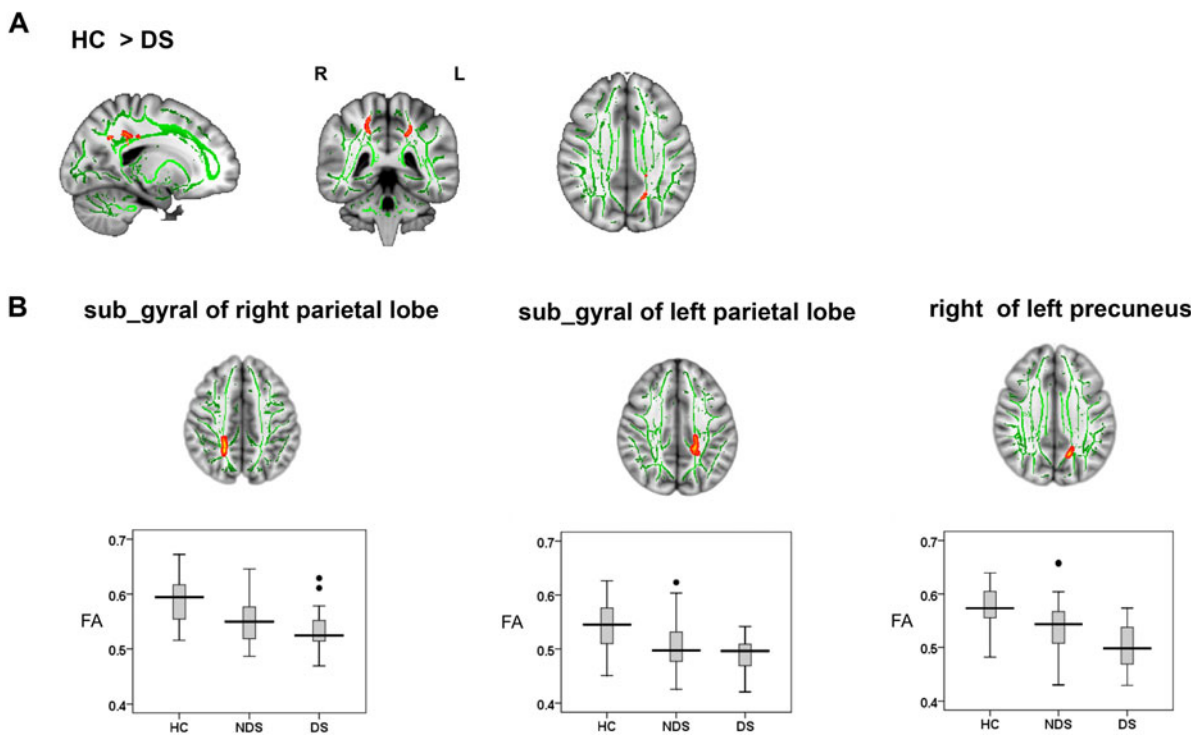

Figure 4. Voxel-wise comparison of FA maps:

Table1. Demographic summary of the FES patients their first-degree relatives and health control.

	NDS (n=44)	DS (n=44)	HC1 (n=44)	NDS_R (n=42)	DS_R (n=25)	HC2 (n=40)
Gender(f/m)	18/26	18/26	18/26	23/19	12/13	22/18
Age	23.16±6.99	22.91±6.89	22.55±6.25	43.00±7.86	44.00±8.06	42.53±9.19
tWMV	0.43±0.05	0.42±0.06	0.43±0.04	0.43±0.04	0.43±0.05	0.44±0.06
WBV	1.17±0.12	1.16±0.13	1.18±0.09	1.11±0.09	1.12±0.11	1.14±0.11
Education years	12.25±2.51	11.45±2.66	12.72±2.41	10.00±3.88	9.00±3.78	10.23±4.71
DUP (months)	6.99±12.10	19.89±29.88*				
Age of Onset	22.58±7.04	21.79±7.56				
PANSS-T	88.39±16.29	95.95±16.82*				
PANSS-P	25.41±6.07	21.95±6.88*				
PANSS-N	16.57±5.76	27.57±7.53*				
PANSS-G	46.01±9.27	46.43±9.68				

Note: Demographic data are shown as mean ±standard deviation; *, $p<0.05$;

Aberrations: DS, first episode deficit schizophrenia patients; NDS, first episode non-deficit schizophrenia patients; HC1, healthy controls age-and sex-matched with DS and NDS; DS_R, first degree relatives of DS patients; NDS_R first degree relatives of NDS patients; HC2, healthy controls age- and sex-matched with DS_R and NDS_R; tWMV, total white matter volume; WBV, whole brain volume= total gray matter volume + total white matter volume; DUP, duration of untreated psychosis; PANSS-T, PANSS total scores; PANSS-P, PANSS positive symptoms subscale scores; PANSS-N, PANSS negative symptoms subscale scores; PANSS-G, PANSS general psychopathological symptoms subscale scores.

P-43-003 The contingent negative variation in patients with deficit schizophrenia and or bipolar I disorder patients with psychotic features measurement and correlation with clinical characteristics

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Objective: The purpose of this study was to assess contingent negative variation (CNV) in patients with first episode and drug-naïve deficit schizophrenia (DS) or bipolar I disorder (BP I) with psychotic features. The study also investigated correlations between CNV and clinical characteristics in DS and BP I.

Methods: We elicited a CNV using an alarm (S1)-imperative (S2) paradigm in patients with DS (n=30) or BP I with psychotic features (n=33) and in healthy controls (n=40). A general linear model was used to compare CNV potentials among the three groups, and partial correlation was used to investigate the relationship between CNV features and clinical characteristics of patients with DS or BP I.

Results: CNV amplitude was significantly smaller and reaction time significantly longer in the DS and BP I groups than in healthy controls. Post-imperative negative variation (PINV) interval was significantly shorter in the DS group than in healthy controls. The onset latency of CNV expectancy wave was significantly longer and PINV area significantly smaller in the DS group than in the other groups. In the DS group, CNV amplitude and PINV interval correlated negatively with the subscale of negative symptoms on the PANSS; CNV amplitude also correlated negatively with disease duration. In the BP I group, CNV amplitude and reaction time showed no correlation with clinical features.

Conclusion: CNV amplitude is a common trait marker for psychosis. The onset latency of CNV expectancy wave appears to be a specific trait marker and may be used to identify candidate genes for DS.

Policy of full disclosure: None.

P-43-004 Effects of the putative antipsychotics D- and L-govadine on disrupted performance of the touchscreen-based paired associates task following acute MK-801 in rats

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Objective: Tetrahydroprotoberberines, such as D- and L-govadine, are novel compounds derived from traditional medicine that have shown promise in treating some symptoms of schizophrenia. The present experiments assessed the effects of D- and L-govadine on the Paired Associates Learning (PAL) task in rats. The PAL task is part of the CANTAB battery and is impaired in patients with schizophrenia and has been adapted for use with rodents using touchscreen-equipped operant chambers with the hope of unifying preclinical and clinical research. The specific objectives of this study were to: 1) examine the effects of acute NMDA receptor antagonism as a model for schizophrenia on performance of the PAL task; and 2) test the effects of the putative antipsychotics, D- and L-govadine on the effects of NMDA receptor antagonism on the task.

Methods: Male Long-Evans rats were trained to perform the PAL task in touchscreen-equipped operant chambers. Following training, they were treated with saline, the NMDA receptor antagonist MK-801 (0.15 mg/kg; i.p.), D-govadine (1 mg/kg; s.c.), L-govadine (1 mg/kg; s.c.) or a combination of MK-801 and one isomer of govadine in a counterbalanced order.

Results: Acute MK-801 significantly reduced the number of trials completed, impaired accuracy, and increased the number of errors in the PAL task. Administration of L-govadine, but not D-govadine, prior to MK-801 significantly improved accuracy and reduced errors compared to MK-801 alone. L-govadine alone, but not D-govadine, reduced errors compared to vehicle. L-govadine, but not D-govadine, also significantly increased latency to make a selection in the task.

Conclusion: These data establish disruptive effects of acute MK-801 treatment on performance of the PAL task and suggest that L-govadine may have properties consistent with a compound useful in the treatment of the cognitive symptoms of schizophrenia.

Policy of full disclosure: None.

P-43-005 Neuroimmunoendocrine interrelationships in long-term treatment of schizophrenic patients with quetiapine

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Objective: Nervous, immune and endocrine systems are integral parts of general adaptation, and peculiarities of neuroimmunoendocrine interactions to significant extent determine individual organism's adaptation. Objective was detection of peculiarities of neuroimmunoendocrine interrelations in schizophrenic patients under long-term treatment with neuroleptic quetiapine.

Methods: We examined 11 paranoid schizophrenic patients aged from 20 to 45 years, 5 men and 6 women. Patients received antipsychotic quetiapine (Ketilept, Hungary) both as maintenance therapy for not less than 6 months and in the process of inpatient treatment. The psychometric scale PANSS was used to estimate the dynamics of psychopathological symptomatology during treatment. The immunological examination included the definition of phenotypes of surface receptors of immunocompetent cells with method of flow cytometry (cytoflow meter FacsCalibur, Becton Dickinson, USA), cortisol, and prolactin and thyroid hormones levels with enzyme immunoassay. The research was carried out in two points: first - at admission, second - in 6 weeks of treatment.

Results: Alteration of subpopulation composition of blood lymphocytes with reduction of number of CD3+- (p=0,040) and CD3+CD4+-cells (p=0,007), increase of number of CD3+HLADR+- (p=0,004) and CD3+CD16+56+-lymphocytes (p=0,000002), level of cortisol (p=0,000001) and thyroid hormones (TSH, p=0,008; T3, p=0,000007; T4, p=0,000331) as compared with healthy persons was revealed. In the process of treatment, positive dynamic of psychopathological symptoms was accompanied by positive dynamic of CD3+- and CD3+CD4+-lymphocytes, level of cortisol and thyroid-stimulating hormone remained high against the background of trend to further heightening of level of prolactin.

Conclusion: Thus, it has been identified that acute period of schizophrenia after long-term maintenance treatment with quetiapine is accompanied by immune-hormonal imbalance with cellular immunodeficiency and activation of thyroid gland function, heightening production of thyroid hormones that heighten metabolic activity and sensitivity of organism's tissues to circulating in blood catecholamines. Findings demonstrate that deviations in neuroimmunoendocrine regulation system are a united mechanism of endogenous disorders development.

Policy of full disclosure: None.

P-43-006 Evaluation of daytime sleepiness in patients with schizophrenia treated with atypical antipsychotics: Results from a randomized, double-blind, placebo-controlled trial

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Objective: The aim of this post-hoc analysis was to compare the effects of 2 atypical antipsychotic agents, lurasidone (80 mg/d or 160 mg/d) and quetiapine XR (600 mg/d), on daytime alertness, and to evaluate the effects of daytime sleepiness (also known as daytime somnolence or sedation)on treatment outcomes in patients with an acute exacerbation of schizophrenia.

Methods: Patients who met DSM-IV-TR criteria for schizophrenia were randomized to 6-weeks of double-blind treatment with fixed doses of lurasidone 80 mg/d (n=125), lurasidone 160 mg/d (n=121), quetiapine XR 600 mg/d (n=119), or placebo (n=121), all dosed once-daily in the evening, with food. Daytime sleepiness was assessed using the Epworth Sleepiness Scale at baseline, week 3, and week 6 visits. A mediation regression approach was applied to explore the effect of daytime sleepiness on changes in agitation (assessed by PANSS-EC), cognition (assessed by CogState Computerized Schizophrenia Battery), and functional capacity (assessed by UPSA-B score).

Results: Daytime sleepiness improved in the lurasidone and placebo-treated groups but worsened in the quetiapine XR treatment group when compared to placebo (p=0.001) and to either dose of lurasidone (both p<0.01). Sedation associated with quetiapine XR treatment mediated an improvement in agitation and a worsening in functional capacity; these mediating relationships were not observed for the lurasidone or placebo treatment groups.

Conclusion: In this 6-week double-blind study, treatment with lurasidone 80 mg or 160 mg, administered once-daily in the evening, was associated with a reduction in daytime sleepiness similar in magnitude to placebo, while quetiapine XR 600 mg/d was associated with a significant increase in daytime sleepiness. Daytime sleepiness was associated with improvement in agitation and worsening in functional capacity for quetiapine XR, but not lurasidone or placebo-treated patients. Our findings suggest that daytime somnolence may have a significant impact on cognitive and functional outcomes in patients with schizophrenia.

Policy of full disclosure: Drs. Cucchiaro, Loebel and Pikalov are employees of Sunovion Pharmaceuticals Inc. Dr. Siu has received payment for consulting from Pfizer Inc., and Sunovion Pharmaceuticals Inc. Dr. Harvey serves as a consultant/advisory board member for Abbvie, Boeheringer Ingelheim, Bristol-Myers-Squibb, Forest Labs, Genentech, Roche, Shire, Sunovion, and Takeda.

P-43-007 BDNF polymorphisms are associated with schizophrenia onset and cognitive performance

M. Lv[1], X. Zhang[1]. [1]*Beijing Hui-Long-Guan Hospital, Beijing, China*

Objective: Accumulating evidence has shown that BDNF may be involved in the pathogenesis of schizophrenia. Moreover, the BDNF genetic variant, especially the Val66Met polymorphism may influence specific aspects of human cognition. This study aimed to investigate the potential association of BDNF gene polymorphisms with susceptibility to schizophrenia, the psychopathological symptoms and cognitive impairments in patients with schizophrenia in a Han Chinese population.

Methods: Four polymorphisms (rs6265, rs12273539, rs10835210 and rs2030324) of the BDNF gene were analyzed in a case-control study of 1892 Han Chinese individuals (849 patients and 1043 controls). Cognitive function was measured using the repeatable battery for the assessment of neuropsychological status (RBANS) in 598 patients and 434 controls. We assessed 825 patients for psychopathology using the Positive and Negative Syndrome Scale.

Results: In single marker analyses the rs10835210 mutant A allele was significantly associated with schizophrenia. Haplotype analyses revealed higher frequencies of haplotypes containing the mutant A allele of the rs10835210 in schizophrenia than controls. We also found that this polymorphism rs10835210 was associated with positive symptoms, and the patients carrying the mutational allele A showed more positive symptoms. Further, we found that the BDNF rs12273539 played a stronger role in cognitive performance among both schizophrenics and healthy controls, especially on attention and language; however, the BDNF rs10835210 had a weak effect on language performance in schizophrenia.

Conclusion: These findings suggest the role of these BDNF gene variants in susceptibility to schizophrenia, in clinical symptom severity and in some aspects of cognitive function.

Policy of full disclosure: None.

P-43-008 Divergent quantitative and qualitative changes in amphetamine-induced hyperlocomotion in BDNF heterozygous mice following chronic methamphetamine exposure

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Objective: Methamphetamine (METH) abuse is associated with increased risk of developing psychotic disorders that closely resemble schizophrenia. Altered brain-derived neurotrophic factor (BDNF) signalling has been implicated in both schizophrenia and the effects of METH. In mice, locomotor hyperactivity following challenge with psychostimulant drugs is used to model aspects of the positive symptoms of schizophrenia, as this behaviour is associated with enhanced subcortical dopamine release similar to what is thought to contribute to psychosis. However, simple measurements of hyperactivity may not adequately describe the effects of psychostimulant drugs on behaviour.

Methods: We compared quantitative and qualitative locomotor activity measures to assess the effects of chronic METH pretreatment on hyperactivity following amphetamine challenge in BDNF heterozygous mice (HETs) and wild-type controls (WT). Starting in late adolescence, BDNF HETs and WTs were treated for three weeks with escalating doses of METH or saline. Following a 2-week drug withdrawal, mice were challenged with saline or amphetamine, and locomotor behaviour was measured using photocell activity chambers. Both quantitative (distance moved) and qualitative (spatial D and entropy) analysis were performed.

Results: In addition to the expected increase in locomotor distance moved, amphetamine reduced spatial D and increased entropy, indicative of straighter locomotor paths and more random locomotor paths, respectively. At 3 mg/kg amphetamine, locomotor hyperactivity was enhanced in METH-treated WT mice, but not BDNF HETs (METH x genotype x dose x time block, $p=0.008$). In contrast, METH pretreatment reduced the effect of amphetamine to increase entropy in BDNF HETs, but had no effect in WT mice (dose x METH x genotype, $p=0.012$) or on spatial D changes.

Conclusion: These studies demonstrate divergence between quantitative and qualitative aspects of amphetamine-induced changes in locomotor behaviour in BDNF HETs following METH treatment. This finding supports the value of analysing qualitative measures of locomotion when studying the effects of psychostimulant drugs.

Policy of full disclosure: None.

P-43-009 An open-label extension study of lurasidone safety and efficacy in patients with schizophrenia previously randomized to lurasidone or risperidone

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Objective: To evaluate the safety and efficacy of lurasidone in patients with chronic schizophrenia who continued on lurasidone (LUR-LUR) or switched from risperidone (RIS-LUR).

Methods: Patients completing a 12-month, randomized, double-blind study evaluating flexibly dosed lurasidone (40-120 mg/d) versus risperidone (2–6 mg/d) entered a 6-month, open-label extension (OLE) study with flexibly dosed lurasidone (40–120 mg/d). Descriptive statistics evaluated safety and efficacy using last observation carried forward (LOCF) and observed case (OC) approaches.

Results: Among 223 patients (136 LUR-LUR, 87 RIS-LUR) who continued into the OLE study, overall discontinuation rates were 19.9% for LUR-LUR and 25.3% for RIS-LUR. Mean change in weight from OLE baseline to endpoint (OC) was −0.6 kg for LUR-LUR and −2.9 kg for RIS-LUR patients. Median changes in metabolic parameters from OLE baseline to endpoint (OC) for LUR-LUR vs RIS-LUR patients were: −4.0 mg/dL vs 4.5 mg/dL for total cholesterol, −4.5 mg/dL vs −5.5 mg/dL for triglycerides, and 0.0 mg/dL vs −3.0 mg/dL for glucose. Prolactin levels showed little median change in LUR-LUR patients and decreased in RIS-LUR patients (−17.1 ng/mL). During the OLE, extrapyramidal symptom-related TEAEs were noted in 8.1% of LUR-LUR and 6.9% of RIS-LUR patients. Discontinuation from the OLE due to a TEAE occurred in 5.1% of LUR-LUR and 6.9% of RIS-LUR patients. At OLE baseline, mean scores on the Positive and Negative Syndrome Scale (PANSS) and Clinical Global Impression-Severity (CGI-S) were 55.5 and 2.9, respectively, for all patients. In both the LUR-LUR and RIS-LUR groups, mean change from OLE baseline (LOCF) was 1.0 on the PANSS and 0.0 on the CGI-S.

Conclusion: Switching to lurasidone after 12 months of treatment with risperidone was generally safe and well tolerated, with improvement in weight and prolactin levels, in this 6-month OLE study. Patients who transitioned from risperidone to lurasidone maintained clinical stability. ClinicalTrials.gov identifier: NCT00641745.

Policy of full disclosure: Dr. Mattingly has no real or apparent conflicts of interest to disclose. All other authors report being employees of Sunovion Pharmaceuticals Inc.

P-43-010 Early response to risperidone treatment in the first episode of schizophrenia (FES) patients and its predictive value to subsequent response

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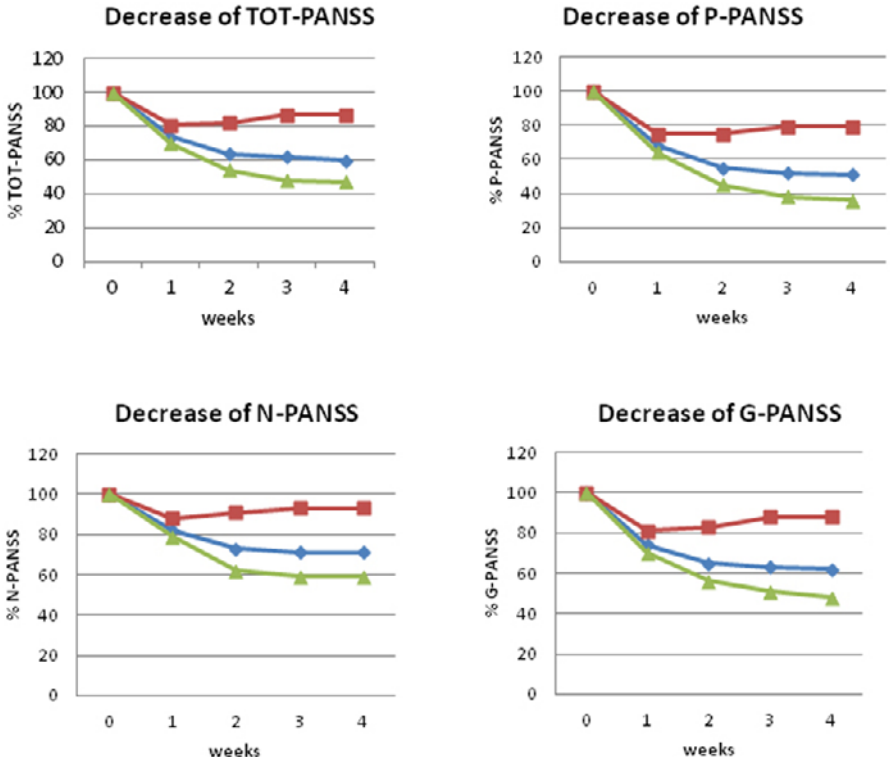
Objective: The time-course of response to AP treatment is important for management of acute treatment of schizophrenia patients. The aim of the study was to investigate whether early response in the second week can predict response in the fourth week of FES patients treated with risperidone.

Methods: FES patients were rated by PANSS in four consecutive weeks of monotherapy with risperidone. Early responders=at least 20% decrease of total PANSS after two weeks of therapy. Later responders=at least 30% decrease of total PANSS after four weeks of therapy.

Results: a) Demographic data: 35 FES patients, average age 25, average duration of schizophrenia 4 months, average total PANSS beginning score 134. b) Response rate to risperidone therapy: 63% (N=22) later responders, 37% (N=13) later non-responders. c) The relationship between early and later response (RESP)/nonresponse (NONRESP): After two-week therapy - Decrease of total PANNS #20% After four-week therapy 27 early RESP 21 RESP, 6 NONRESP 8 early NONRESP 7 NONRESP, 1 RESP After two-week therapy # Decrease of total PANSS # 30% After four- week therapy 19 early RESP 18 RESP, 1 NONRESP 16 early RESP 4 RESP, 12 NONRESP A 20% decrease of total PANSS is adequate criteria for the prediction of nonresponse after four weeks. For the prediction of response, the criteria should by higher # 30% decrease of total PANSS. d) Differences in PANSS decrease between later responders and later non-responders: viz grafs (red=nonresponders, green=responders, blue=all)-

Conclusion: FES patients are characterized by the high reactivity to the risperidone therapy. The most noticeable improvement of schizophrenic symptomatology occurs during the first two weeks of treatment. Early response/nonresponse in the second week predicts consecutive response/nonresponse in the fourth week of the therapy.

Policy of full disclosure: None.



P-43-011 The electronic schizophrenia treatment adherence registry-e-STAR. Results from Romania

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Objective: To assess prospectively (2 years) the medication usage patterns in schizophrenia patients; to document clinical efficacy and long-term treatment outcomes of Risperidone Consta (RLAI) in a naturalistic setting; to collect 2 years retrospective data in order to a more accurate comparison of the evolution after initiation with RLAI; to prospect reasons for initiation of RLAI.

Methods: e-Star is part of an international non-interventional observational registry on the usage of RLAI in daily clinical practice. 290 Romanian patients from 50 sites were enrolled. Inclusion criteria were the start or switch to a new antipsychotic medication either RLAI or oral antipsychotics. A secured web-based system was employed to capture 24 months retrospective and 24 months prospective data regarding demographics, duration of diagnosis treatment and hospitalization history, reasons for initiating the new treatment, periodic assessment of severity of illness-CGI, functioning-GAF and reports of adverse events, dosing regimen, and concomitant treatments.

Results: The duration of the diagnosis was 7.5 years in RLAI, respectively 9.5 years in the oral group. Over 61% of patients were not working. Number and lengths of hospitalizations dropped after the new treatment in both groups. Inpatients initiated on RLAI, showed a statistically decrease of hospital stays in all follow-up intervals of interest, compared to the retrospective period (all p values<0.009). Mean CGI-S scores gradually decreased over time, reaching changes at the end of the 24 months of 1.63 (SD=1.25) in the RLAI group, and 1.51 (SD=1.23) in the oral antipsychotic group. Subjects were more often switched to RLAI due to insufficient efficacy and compliance issues.

Conclusion: The Romanian sub study of e-STAR emphasized the fact that although more sever patients were treated with RLAI, they registered more evident improvements, lower hospitalizations and discontinuation rates.

Policy of full disclosure: The Romanian e-STAR sub study has been initiated and supported by Janssen Romania.

P-43-012 Prospective naturalistic survey of safety of risperidone long acting injectable (RLAI) in Romanian schizophrenia patients

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Objective: To confirm the safety of risperidone long-acting injectable under marketed conditions. Secondary objectives were to investigate the reasons of initiation of treatment, effectiveness of RLAI, and clinical outcome.

Methods: 1354 subjects were recruited by 253 investigational sites in Romania. Subjects, consenting to participate in the study, were either patients requiring a switch from previous antipsychotic medication, or patients at onset of schizophrenia. Data was collected at baseline 1, 3, 6 and 12 month later. Alongside to the psychiatric and hospitalization history and collection of demographic data, dosing of RLAI, concomitant medication, reasons for initiation, adverse events; following tools were applied: CGI, CGI improvement, GAF.

Results: Reasons for initiation ofRLAI were insufficient efficacy (46.4%) and non-compliance to the previous medication. 31.2% of the patients experienced a treatment-emergent AE. The most common reported AEs were insomnia, anxiety, depression and psychotic disorder. Other reported AEs included extrapyramidal symptoms, weight gain, and endocrine disorders (amenorrhea, galactorrhea). All parameters assessing drug efficacy showed a statistical significant improvement except for the number and the duration of hospitalizations, which increased compared to the 6 months pre-study period. CGI increased significantly (p<0.001) from baseline to both 6 and 12 months. GAF score improved significantly (p<0.001) from baseline to both 6 and 12 months, with an average increase of 22.8 and 39.7 points, respectively.

Conclusion: Treatment-emergent AEs observed during this study were consistent with the established safety profile of risperidone long-acting injectable. In addition, treatment with risperidone long-acting injectable resulted in the expected, statistically relevant improvement of psychiatric status in subjects eligible for such treatment.

Policy of full disclosure: the current study has been initiated and supported by Janssen Romania.

P-43-013 Lurasidone in contrast to other antipsychotics does not produce deficits in social exploration and social recognition in the rat

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Objective: Social deficits are believed to be important predictor of functional outcome in schizophrenia. Although currently used antipsychotics are effective in treating positive symptoms of schizophrenia, social deficits are still one of the major unmet medical needs. Animal models of social behavior and social memory are thought to be useful tools in the search for new psychoactive medications for schizophrenia, depression, and other neuropsychiatric disorders in which social deficits are seen. In the present study, we compared first-generation antipsychotic (haloperidol) and second-generation antipsychotics (olanzapine, aripiprazole, clozapine, sertindole, lurasidone) as well as escitalopram and diazepam in terms of their influence on social behavior and social memory in the rat.

Methods: The social exploration and recognition test consisted of two trails. During the first trial, an unknown juvenile rat (100–150 g) was placed into the home cage of an adult rat (500–550 g). The time spent by the adult in active social investigation (close following, sniffing, grooming, crawling over or under juvenile rat) was measured. Each adult rat was re-exposed to the same juvenile fifteen minutes later and again social investigation time was measured (trial 2). Social recognition was defined as a difference between investigation times during trial 1 and trial 2.

Results: Except lurasidone, all the tested drugs significantly suppressed social exploration. Significant changes were observed for haloperidol (Minimal Effective Dose: 0.1 mg/kg), olanzapine (10 mg/kg), aripiprazole (10 mg/kg), clozapine (3 mg/kg), sertindole (1 mg/kg), escitalopram (30 mg/kg), and diazepam (10 mg/kg). Interestingly, none of the tested antipsychotics influenced social recognition. In contrast, escitalopram and diazepam produced considerable recognition deficits at the dose of 10 mg/kg and 3 mg/kg, respectively.

Conclusion: In conclusion, our data indicate that lurasidone do not impair social behavior in the rat and suggest that the drug can be a good treatment choice for patients with social deficits.

Policy of full disclosure: The study was supported by Adamed Ltd., Pienkow, Poland and Polish Agency for Enterprise Development (PARP project no. UDA-POIG.01.04.00-14-055/10-00).

P-43-014 Effect of long-term treatment with lurasidone or risperidone on metabolic syndrome status in patients with schizophrenia

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Objective: This post hoc analysis evaluated the effect of long-term treatment with lurasidone or risperidone on metabolic syndrome status.

Methods: Outpatients with clinically stable schizophrenia were randomized 2:1 to flexibly dosed, once-daily lurasidone (40–120 mg/d) or risperidone (2–6 mg/d) in a 12-month, multiregional, double-blind study followed by an open-label extension (flexibly dosed lurasidone 40–120 mg/d for up to 6 months). International Diabetes Federation criteria were used to evaluate metabolic syndrome, defined as elevated waist circumference (using ethnic group-specific norms) or BMI >30 kg/m^2 plus $\geqslant$2 of the following: triglycerides $\geqslant$150 mg/dL, HDL cholesterol <40 mg/dL in men or <50 mg/dL in women, blood pressure $\geqslant$130/85 mmHg, or blood glucose $\geqslant$100 mg/dL.

Results: The prevalence of metabolic syndrome at baseline of the double-blind phase was similar for the lurasidone (32.5%; 134/412) and risperidone (32.7%; 65/199) groups. After 12 months of treatment, the prevalence of metabolic syndrome (observed cases) was 31.5% (47/149) with lurasidone and 44.1% (41/93) with risperidone ($p<0.05$). For patients taking lurasidone in the double-blind phase who continued on lurasidone in the open-label phase (n=109), the prevalence of metabolic syndrome was 33.3% at double-blind baseline and 26.6% after 18 months of treatment. In a similar analysis of risperidone-treated patients switched to open-label lurasidone after 12 months (n=65), the prevalence of metabolic syndrome was 42.9% at double-blind baseline, 48.4% at open-label baseline (after 12 months of risperidone), and 38.5% after 6 months of open-label lurasidone.

Conclusion: Treatment with lurasidone was associated with a lower prevalence of metabolic syndrome compared with risperidone treatment. The prevalence of metabolic syndrome remained stable over 18 months of continuous treatment with lurasidone, in contrast to increased prevalence during 12 months of treatment with risperidone. The prevalence of metabolic syndrome decreased in risperidone-treated patients who were switched to lurasidone for 6 months. ClinicalTrials.gov identifier: NCT00641745

Policy of full disclosure: Dr. Newcomer reports financial involvement with Bristol-Myers Squibb Company, Merck & Co., Inc., and VIVUS Inc.; and research grants from Pfizer Inc. All other authors report being employees of Sunovion Pharmaceuticals Inc.

P-43-015 Tolerability and safety profile of aripiprazole once-monthly in the treatment of schizophrenia: A pooled analysis from the safety database of 11 completed or ongoing trials

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Objective: To evaluate the long-term tolerability and safety profile of aripiprazole once-monthly (AOM).

Methods: Data from the safety database of 11 completed or ongoing AOM trials in subjects with schizophrenia were pooled; 2 completed phase 3 trials (pivotal), 4 ongoing phase 3/3b trials (as of 02 April 2012), 4 completed phase 1/1b trials, 1 ongoing phase 1b trial. Exposure and treatment emergent adverse event (AE) data are summarized for AOM-400/300 mg, and the sub-therapeutic doses <AOM-300 mg.

Results: 1,539 subjects received AOM-400/300 mg and 168 received AOM<300 mg (ie, 15 mg, 25 mg, 50 mg, 100 mg, or 200 mg; 131 received 25/50 mg). 995 subjects received at least 7 aripiprazole injections (ie 6 months of exposure), 784 subjects at least 13 injections (ie 12 months of exposure), and 244 subjects at least 26 injections (ie 2 years of exposure). Treatment-emergent AEs resulted in trial discontinuation for 9.4% (145/1539) of AOM-400/300 mg treated subjects and 14.9% (25/168) of a subjects treated with AOM<300 mg. Treatment-emergent AE (>=10% of AOM-400/300 mg subjects) was insomnia 11.0% (n=169/1539). Treatment-emergent AEs (<10% to >=5% of AOM-400/300-mg subjects) were headache 9.6% (n=147/1539,), anxiety , 8.8% (n=136), increased weight 7.7% (n=119), nasopharyngitis 7.5% (n=115), akathisia 7.1% (n=109), injection site pain 7.0% (n=108), and upper respiratory tract infection 5.5% (n=84). The incidences of these events were comparable with AOM<300 mg except for injection site pain [AOM-400/300 mg 7.0% (n=108/1539); AOM<300 mg, 3.0% (n=5/168)]. The majority of treatment emergent AEs were either mild or moderate in severity.

Conclusion: A substantial number of patients have been actively monitored for side effects after treatment with aripiprazole once-monthly for >=1 year, and some for >=2 years. The long-term tolerability and safety profile was consistent with the known safety profile of oral aripiprazole.

Policy of full disclosure: Supported by Otsuka Pharmaceutical Development & Commercialization, Inc., and H. Lundbeck A/S. R. Baker, N. Jin, R. Duffy, R. McQuade, and T. Peters-Strickland are employees of Otsuka Pharmaceutical Development & Commercialization, Inc. P. Hertel, AG Nylander, and A Eramo are employees of H. Lundbeck A/S.

P-43-016 The effect of previous dose of oral aripiprazole (10 or 30 mg/day) on the efficacy and tolerability of aripiprazole once-monthly: Post-hoc analysis of two double-blind, randomized, controlled trials

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Objective: To present the efficacy and tolerability of aripiprazole once-monthly (AOM) in patients stabilized on 10 or 30 mg/day oral aripiprazole (ARI) before switching to aripiprazole once-monthly AOM.

Methods: Data from 2 pivotal double-blind, placebo- or active-controlled trials assessing AOM in patients with schizophrenia (study 246, NCT00705783; study 247, NCT00706654) were analyzed post-hoc. Efficacy was evaluated by change from baseline in the Positive and Negative Syndrome Scale (PANSS) Total Score at 4 weeks after initiation of AOM. Tolerability was measured as common adverse events in this period.

Results: 841 stable patients (study 246: n=576, study 247: n=265) received AOM-400/300 mg. Of these, 105 had been stabilized on 10 mg/day ARI (study 246: n=75, study 247: n=30) and 212 on 30 mg/day ARI (study 246: n=147, study 247: n=65). In each study, AOM maintained stability of symptoms: 246 study, change in PANSS total from baseline to Week 4: 10 mg group=0, 30 mg group=−0.18; 247 study 10 mg group=−1.03, 30 mg group=−1.83. The most common

adverse events (>=5%) were injection site pain (range: 9.3% [10 mg/study 246] to 0% [30 mg/study 247]); insomnia (9.2% [30 mg/study 247] to 2.7% [10 mg group/ study 246]); weight increase (8.2% [30 mg/study 246] to 1.3% [10 mg/study 246]); agitation (6.2% [30 mg/study 247] to 0% [10 mg/study 247]); dizziness (5.3% [10 mg/study 246] to 0% [30 mg/study 246 and 10 mg/study 247]); akathisia (7.7% [30 mg/study 247] to 2.7% [10 mg/study 246]); and anxiety (6.7% [10 mg/study 247] to 1.5% [30 mg/study 247]).

Conclusion: Aripiprazole once-monthly maintained stability of symptoms in the month after initiation regardless of whether patients had been stabilized on 10 or 30 mg/day oral aripiprazole. Adverse events occurred at similar rates (none exceeding 10%) for patients converted from oral aripiprazole 10 or 30 mg/day; and were similar to the entire study population.

Policy of full disclosure: Supported by Otsuka Pharmaceutical Development & Commercialization, Inc., and H. Lundbeck A/S. A. Eramo and AG Nylander are employees of H. Lundbeck A/S. R. Baker, L-F Tsai, T. Peters-Strickland, and R. Sanchez are employees of Otsuka Pharmaceutical Development & Commercialization, Inc.

P-43-017 Defects of neurocognitive performance and social functioning in non-prodromal individuals with high genetic loading for schizophrenia

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Objective: Neurocognitive dysfunction in unaffected relatives of individuals with schizophrenia was regarded as evidence of an endophenotype and examined in relation to social functioning. Although previous research has investigated this relationship, these studies included relatives at the prodromal stage. Given recent clinical high-risk studies showing that such individuals may have neurocognitive or neurobiological alterations similar to, albeit less serious than, those observed in schizophrenia, this relationship remains unclear. This study examined neurocognitive and social functioning in non-help-seeking individuals with genetic loading but without psychosis-risk syndrome (GHR) to determine whether neurocognitive deficits account for social functioning impairment.

Methods: The GHR group included unaffected individuals with high genetic loading for schizophrenia, and were compared with the healthy control group. GHR individuals fulfilling the psychosis-risk syndrome criteria were excluded. Measures of neurocognitive and social cognitive function, as well as Social Functioning Scale, were administered.

Results: The GHR group showed significant impairment on the Trail Making Test and the Wisconsin Card Sorting Test(WCST) compared with healthy control group even after controlling for general intelligence, age, and education. Subscores of the Social Functioning Scale were found to be significantly lower in the GHR subjects. Categories completed from the WCST significantly predicted impairment on the social functioning scale in the GHR group, but not in the healthy control group.

Conclusion: These result suggest that neurocognitive impairment, especially executive dysfunction, plays an important role in social functioning impairment in GHR subjects without psychosis-risk syndrome.

Policy of full disclosure: None.

P-43-018 The change of polyunsaturated fatty acid (PUFA) concentration during paliperidone extended-release treatment and the plasma concentration of paliperidone ER at week-2 and week-3

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Objective: The aim of our study was to investigate the change of polyunsaturated fatty acid (PUFA) concentration during 8 week treatment of paliperidone extended-release(paliperidone ER). We also investigate the plasma concentration of paliperidone at week-2 and week-3.

Methods: This study was conducted as a part of the Efficacy and Safety of Paliperidone ER in Patients with First Episode Psychosis. The study population consisted of 75 patients of first-episode psychosis. The initial recommended dose of paliperidone ER was 3–6 mg/day, increasing up to 12 mg/day depending on treatment response. Plasma PUFA concentrations were measured using a gas chromatography system at baseline (n=62) and week-8(n=42). For assay of plasma concentration, blood samples were taken on week-2(n=30) and week-3(n=29).

Results: Baseline PUFA concentration didn't show significant association with PANSS, SANS, GAF, and the Cognitive Assessment Interview (CAI). After 8-week treatment, PUFA concentration did not show significant change except for an increase in eicosapentaenoic acid (EPA) concentration. At week-2 and week-3, the mean plasma concentration of paliperidone was significantly associated positively with 9-hydroxy risperidone. The mean plasma concentration was 17.08±9.30 ng/ml at a daily oral dosage of 7.96±2.59 mg (week-2), and 21.51±14.82 ng/ml at 8.50±2.77 mg(week-3). At week-2 or week-3, the mean plasma concentration of non-response group was significantly higher than that of response group. When defining the treatment response as >=30% decrease in PANSS0-6 total score from baseline, plasma concentration at week-3 significantly associated negatively with treatment response at week-8.

Conclusion: After 8-week treatment with paliperidone, there was significant increase in EPA concentration. However, the effect of paliperidone on PUFA concentration warrants further investigation. The response rate at week-8 was negatively associated with higher plasma concentration of paliperidone at week-3.

Policy of full disclosure: None.

P-43-019 Convergence of clozapine induced ErbB1-ERK and ErbB4-PI3 K/AKT signalling in prefrontal cortical neurons: Relevance to therapeutic efficacy

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Objective: Dysregulation of the epidermal growth factor (EGF) system, implicated in synaptic plasticity, long-term potentiation and dendritic spine connectivity has been linked to schizophrenia. For instance, in patient brain and blood low EGF levels resulting in compensatory up-regulation of the EGF receptor (ErbB1) is postulated to represent a hypofunctioning signalling state. Consistent with this hypothesis our preclinical in-vitro and in-vivo data demonstrate that the antipsychotic drug clozapine increases ErbB1 signalling via GPCR transactivation of the extracellular signal-regulated kinase (ERK) pathway in cortex and striatum. Here we investigate whether ERK intersects with the AKT pathway via the mediators PI3 K, Src, beta-arrestin and Ca2+ which may govern the ErbB1 transactivation mechanism induced by clozapine, since both pathways are implicated in schizophrenia through cell and genetic based studies.

Methods: Frontal cortical neurons were exposed to wortmannin (PI3 K inhibitor), (BMK120, pan-Class I PI3 K inhibitor), monodansylcadaverine (MDC) (receptor endocytosis inhibitor) and BAPTA-AM (Ca2+ inhibitor), and the effect on clozapine-mediated ErbB1-ERK, ErbB4-PI3 K/AKT and Src phosphorylation examined to assess pathway cross-talk.

Results: AKT phosphorylation was significantly inhibited by clozapine in the absence of changes in PI3 K p110delta isoform expression. Wortmannin caused significant dose-dependent inhibition of ERK1/2 phosphorylation in the presence of clozapine while beta-arrestin or intracellular calcium release were not involved. BMK120 had limited effect on ERK phosphorylation but further reduced AKT phosphorylation upon exposure to clozapine contingent on dose. Parallel detection of Src phosphorylation indicated a time disconnect with ERK phosphorylation.

Conclusion: Our data demonstrate convergence of ERK and PI3 K/AKT signalling induced by clozapine through mediators such as Src and PI3 K contingent on cell and tissue type. We therefore propose that there is a complex reciprocal relationship between ErbB1 and ErbB4 signalling to ERK1/2 and PI3 K in neurons that may be disrupted in schizophrenia and ameliorated by clozapine.

Policy of full disclosure: None.

P-43-020 Efficacy and tolerability of paliperidone palmitate long-acting injectable antipsychotic in first-episode schizophrenic patients

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Objective: Aim of the paper is to assess the therapeutic efficacy and tolerability of paliperidone palmitate long-acting injectable antipsychotic in first-episode schizophrenic patients. The management of patients with a first-episode of psychosis remains a challenge. Treating patients with paliperidone palmitate avoids the issue of non-compliance.

Methods: The research included 17 patients aged 16 to 22 years who were diagnosed in accordance with the Diagnostic and Statistical

Manual of Mental Disorders, Fourth Edition. All patients were assessed six times over six months using the following clinical scales: Positive and Negative Syndrome Scale, Clinical Global Impression - Severity and Improvement Scale, Personal and Social Performance Scale. Primary safety measures included incidence of adverse events.

Results: In this six months analysis 88.2% of patients with first-episode psychosis achieved remission, which was significantly associated with early treatment response. Patients achieving remission demonstrated a trend towards greater improvement in function, health status and productivity.

Conclusion: All doses of once-monthly paliperidone palmitate were efficacious and generally tolerated. Earlier application of paliperidone palmitate results in lower relapse rates, better reaction to therapy, achieving remission and full recovery.

Policy of full disclosure: None.

P-43-021 A mirror-image study to compare the efficiency of paliperidone palmitate with oral antipsychotics in schizophrenic patients

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Objective: We aimed to compare the efficiency of paliperidone palmitate (PP) with usual oral antipsychotic therapy in a psychiatric hospital in Quebec. Specific objectives were to compare total annual hospitalisation days and the annual cost of both treatments.

Methods: We undertook a retrospective mirror-image study where one year of hospitalisation days on oral antipsychotics was compared to one year of hospitalisation days on PP. Patients were selected if they had received the 3rd dose of PP, if they were prescribed oral antipsychotics one year before, and if they consented to the study. They were excluded if they had received clozapine, if they switched to PP from another long acting antipsychotic, or if they were known to be refractory to treatment. Mean possession ratios (MPR) were obtained from community pharmacists.

Results: Seventeen patients were recruited from a pool of 200 candidates. Principal reasons for exclusion was use of clozapine or another long acting therapy in the year prior enrolment. Mean patient demographics were 36 years, 76% male, 76% paranoid schizophrenia, 24% of community treatment orders, 41% of substance abuse disorder, and 52% of anterior exposure to risperidone. The most frequent reason to switch to PP was acute psychotic episode and non adherence. Mean annual hospitalisation days was 55 (range 21–116) and 11 (range 0–62) for the one year before and one year after periods, respectively ($p<0$, 01). MPR was 60% (range 0–100%) with oral therapy and 90% with PP. 741 days of hospitalisation were saved for those patients, making savings of 9422 $ per patient per year after controlling for drug cost.

Conclusion: PP is clinically more efficient than oral therapy, as it diminishes patient suffering and total spending for the treatment of schizophrenia, but the present results cannot be distinguished from improved adherence, or simply use of long acting injectable antipsychotic.

Policy of full disclosure: This study was done with a non-restrictive educational grant from Janssen.

P-43-022 Prefrontal GABA-blockade and decision making: Relevance for schizophrenia

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Objective: The prefrontal cortex (PFC) plays a critical role in decision making, and is thought to be an area of pathology in schizophrenia. Individuals with schizophrenia display alterations in cost/benefit decision making involving evaluations of a variety of costs (uncertainty, delays, effort). PFC neurotransmission is thought to be compromised in the disorder, including hypofunction of GABA interneurons. Given that these neurons are thought to be critical for cognitive functioning, we sought to test how decreasing GABA function affects different forms of decision making that are perturbed in schizophrenia.

Methods: Male rats were well-trained on separate decision making tasks. To assess the impact of GABAergic hypofunction (intended to mimic part of the PFC pathology observed in schizophrenia), rats received intra-medial PFC infusion of the GABA-receptor antagonist bicuculline (50 ng) or saline prior to a test session. On each task, rats chose between one, 'low cost' lever that gave an immediate, certain reward (sucrose pellets) after one press and a high-cost lever that delivered a larger reward associated with a form of cost; 1) uncertainty, delivering the reward in a probabilistic manner 2) delays to receiving the reward or 3) requiring more effort to obtain the larger reward.

Results: PFC GABA-blockade decreased risky choice, similar to the risk-averse phenotype observed in schizophrenia. These treatments did not affect delay discounting, but did cause a slight decrease in preference for the large/delayed reward when it was not delayed. PFC GABA blockade also reduced slightly the preference for larger rewards associated with greater effort costs. Control experiments suggested that mPFC GABA-blockade does not affect basic motivational process, but does cause mild deficits in preference for larger vs. smaller rewards.

Conclusion: GABA-blockade of the mPFC produces discrete alterations in some forms of cost/benefit decision making, some of which may be related to those observed in schizophrenia.

Policy of full disclosure: None.

P-43-023 Extracellular matrix metabolism was unveiled in physiophology of schizophrenia by interacted genome-wide association study and consequent downstream analysis

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Objective: To capture common variants of schizophrenia by using quantitative trait, DMS (delay matching to sample) and to detect possible functional network meditating effect of captured genes on schizophrenia.

Methods: 100 first-episode schizophrenia patients and 140 healthy controls were recruited for DMS test, linear regression model was built to associate DMS test results and SNP × diagnosis, geneMANIA was applied to predict more genes sharing smiliar function with query genes and to plot functional pathway most relevant to the query genes from early association study.

Results: 32 SNPs located in 26 genes reached P-value threshold of association significance (5 × 10–5) with the highest P-value generated from FHIT in chromosome 3(3.69 × 10–8) when interacted with DMS_PC_A and DMS_PEGC. Downstream functional analysis showed that most genes found from association test are enriched in metabolic pathway of extracellular matrix.

Conclusion: Genes passing significance threshold after using DMS as quantitative traits were most relevant to chondrontin metabolic process, proving DMS as a viable intermediate phenotype for GWAS of schizophrenia and also suggesting possible mechanism DMS deficits exerted on in schizophrenia pathology.

Policy of full disclosure: None.

Significance of GWAS Genotyped SNPs of the 400 kb region in chromosomal region of FHIT., adapted from LocusZoom output:

Please see diagram appearing on page 152.

P-43-024 Efficacy of lurasidone in the treatment of schizophrenia with prominent negative symptoms: A post-hoc analysis of short-term trials

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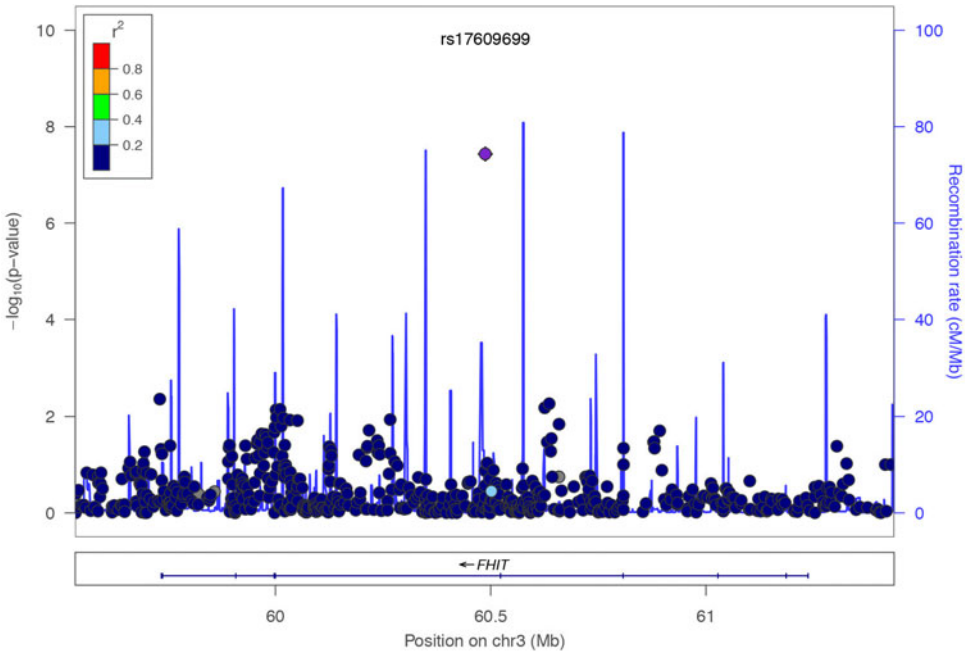
Objective: To evaluate the efficacy of lurasidone in patients with prominent negative symptoms (PNS).

Methods: This post-hoc analysis utilized pooled data from three 6-week, double-blind, placebo-controlled trials of patients (N=1206) with an acute exacerbation of schizophrenia who were randomized to lurasidone 40–160 mg/d. Patients with PNS at baseline were identified based on the following criteria: a PANSS negative subscale score ⩾25 (median) and a PANSS positive score <26 (median). MMRM analyses were performed for change in PANSS total, negative subscale, and CGI-S scores. Responders were defined as reduction from baseline in PANSS total of ⩾20%, ⩾30%, or ⩾40% (LOCF-endpoint).

Results: A total of 20.5% patients met criteria for PNS. Treatment of the PNS group with lurasidone (vs placebo) was associated with significantly greater week-6 improvement in the PANSS total score (−23.1 vs −16.2; $p<0.01$), PANSS negative subscale score (−6.7 vs −4.5; $p<0.01$), and CGI-S (−1.4 vs −1.0; $p<0.01$). Treatment of the PNS group with lurasidone (vs placebo) was associated with significantly greater endpoint response using the PANSS total ⩾20% improvement criterion (71.3% vs 52.5%; $p<0.01$), ⩾30% criterion (55.1% vs 37.5%; $p<0.01$), and ⩾40% criterion (42.5% vs 28.8%; $p<0.05$). In the group without PNS, treatment with lurasidone was also associated with significantly greater ($P<0.01$) endpoint responder rates using these PANSS criteria. Discontinuation due to adverse events, for lurasidone vs placebo, respectively, was low in both the PNS group (5.4% vs 1.2%) and the group without PNS (5.9% vs 4.7%). In the prominent negative symptom group, the 3 most common adverse events reported for lurasidone vs placebo were headache (22.2% vs 18.8%), somnolence (22.2% vs 2.5%), and akathisia (15.0% vs 3.8%).

Diagram reference P-43-023



Conclusion: Patients presenting with PNS responded well to lurasidone with significant improvement in PANSS total and negative subscale scores. Treatment with lurasidone was generally safe well-tolerated in the PNS group.

Policy of full disclosure: Dr Schooler has received grants from Otsuka, Neurocrine and Genentech. She has participated in advisory boards to provided other consultation to Abbott, Eli Lilly, Shire, Janssen Psychiatry, Amgen, Lundbeck and Roche. Dr. Pikalov, Hsu, Cucchiaro, Goldman, and Loebel are full-time employees of Sunovion Pharmaceuticals, Inc.

P-43-025 Pitfall of using absolute Framingham Risk Score for primary prevention strategy in schizophrenia

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Objective: In a Lancet Comment published on 30–11–2014, Ridker and Cook reported that the new ACC/AHA prediction algorithm systematically overestimated the absolute risk for atherosclerotic cardiovascular disease in 5 cohorts, which featured better smoking, cholesterol and blood pressure profiles compared to the cohorts used in deriving the guidelines. The objective of this paper was to examine the recalibration procedure for absolute risk survival model, using the Framingham Risk Score (FRS) risk estimate in the CATIE study as an example.

Methods: We recalibrated the FRS risk estimates for the CATIE study population, and applied a risk ratio approach to improving the risk prediction algorithm, defined as the absolute risk divided by the absolute risk for an optimal risk profile (i.e. a total cholesterol 170 mg/dL, HDL-cholesterol 50 mg/dL, and untreated systolic blood pressure 110 mm Hg, nonsmoker and without diabetes).

Results: We compared the mean for each of the categories of the FRS risk factors in CATIE and FHS studies: mean age 40 in CATIE versus 49 in FHS, total cholesterol >=240 mg/dL is 20% in CATIE versus 26% in FHS, HDL<35 mg/dL is 25% in CATIE versus 11% in FHS, Stage I-IV hypertension 28% in CATIE versus 32% in FHS, Diabetes mellitus (women 16% and men 11%) in CATIE versus (women 4% and men 5%) in FHS, and smoker (women 56% versus men 73%) in CATIE versus (women 38% and men 40%) in FHS. Unlike the substantially marked contrast in absolute risk scores, virtually identical risk ratios would be obtained for both the FHS and the new recalibrated models for CATIE.

Conclusion: Our findings suggest that risk ratio (relative to low risk state) instead of absolute risk might be more appropriate for prediction of cardiovascular risk in schizophrenia patients using Framingham Scoring Model.

Policy of full disclosure: C Siu is a consultant to Sunovion Pharmaceuticals. No conflict of interest for C Brambilla.

P-43-026 Insight into illness and uncooperativeness in chronic schizophrenia

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Objective: The objective of this study was to examine factors that might influence insight, uncooperativeness, and self-assessment of quality-of-life using the large National Institute of Mental Health Clinical Antipsychotic Trials of Intervention Effectiveness CATIE dataset.

Methods: Insight was assessed by the Insight and Treatment Attitudes Questionnaire (ITAQ) and PANSS item G12 "lack of judgment and insight". Social and occupational functioning was assessed using the Heinrichs-Carpenter Quality of Life (HCQoL) scale, while self-report well-being overall was assessed with the Lehman QoL Interview (LQOLI). Uncooperativeness was assessed by PANSS item G8 (#Uncooperativeness#).

Results: : Consistent with previous reports, we found better insight into illness was associated with higher functioning ($p<0.05$), greater neurocognitive composite ($p<0.05$) and reasoning ($p<0.05$) performance, but there was an inverse correlation to lower self-report well-being overall ($p<0.05$) and a higher level of depressive symptoms ($p<0.05$) in patients with chronic schizophrenia. We also found the inverse relationship at baseline between insight and self-report LQOLI was explained, in part, by levels of depressive symptoms ($p<0.001$) and neurocognitive reasoning impairment ($p<0.05$). Overall cognitive performance was not significant after adjusting for depression effect ($p>0.05$). Among subjects with mild or no depressive symptoms on all 9 items of the Calgary Depression Scale (N=839), better self-report well-being overall (LQOLI) was associated with poorer insight ($p<0.05$) and lower cognitive reasoning performance ($p<0.05$) after adjusting for age and symptom severity (CGI-S). Improved insight into illness over time was longitudinally associated with reductions in uncooperativeness symptoms (PANSS G12) ($p<0.001$).

Conclusion: Our findings suggest that poorer insight and attitudes toward treatment had significant associations with higher level of uncooperativeness, lower level of neurocognitive reasoning, and less depression, which in turn impacts self-report assessment of well-being overall. These results suggest the importance of reducing insight and cognitive impairments both for functional improvement and willingness to accept treatments.

Policy of full disclosure: C Siu: a consultant to Sunovion; O. Agid: consultant to Eli Lilly Inc. Canada, Eli Lilly USA, Janssen-Ortho Inc., Pfizer, Inc.; G Remington: Research support from Novartis, Medicure, and Neurocrine, Speaker for Norvatis, Consiltant to Roche; P Harvey serves as a consultant/advisory board member for Abbvie, Boeheringer Ingelheim, Bristol-Myers-Squibb, Forest Labs, Genentech, Roche, Shire,

Sunovion, and Takeda. No conflict of interest for M Waye, C Brambilla and WK Choi.

P-43-027 Inhaled loxapine and intramuscular lorazepam in healthy volunteers: Results of a randomized, placebo-controlled drug-drug interaction study

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Objective: Inhaled loxapine administered via the Staccato® system reduces agitation in patients with schizophrenia or bipolar I disorder. This study compared the pharmacodynamic effects and safety of single-dose inhaled loxapine and intramuscular (IM) lorazepam vs. each agent alone in healthy volunteers. (NCT01877642).

Methods: Randomized, double-blind, cross-over study. Primary endpoints were maximum effect (minimum value) and area under the curve (AUC) from baseline to 2hr post treatment for respirations/min and pulse oximetry with: concomitant inhaled loxapine 10 mg+IM lorazepam 1 mg compared with either inhaled loxapine 10 mg+IM placebo, or IM lorazepam 1 mg+Staccato® placebo. LS-means [90% CI] for ratios of values for concomitant treatment vs. either agent alone were derived and equivalence confirmed by 90% CI within 0.8–1.25. Subjects were exposed to each treatment in random order, with a 3-day washout between. Blood pressure (BP), heart rate, and sedation (100 mm visual analog scale [VAS]) were assessed, and AEs recorded.

Results: All 18 subjects (mean 20.4 years; 61% male) completed the study. No significant interaction was seen for inhaled loxapine+IM lorazepam on respiration or pulse oximetery vs. either agent alone during the 12hr post-dose period, with 90% CI for AUC and Cmin ratios confirming equivalence. BP and heart rate were unchanged for 12hr post-dose with inhaled loxapine+IM lorazepam vs. either agent alone. Results clearly demonstrated the central nervous system sedative effects of IM lorazepam, inhaled loxapine, and the combination of inhaled loxapine+IM lorazepam in healthy volunteers. No deaths, serious AEs, premature discontinuations due to AEs, or treatment-related AEs were reported.

Conclusion: No effects on respiration or vital signs were seen for inhaled loxapine+IM lorazepam vs. each drug alone. There was greater sedation with inhaled loxapine+IM lorazepam compared with either drug administered alone in these healthy volunteers.

Policy of full disclosure: Study funded by Alexza Pharmaceuticals. Medical writing support, funded by Teva Pharmaceuticals, was provided by Annie Rowe, PhD, of Excel Scientific Solutions. DAS and JVC are employees of Alexza Pharmaceuticals, Inc. RRS is an employee of 2Covance Clinical Research Unit. PY is an employee of Teva Pharmaceuticals.

P-43-028 Quality of life and first epizode of schizophrenia

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Objective: Quality of life in first epizode schizophrenia patients, who suffer weighty mental illnesses is without question influence in important way. Return to normal life functioning is very often difficult and protracted. Studying of this problematic can offer ideas on which parts need to be rehabilitated and thereby may return pacients back to normal functional life quickly and effectively.

Methods: Our research group is formed by 40 patients who have been investigated during first epizode schizophrenia and by 80 healthy controls. Patients were invited after one year period to the control investigation. Questionaire Subjective Quality of Life Analysis SQUALA was chosen as an indicator of subjective level of quality of life. Patients were divided to 3 categories according to used medication (olanzapine, risperidone and other).

Results: Results show that patients with schizophrenia have demonstrably lower level of quality of life than healthy controls. Same phenomenon was detected in areas of health, close relationships, free time activities and abstract qualities. Only part of basic needs feel these patients same as healthy controls. We also detected that quality of life, especially part of close relationships, corelate negatively with thought and perception disorder, while performance in executive tasks corelate negatively with level of perception of basic needs, which contain evaluation of surrounding and housing, finance and food. In case of increase of subjectively perceived depresivity patients reffer worse quality of functioning in close relationships. In connection with psychopharmacological treatment were not found any statistically significant relationships. After one year from first epizode remains level of subjective quality of life without any chase, even though that presence of positive symptoms and global scale of psychopatology is statistically lower.

Conclusion: From the mentioned findings is obvious, that quality of life of patients with schizophrenia is lower in comparison with healthy controls and this deficit is unfortunatelly stabile in time.

Policy of full disclosure: None.

P-43-029 Cognition and schizophrenia: Neuropsychological profile, dynamics, psychopatology and pharmacotherapy

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Objective: Maping of cognitive abilities in schizophrenia pacients is indivisible part of psychodiagnostics of this disease. Neuropsychological clinical scan is still not fully clear and studies dedicated to this topic offer many diferent information. Aim of this study is to map this issues and bring new information about cognitive functioning and dynamics in schizophrenia.

Methods: Our research group is formed by 41 in patients who were observed during first epizode schizophrenia in Clinic of Psychiatry at Faculty hospital Brno. One year after the first epizode were performed controling investigations. After retreat of acute psychotic proces durig first epizode the patients undergone complex neuropsychological investigation including submission of questionaires maping quality of life and depresion. Patients were also scaled by the method PANSS and divided into 3 categories acording to the used medication (olanzapine, risperidone and other).

Results: Results show that in the first epizode schizophrenia patients partial cognitive deficit is present. This deficit is the strongest in verbal memory abilities (phase imprinting and recall), visual memory and psychomotor speed. Cognitive weaknesses include most of attention components as working memory, verbal fluency and distribution of attention. Improvement of cognitive capacity in area of working memory, visual memory, verbal memory in phase recall and quality of conception thinking was evidenced after one year from the first. At the same time has not been found statisticaly significant dependance between types of pharmacotherapy and cognition quality. Contrariwise we have found negative corelation between rate of positive symptoms and flexibility of thinking, negative symptoms and quality of attention, short-term memory and global cognitive functioning. General psychopatology corelate positively with level of subjective depression and negatively with flexibility of thinking, distribution of attention and short-term memory.

Conclusion: From the perspective of psychopatology cognitive functioning is fundamentally influenced by negative and general symptoms.

Policy of full disclosure: None.

P-43-031 A double-blind, placebo-controlled, randomized withdrawal study of lurasidone for the maintenance of efficacy in patients with schizophrenia

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Objective: To evaluate lurasidone for maintenance treatment of patients with schizophrenia.

Methods: Adult patients experiencing an acute exacerbation of schizophrenia were enrolled in the 12- to 24-week open-label stabilization phase of the trial and treated with lurasidone (40–80 mg/d, flexibly dosed). Patients who maintained clinical stability during the initial open-label study phase for $\geqslant$12 weeks were subsequently randomized to placebo or lurasidone (40–80 mg/d, flexibly dosed) at baseline of the 28-week, double-blind study phase. The primary efficacy endpoint was time to relapse in the double-blind phase. Secondary efficacy measures included the Positive and Negative Syndrome Scale (PANSS) and Clinical Global Impression–Severity (CGI-S). Safety assessments included treatment-emergent adverse events, discontinuations due to AEs, and laboratory measures.

Results: Of 676 enrolled patients, 285 met protocol-specified stabilization criteria and were randomized to lurasidone (N=144) or placebo (N=141). Relapse occurred in a greater proportion of patients receiving placebo (41.1%) than lurasidone (29.9%). Time to relapse was significantly longer for lurasidone compared with placebo (log-rank test, p=0.039). Lurasidone was associated with a 33.7% reduction in risk of relapse versus

placebo (Cox hazard ratio [95% confidence interval], 0.663 [0.447, 0.983]; p=0.041). Patients receiving placebo demonstrated significantly greater worsening on PANSS and CGI-S scores compared to lurasidone-treated patients (PANSS mean change, +12.4 vs +8.3, p=0.029; CGI-S mean change, +0.7 vs +0.4, p=0.015; analysis of covariance with the last observation carried forward). The discontinuation rate due to adverse events during the double-blind phase was 13.9% for lurasidone and 15.6% for placebo. Minimal changes in weight, prolactin, lipid, and glucose parameters were observed in both groups during the double-blind phase.

Conclusion: This placebo-controlled, randomized withdrawal study demonstrated the efficacy of lurasidone for the maintenance treatment of patients with schizophrenia. Lurasidone was generally well tolerated, with minimal effects on weight and other metabolic parameters. ClinicalTrials.gov identifier: NCT01435928

Policy of full disclosure: Dr. Tandon reports serving as a consultant for Sunovion Pharmaceuticals Inc. All other authors report being employees of Sunovion Pharmaceuticals Inc.

P-43-032 Risperidone monotherapy influences cortical inhibition in patients with first episode of schizophrenia: A TMS study

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Objective: Cortical inhibition is a neurophysiological mechanism whereby GABA interneurons attenuate the activity of other neurons. The inhibitory and excitatory mechanisms can be assessed using transcranial magnetic stimulation (TMS). One of the inhibitory paradigms is known as cortical silent period (CSP). Recent metanalysis did not find significant differences in CSP in patients with schizophrenia. But there are several studies showing that CSP is shortened in patients with schizophrenia and antipsychotic medication (especially clozapine) can cause its prolongation. The aim of our study was to assess the ability of risperidone to influence CSP in patients with first episode of schizophrenia (FES).

Methods: Drug-naive patients with FES were included to our study (N=13). They were treated with risperidone monotherapy. The CSP duration was measured using TMS before the treatment and after four weeks of risperidone monotherapy. The psychopathology was assessed using Positive and Negative Syndrome Scale (PANSS). The CSP duration was obtained in moderately tonically active musculus abductor digiti minimi by stimulating the motor cortex with an intensity of 150% of motor threshold. CSP was defined as a time between the initiation of motor-evoked potential (MEP) and return of any voluntary EMG activity.

Results: Mean CSP duration increased during the treatment from 134.2 ms (SD=41.8) to 162.9 ms (SD=62.0) which was statistically significant ($p<0.05$). We did not find any correlation with the PANSS total score or its subscores.

Conclusion: We found in our study that risperidone monotherapy can influence cortical inhibition in drug-naive patients with FES.

Policy of full disclosure: This work was supported by the project 'CEITEC – Central European Institute of Technology' (CZ.1.05/1.1.00/02.0068) from European Regional Development Fund and by the project (Ministry of Health, Czech Republic) for conceptual development of research organization 65269705 (University Hospital Brno, Czech Republic).

P-43-033 Polydipsia in a patient with a chronic, severe mental illness

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Objective: Disturbances of water homeostasis among psychiatric clients have been noticed, particularly the consumption of excessive quantities of liquid ("polydipsia"). Purpose: To describe the particularities of a polydipsic patient with schizoaffective disorder, the risk factors involved, the possible mechanisms, reasons delaying diagnosis, and the screening strategies.

Methods: Data collection includes: chart review and structured interviews. We did weight measurements and urine collections twice daily on three different days, at two weeks interval.

Results: The case studied was that of DG, diagnosed with Schizoaffective Disorder 25 years ago. He has been living in a home for special care for 20 years. He has been presenting permanent excessive drinking behavior for the last 15 years, along with episodic aggressive behavior and urine incontinence. He stated that he drinks around 6 liters of water per day.

Conclusion: Possible risk factors involved in triggering DG#s water seeking behavior are: treatment with Lithium for the last 20 years, long term classic neuroleptic treatment, and heavily drinking and smoking behavior. The water drinking pattern was interesting – he was waking up at 2 am and drinking large quantities of water to the point that his maximum body weight per day was at 8 in the morning, with a baseline at 8 p.m. He admitted having a psychological reason # dizziness and #feeling high,# along with thirst. This patient was only recently diagnosed with polydipsia. In this presentation, we are discussing some potential screening strategies for polydipsia in order to avoid this situation in the future.

Policy of full disclosure: None.

P-43-034 Vitamin C as an adjunct in schizophrenia treatment: A literature review of the theoretical bases and clinical applications

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Objective: Schizophrenia is a devastating illness thought to result from a combination of genetic and environmental factors. Its etiology and treatment remain under active investigation. There is a growing body of evidence that perioxidative neuronal damage is a contributing factor. In this review, we focused on the results of the existing Vitamin C supplementation trials in Schizophrenia and the theoretical bases for considering the role of oxidative stress in its pathophysiology.

Methods: We searched the available English language literature in PubMed/Medline, Embase, Cochrane and Web of Science, using key words such as schizophrenia, vitamin C, ascorbic acid, antioxidant supplementation, oxidative stress, adjunctive treatment for schizophrenia. Bibliographies from primary sources and reviews were used to supplement our search.

Results: Supplementation of antipsychotic regimens with antioxidants was found beneficial in several trials. In particular, Vitamin C has been incorporated into NICE guidelines for treatment resistant schizophrenia, among adjunctive treatment options. It was found to improve brief psychiatric rating scale scores, and appears to be a useful, inexpensive and safe option. However, the clinical trials of Vitamin C supplementation remain scarce.

Conclusion: Vitamin C is an inexpensive and safe adjunctive option to supplement schizophrenia treatment. It has sound theoretical basis behind it and has shown promise in the existing clinical investigations. However clinical trials remain scarce and more research is needed to delineate the extent of its usefulness.

Policy of full disclosure: None.

P-43-035 How does the NSA-4 compare to the NSA-16?

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Objective: The 16-item Negative Symptom Assessment (NSA-16) is increasingly used as a validated measure to track response to treatment of negative symptoms of schizophrenia. The NSA-4 has been proposed as a reliable and valid alternative. Alphs et al., examined the psychometric properties of the NSA-4 in two randomized clinical trials. The current study is an effort to replicate their findings.

Methods: Subjects with prominent negative symptoms of schizophrenia were interviewed by videoconferencing Blinded remote raters administered the PANSS immediately followed by the NSA-16. Correlation coefficients between NSA-16 and NSA-4 were calculated for the NSA global rating, the PANSS negative and positive subscales, and several PANSS Marder factors. Cronbach#s alpha and interrater reliability (calculated as an ICC) were determined for the NSA-16 and NSA-4.

Results: The NSA-16 was administered 2804 times by 29 Central Raters, to a total of 483 subjects at 13 visits, including end point. Overall, the correlation between the total scores of the NSA-4 and NSA-16 was high (0.86). Good convergent validity of the NSA-4 was demonstrated by correlations between the NSA-4 and the NSA global rating (r=0.67), as well as the PANSS negative subscale (r=0.73) and the PANSS negative symptoms Marder factor (r=0.73). Divergent validity was demonstrated by low correlations between the NSA-4 and PANSS Marder factors anxiety/depression (r=−0.11), disorganized thought (r=0.29), hostility/excitement (r=0.03), and PANSS positive symptoms (r=0.13). Cronbach's alpha was lower for NSA-4 (#=0.65) compared to NSA-16 (#=0.87). Finally, the interrater reliability estimates for NSA-4 and NSA-16 were 0.94 and 0.97, respectively.

Conclusion: The NSA-4 had very good overall agreement with the NSA-16, and even higher convergent and divergent validity with the selected PANSS subscales and interrater reliability than was demonstrated by Alphs et al.,

Policy of full disclosure: Authors are affiliated with MedAvante.

P-43-036 Effects of 17beta-estradiol on spatial memory and protein expression of BDNF and parvalbumin in WT mice are absent in BDNF heterozygous mice

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Objective: Cognitive impairments are a core feature of schizophrenia which are poorly responsive to current antipsychotics. Brain-derived neurotrophic factor (BDNF) and estradiol (E2) are known for their cognitive enhancing effects. We sought to determine the consequences of ovariectomy (OVX) and hormone replacement on memory performance and expression of proteins implicated in cognitive function at young adulthood in wild-type (WT) and BDNF heterozygous (+/−) mice.

Methods: Prepubescent OVX and hormone replacement (E2 or progesterone (P4)) were conducted in 5 week old female WT and BDNF+/− mice. Spatial memory and recognition memory were examined at 10–11 weeks of age using Y-maze and novel object recognition tasks, respectively. Protein expression of BDNF and parvalbumin (PV) were measured by Western blot in the dorsal (DHP) and ventral (VHP) hippocampus at 12 weeks.

Results: OVX significantly impaired spatial and recognition memory in WT mice while E2 replacement only restored the Y-maze deficit. BDNF+/− intact mice showed a significant deficit in spatial, but not recognition memory compared to WT intact controls. However, OVX improved this spatial memory deficit in BDNF+/− mice as they performed significantly better than WT OVX. Furthermore, E2 replacement reversed this positive effect of OVX in BDNF+/− mice. BDNF and PV expression were significantly reduced in DHP of WT OVX mice compared to intact controls. E2 replacement effectively maintained BDNF and PV expression in WT OVX mice. By contrast, BDNF and PV expression were significantly lower in BDNF+/− compared to WT mice, however OVX and E2 replacement had no further impact on their expression.

Conclusion: These data confirm the cognitive enhancing effects of E2 on spatial memory, and suggest that BDNF and PV expression may mediate this effect in WT mice. Conversely, the effects of E2 are absent in BDNF +/− mice indicating an altered neuroendocrine status in these animals.

Policy of full disclosure: None.

P-43-037 Gray matter volume correlates with comt gene val158met polymorphism in first-episode treatment-naïve patients with schizophrenia

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Objective: Catechol-O-methyltransferase (COMT) plays an important role in modulating cortical dopaminergic catabolism and has been associated with schizophrenia. However, it remains unclear if the variations in dopamine signaling affect the gray matter (GM) structural maturation in typically developing individuals, and whether such effect are disrupted in schizophrenia patients. The aims of this study are: (1) to explore the relationship between the functional polymorphisms Val158Met of COMT gene and GM volume in first-episode treatment-naïve patients with schizophrenia and healthy controls, (2) to investigate the relationship among GM volume and psychiatric symptoms.

Methods: Whole GM volume which was computed by an automated voxel based morphometry by statistical parametric mapping and clinical performances were evaluated in 150 first-episode treatment-naïve patients with schizophrenia and 100 healthy controls. In addition,2-sample t-tests was used to explore the main effect of diagnostic group, a full factorial model was used to obtain genotype-by-diagnostic interaction in the volume of GM according to genotypes of the mentioned polymorphism, and multiple regression was used to explore the correlation between whole GM volume and clinical syndromes, with age and sex as covariance.

Results: GM volume was significantly reduced in the right precentral gyrus[MNI: 37 −16 70], right cerebellum anterior lobe [MNI: 6 −56 26] and left Postcentralgyrus[MNI: −8 −36 80](P<0.05, FWE corrected) in schizophrenia. There was also a strong group×genotype interaction on the right precuneus(P<0.001, uncorrected). A significant positive correlation of the GM volume over the cluster located at middle frontal gyrus [MNI: 36 60 15] with PANSS subscales for general psychopathological symptoms within schizophrenic patients, the negative correlation of the GM volume over the cluster located at parahippocampagyrus [MNI: 27 −10 −25] with PANSS subscales for negative symptoms within schizophrenic patients (FDR correction at p<0.05).

Conclusion: These _ndings suggest that COMT Met variant was associated with disruption of dopaminergic influence on GM maturation and may be the pathogenesis of schizophrenia, and maybe that the abnormal GM structure were association with clinical syndromes.

Policy of full disclosure: None.

P-43-039 A randomized, placebo-controlled repeat-dose thorough QT study of inhaled loxapine in healthy volunteers

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Objective: Single-dose administration of inhaled loxapine via the Staccato® system was not associated with clinically relevant QT prolongation, but the effect of repeat dosing of inhaled loxapine on QTc prolongation has not been previously studied. This study was therefore conducted to investigate potential effects on cardiac repolarization (QT-interval) of 2 consecutive doses of inhaled loxapine administered 2 hours apart (NCT01854710).

Methods: This randomized, double-blind, positive-controlled, crossover study was conducted in healthy volunteers (18–65 years of age). Each subject received: 2 doses of inhaled loxapine (10 mg)+oral placebo; 2-doses of inhaled placebo+oral placebo; or 2 doses of inhaled placebo +oral moxifloxacin (400 mg; [positive control), with >3-days washout between treatments. Inhaled doses were spaced by 2 hours. Primary outcome was maximum effect of inhaled loxapine on QTc interval duration vs. placebo at 12 preselected time points across the 24-hour post-dose interval.

Results: Of 60 enrolled subjects (mean 33.8 years; 52% male), 45 (75%) completed the study. Inhaled loxapine did not increase QT interval across 24-hour post-dose follow-up, as demonstrated by a maximum mean increase in the placebo-corrected change in QTc from baseline of 4.04 msec with the upper 95% CI of 6.31 msec at 5 minutes post second-dose. As a positive control, the lower one-sided 95% CI for moxifloxacin effect was >5 msec at all 4 predefined post-dose time points.

Conclusion: No clinically relevant change in QTc was seen with multiple doses of inhaled loxapine in this population of healthy volunteers. Inhaled loxapine did not significantly prolong the QTc interval in this study. These findings suggest that inhaled loxapine is not associated with cardiac re-polarization liability.

Policy of full disclosure: Study funded by Alexza Pharmaceuticals. Medical writing support, funded by Teva Pharmaceuticals, was provided by Annie Rowe, PhD, of Excel Scientific Solutions. JVC and DAS are employees of Alexza Pharmaceuticals, Inc. PPY is an employee of Teva Pharmaceuticals.

P-43-040 The psychometric properties of night eating questionnaire in Korean schizophrenic outpatients

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Objective: The purpose of this study was to evaluate psychometric properties of the Night Eating Questionnaire (NEQ) as a measure of the Night Eating Syndrome (NES) in schizophrenic outpatients.

Methods: The behavioral and psychological symptoms of NES were assessed with the 14-item self-reported questionnaire (NEQ). Body weight and height were measured to assess the body mass index (BMI). Subjective estimates of depression, binge eating patterns, sleep quality and weight-related quality of life were evaluated using Beck's Depression Inventory (BDI), Binge Eating Scale (BES), Pittsburgh Sleep Quality Index (PSQI) and Korean version of Obesity-related Quality of Life scale (KOQoL).

Results: Results Among 223 schizophrenic outpatients who completed the NEQ, 25 (11.2%) patients screened as having NES (total NEQ >25). NEQ demonstrated high internal consistency (Crobach's alpha=0.74) and item-total correlations (r=0.29~0.75; p<0.001, respectively) were acceptable except morning anorexia. Principal components analysis revealed the presence of four factors (nocturnal ingestions, evening hyperphagia, mood/sleep, and morning anorexia), explaining 56.8% of total variance. Although total score of NEQ was not correlated with BMI, age at onset, duration of illness, use of atypical antipsychotics, it was significantly correlated with total scores of BDI, BES, PSQI and KOQoL. Test-retest reliability was also good (r=0.74, p<0.001).

Conclusion: Our results showed that NEQ appears to be an efficient, valid measure of NES in Korean schizophrenic outpatients.

Policy of full disclosure: None.

P-43-041 Antipsychotics promote the differentiation of oligodendrocyte progenitor cells by regulating oligodendrocyte lineage transcription factors 1 and 2

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Objective: Oligodendrocyte/myelin abnormalities may be an important component of the pathogenesis found in schizophrenia. The aim of this current study was to examine the possible effects of the antipsychotic drugs (APDs) haloperidol (HAL), olanzapine (OLA), and quetiapine (QUE) on the development of oligodendroglial lineage cells.

Methods: CG4 cells, an oligodendrocyte progenitor cell line, were treated with various concentrations of HAL, OLA, or QUE for specific periods. The proliferation and differentiation of the CG4 cells were measured. The regulation of CG4 cell differentiation by oligodendrocyte lineage transcription factors 1 and 2 (Olig1 and Olig2) was examined.

Results: The APDs used in this study had no effect on the proliferation of CG4 cells. The APDs elevated the expression of 2′,3′-cyclic nucleotide 3′-phosphodiesterase (CNP), a specific marker of oligodendrocytes, and promoted the CG4 cells to differentiate into CNP positive oligodendrocytes. QUE and OLA increased the expression of both Olig1 and Olig2 whereas HAL only increased the expression of Olig2.

Conclusion: Our findings suggest that oligodendrocyte development is a target of HAL, OLA, and QUE and provide further evidence of the important role of oligodendrocytes in the pathophysiology and treatment of schizophrenia. They also indicate that the expression level of oligodendrocyte/myelin-related genes could be profoundly affected by APDs, which should be considered in future studies aiming to measure the oligodendrocyte/myelin-related gene expressions in schizophrenia patients.

Policy of full disclosure: Dr.Xin-Min Li receives research grants from Pfizer Canada Inc., Astrazeneca Canada. Dr.Yanbo Zhang receives fellowship from The Rx&D Health Research Foundation (HRF). Drs. Handi Zhang and Junhui Wang have no conflict of interest.

P-43-042 Differences in weight education programs, eating habits, energy levels, and physical activities of patients with schizophrenia or bipolar disorder treated with olanzapine across four countries

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Objective: This post hoc analysis of a multinational observational study assessed the use of weight education programs, eating habits, energy levels, and physical activities in patients initiating or switching to oral olanzapine for the treatment of schizophrenia or bipolar disorder.

Methods: Outpatients with schizophrenia or bipolar disorder from China, Mexico, Romania, and Taiwan who initiated or switched to oral olanzapine (N=622) were assessed monthly (#6 months). A general linear model adjusting for patient baseline characteristics, country, and participation in a weight education program was used to estimate weight changes in relation to program participation.

Results: Less than half of patients participated in a weight education program (China 153/330 patients [46.4%]; Mexico 39/91 [42.9%]; Romania 49/151 [32.5%]; Taiwan 11/50 [22.0%]). At the first program visit, most programs were delivered as individual sessions (range: 72.7%−86.3%); lifestyle/behavioral consultation were used commonly in China (40.5%/37.3% of programs) and Romania (40.8%/34.7%), but rarely in Mexico (7.7%/5.1%); nutritional consultation was used most commonly in Taiwan (72.7%). The potential consequences of weight gain were commonly discussed in China (64.7%) and Romania (65.3%), but rarely in Mexico (2.6%). The least squares mean increase from baseline in weight was significantly higher ($P<0.05$) in patients who did not participate in a program than in those who did in China (1.06 kg) and Romania (2.78 kg). Program compliance significantly improved ($P<0.05$) during the study in China and Romania. There were some country differences in eating habits, energy levels, and physical activities.

Conclusion: Awareness of country differences in weight education programs, eating habits, energy levels, and physical activities may help clinicians identify those patients who would benefit most from these programs after initiation of antipsychotic treatment. Results should be interpreted conservatively due to the observational design.

Policy of full disclosure: Funding source: Eli Lilly and Company.

P-44. Neurodegeneration C

P-44-001 Protective role of 17#-estradiol on glucose transporter and mitochondrial enzymes in brain of aging female rats

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Objective: Aging is a multifactorial process involving neurodegenerative changes in cell morphology and biochemistry. Aging in females and males is considered as the end of natural protection against age related diseases like osteoporosis, coronary heart disease, diabetes, Alzheimer's disease and Parkinson's disease. These changes increase during menopausal condition in females when the level of estradiol is decreased.

Methods: The objective of this study was to observe the changes in activities of mitochondrial enzymes (monoamine oxidase (MAO), Na+K+ ATPase and Ca+ATPase), DNA degradation, and glucose transporter 4 (GLUT4) expression in brains of female rats of 3 months (young), 12 months (adult) and 24 months (old) age groups, and to see whether these changes are restored to normal levels after exogenous administration of estradiol (0.1 µg/gm body weight for one month).

Results: The results obtained in the present work revealed that normal aging was associated with significant decrease in the activity of Na+K +ATPase, Ca+ATPase and GLUT4 levels in the brains of aging female rats, and an increase in DNA degradation and MAO activity. The present study showed that estradiol treatment significantly decreased DNA degradation, and MAO activity in brain of aging rats, and a reversal of Na+K+ATPase, Ca+ATPase and GLUT4 levels was achieved.

Conclusion: It can therefore be concluded that estradiol's beneficial effects seemed to arise from its antilipofuscin, antioxidant, antilipidperoxidative effects, implying an overall anti-aging action. The results of this study will be useful for pharmacological modification of the aging process and applying new strategies for control of age related disorders.

Policy of full disclosure: None.

P-44-002 Pharmacogenetics of angiotensin-converting enzyme inhibitors in patients with dementia due to Alzheimer's disease

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Objective: The angiotensin-converting enzyme is an amyloid-beta-degrading enzyme, with ACE gene polymorphisms rs1800764 and rs4291 accountable for higher angiotensin-converting enzyme activity and local boosting effects upon angiotensin-converting enzyme levels, while showing the most significant effects for risk and age of onset of dementia due to Alzheimer's disease (AD). We aimed to investigate whether rs1800764 and rs4291 are also associated with cognitive change in patients with AD who have systemic hypertension under treatment with angiotensin-converting enzyme inhibitors.

Methods: Participants with late-onset AD according to National Institute on Aging – Alzheimer's Association criteria were screened with Mini-Mental State Examination (MMSE) and Clinical Dementia Rating Sum-of-Boxes (CDR-SB) and followed for one year. Genotyping was undertaken with TaqMan® Real-Time PCR technology for rs1800764 and rs4291, and also for APOE haplotypes. Presence of each ACE gene polymorphism was correlated with APOE haplotypes and treatment using angiotensin-converting enzyme inhibitors. Mann-Whitney test and two-way ANOVA were employed for statistical analysis, significance at $p<0.05$.

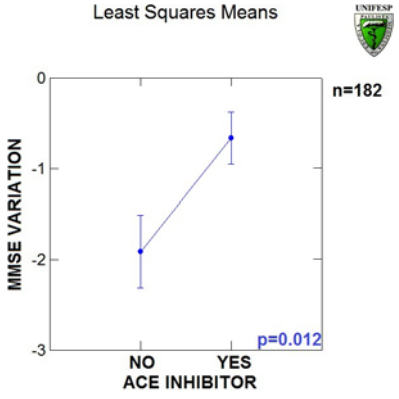
Results: A total of 182 consecutive patients were included, with minor allele frequencies of 0.49 (rs1800764 – C) and 0.34 (rs4291 – T). Overall 173 patients (95.1%) used cholinesterase inhibitors, whereas 149 (81.9%) had systemic hypertension, and 120 (65.9%) used angiotensin-converting enzyme inhibitors. Patients with the APOE-e4/e4 haplotype had earlier onset of AD ($p<0.007$), while rs1800764 and rs4291 genotypes had no influence over age of dementia onset ($p>0.07$). All patients who used angiotensin-converting enzyme inhibitors had slower cognitive decline according to the MMSE ($p=0.012$). Carriers of the rs4291 – TT genotype had slower worsening of CDR-SB scores when they used angiotensin-converting enzyme inhibitors ($p=0.019$), as well as carriers of the rs1800764 – CC : rs4291 – TT haplotype ($p=0.007$).

Conclusion: Angiotensin-converting enzyme inhibitors may slow the cognitive decline of patients with AD, more remarkably for carriers of specific ACE gene polymorphisms.

Policy of full disclosure: This work was supported by CAPES - Coordenação de Aperfeiçoamento de Pessoal de Nível Superior. The authors report the following disclosures: 1. Fabricio Ferreira de Oliveira,

MD, MSc, is a PhD student at the Federal University of São Paulo - UNIFESP in São Paulo, Brazil; he receives a scholarship for academic research from CAPES – Coordenação de Aperfeiçoamento de Pessoal de Nível Superior, a governmental agency in Brazil, and receives personal compensation for acting as a Healthcare Council Member for Gerson Lehrman Group. 2. Paulo Henrique Ferreira Bertolucci, MD, MSc, PhD, is a professor at the Department of Neurology and Neurosurgery of the Federal University of São Paulo – UNIFESP in São Paulo, Brazil; he has received personal compensation for acting as a consultant for Janssen, Lundbeck, Novartis, Pfizer and Support. 3. Elizabeth Suchi Chen, MSc, PhD, is a professor at the Department of Morphology and Genetics of the Federal University of São Paulo – UNIFESP in São Paulo, Brazil. 4. Marilia de Arruda Cardoso Smith, MSc, PhD, is a full professor at the Department of Morphology and Genetics of the Federal University of São Paulo – UNIFESP in São Paulo, Brazil; she receives support for research activities from the following Brazilian public agencies for research: FAPESP – The State of São Paulo Research Foundation, CNPq - Conselho Nacional de Desenvolvimento Científico e Tecnológico, and CAPES - Coordenação de Aperfeiçoamento de Pessoal de Nível Superior.

Effects of angiotensin-converting enzyme inhibitors over Mini-Mental State Examination scores within one year for patients with dementia due to Alzheimer's disease:



P-44-003 Neurotranslational analysis of the role of cholesterol-lowering drugs over cognitive change in Alzheimer's disease

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Objective: To investigate whether polymorphisms of LDLR and CETP genes are associated with cognitive change in patients with dementia due to Alzheimer's disease (AD) who have hyperlipidemia under treatment with statins or Ezetimibe.

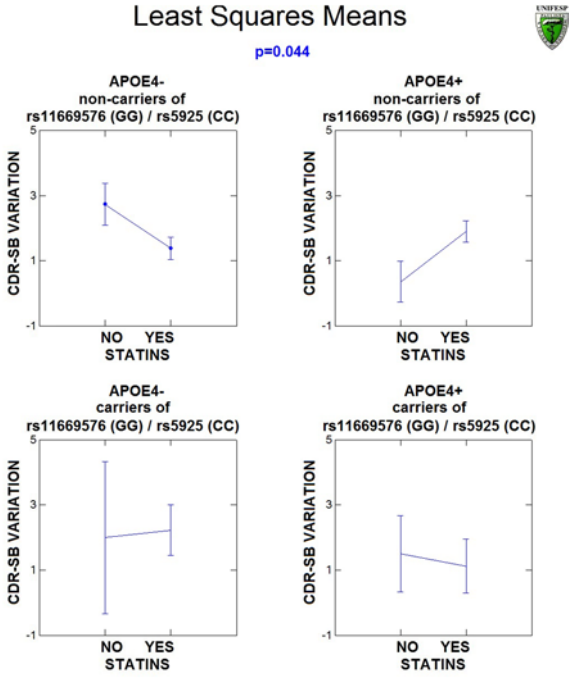
Methods: Participants with late-onset AD according to National Institute on Aging – Alzheimer's Association criteria were screened with Clinical Dementia Rating Sum-of-Boxes (CDR-SB) and Mini-Mental State Examination (MMSE) and followed for one year. Genotyping was undertaken with TaqMan® Real-Time PCR technology for CETP polymorphisms I422 V and TaqIB, and also for APOE, rs5930 (LDLR10), rs11669576 (LDLR8) and rs5925 (LDLR13). Presence of each LDLR or CETP polymorphism was correlated with APOE haplotypes and treatment using Simvastatin, Atorvastatin, Rosuvastatin and/or Ezetimibe. Mann-Whitney test and two-way ANOVA were employed for statistics, significance at $p<0.05$.

Results: A total of 148 consecutive patients were included, considering 101 females (68.2%) and 47 males (31.8%), with minor allele frequencies of 0.07 (rs11669576 – A), 0.35 (rs5930 – A), 0.47 (rs5925 – C), 0.36 (I422 V – G) and 0.37 (TaqIB – A). Carriers of the I422 V-AA genotype had later onset of AD ($p=0.0035$), while carriers of the APOE-e4/e4 haplotype had earlier dementia onset ($p=0.0121$). According to CDR-SB scores, statins slowed the cognitive decline of patients who were APOE4- ($p=0.013$), and also of carriers of the haplotype rs11669576 – GG: rs5925 – CC who were APOE4+ ($p=0.044$). According to MMSE scores, statins led to faster cognitive decline for carriers of the haplotype I422 V – AA : TaqIB – GG ($p=0.012$). Use of Ezetimibe was unrelated with cognitive change, regardless of any genotypes or haplotypes.

Conclusion: Statins may differentially affect the cognitive decline of patients with AD who carry specific genetic profiles.

Policy of full disclosure: This work was supported by CAPES – Coordenação de Aperfeiçoamento de Pessoal de Nível Superior. The authors report the following disclosures: 1. Fabricio Ferreira de Oliveira, MD, MSc, is a PhD student at the Federal University of São Paulo – UNIFESP in São Paulo, Brazil; he receives a scholarship for academic research from CAPES – Coordenação de Aperfeiçoamento de Pessoal de Nível Superior, a governmental agency in Brazil, and receives personal compensation for acting as a Healthcare Council Member for Gerson Lehrman Group. 2. Paulo Henrique Ferreira Bertolucci, MD, MSc, PhD, is a professor at the Department of Neurology and Neurosurgery of the Federal University of São Paulo – UNIFESP in São Paulo, Brazil; he has received personal compensation for acting as a consultant for Janssen, Lundbeck, Novartis, Pfizer and Support. 3. Elizabeth Suchi Chen, MSc, PhD, is a professor at the Department of Morphology and Genetics of the Federal University of São Paulo – UNIFESP in São Paulo, Brazil. 4. Marilia de Arruda Cardoso Smith, MSc, PhD, is a full professor at the Department of Morphology and Genetics of the Federal University of São Paulo - UNIFESP in São Paulo, Brazil; she receives support for research activities from the following Brazilian public agencies for research: FAPESP - The State of São Paulo Research Foundation, CNPq – Conselho Nacional de Desenvolvimento Científico e Tecnológico, and CAPES – Coordenação de Aperfeiçoamento de Pessoal de Nível Superior.

Effects of statins for carriers and non-carriers of rs11669576 - GG: rs5925 - CC according to APOE status:



P-44-004 A case study of primary progressive aphasia, logopenic type – 3 years longitudinal follow-up in a frontotemporal neurocognitive disorder, possible (DSM V)

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Objective: PPA (primary progressive aphasia) was initially described by Mesulam and diagnosis can now be made in any patient who has a language disorder (aphasia) that is due to a neurodegenerative disease (progressive) and in whom the aphasia is initially the most salient feature of the clinical picture (primary). PPA have been the focus of several studies during the past decades. The progression occurs in the course of years rather than months, and the primary nature of the aphasia is demonstrated by showing that memory for recent events, the recognition of familiar faces and objects, reasoning, and basic aspects of comportment are relatively preserved at the initial stages. Dementia may develop later in the course, but the aphasia predominates. There are now described 3 variants: agrammatic/dysfluent, semantic, and logopenic. The logopenic variant is characterized by interruptions of fluency due to frequent word finding pauses but relatively intact syntax and word

comprehension. Anomia is present in all variants but may become the principal feature of the logopenic subtype. We report a 57-years old woman suffering from problems in recalling names of objects for 2,3 years (2011). Screening measures showed mild cognitive decline in 2011, and important now. We discuss the various diagnoses that the patient had during 3 years, and the difficulty to find the correct one in such cases.

Methods: Clinical, neuro-imagistic aspects, lab results, as well as evolution and treatment are being discussed.

Results: The final diagnosis was PPA, logopenic type – Frontotemporal Neurocognitive disorder, Possible (DSM V).

Conclusion: In this moment there is no treatment approved for the treatment of this disorder but there are some studies related to the effect of mementine, so we have started this treatment and symptomatic treatment (antipsychotics, anxiolytics). The prognosis is 6–11 years since the first apparition of the symptoms.

Policy of full disclosure: None.

P-44-005 A common target in type 2 diabetes mellitus and Alzheimer's disease (AD)

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Objective: AD is characterized by the presence of senile plaques, neurofibrillary tangles, and neuronal loss in defined regions of the brain. Type 2 Diabetes Mellitus (T2DM) has been shown to be highly correlated with AD development. Pathologies common to both diabetes and AD include vascular impairment, neurodegeneration and plaque accumulation, and these AD symptoms may be exacerbated by T2DM. However, the precise mechanism by which T2DM is associated with AD remains unclear. To address this question, we induced a diabetic complication, using a pharmacological drug, streptozotocin (STZ) to study the mechanisms of insulin signaling impairments in the context of how T2DM may contribute to AD pathologies. We further targeted insulin-related potential signaling molecules, glucagon like peptide-1 (GLP-1) and glycogen synthase kinase 3 beta (GSK3#).

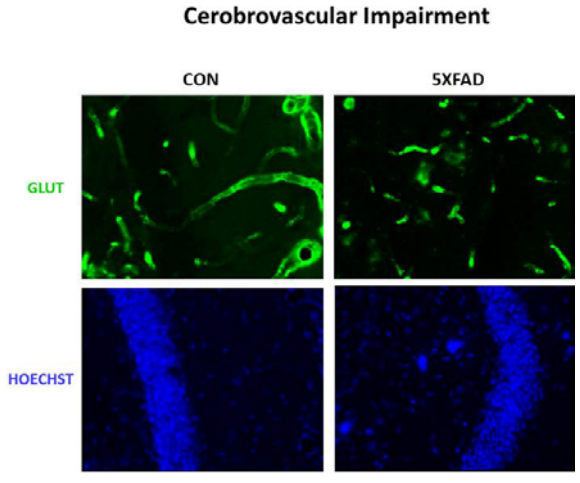
Methods: Peritoneal injection of STZ was performed to induce T2DM in APP/PS1 mice. Blood glucose level was measured using ELISA for validation of STZ- induced diabetes, and immunohistochemistry and microscopic methods were used for characterizing cerebrovascular integrity, neurodegeneration and glia-induced inflammation.

Results: Cerebrovascular impairment was associated with plaques in APP/PS1 mouse brains, while there were no signs of comparable damage in WT mice. This impairment was accompanied by excessive activation of astrocytes, a sign of inflammation. Our immunoblotting data showed that the expression of glucose transporter (GLU-T), a marker for blood vessel integrity, was decreased in APP/PS1 mouse brain. This measure of reduced GLU-T levels, was associated with damaged cerebrovascular system, was supported by GLU-T immunohistochemistry. We conclude that these pathologies are accelerated by STZ-induced diabetes and GLP-1, demonstrating the potential links between diabetes and AD.

Conclusion: Our data indicate that vascular damage is accompanied by excessive activation of astrocytes, associated with accumulated plaques. STZ-induced diabetes provides a valid animal model to study diabetes-associated AD, and as a model for sporadic cases of AD.

Policy of full disclosure: None.

Vascular impairment in APP/PS1 mouse brain:



P-44-006 Dopamine D2/3 agonist ropinirole medication differentially affects decision-making under risk or uncertainty on rodent models of gambling behaviour

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Objective: The more traditional drug treatment for Parkinson's Disease (PD), L-DOPA, has shown over time to produce debilitating side-effects such as dyskinesia. Selective dopamine agonists that act on the D2/3 receptors such as pramipexole and ropinirole have been used to treat the motor symptoms of PD, but these drugs may lead to a variety of Impulse Control Disorders (ICDs) including pathological gambling in some patients. Few studies have looked at the effect of ropinirole on impulsive or risky behaviours.

Methods: Rats learned either the rat gambling task (rGT)- a rodent analogue of the Iowa Gambling Task used clinically to assess decision-making under risk, where rats chose between four options, each associated with differing probabilities of reward and punishment, or the Betting task- a paradigm which captures irrational decision-making under uncertainty in which rats choose between a guaranteed reward versus a 50:50 chance of double that reward or nothing. The behaviour of 24 rats on each task was assessed before and following implantation of an osmotic mini-pump delivering either ropinirole at 5 mg/kg/day or a saline solution for 28 days.

Results: Chronic ropinirole increased premature responses on the rGT, but did not affect choice of the risky option. In the Betting task, chronic administration of ropinirole led to an increase in choice of the uncertain lever regardless of the baseline preference characteristic of each rat.

Conclusion: This bias towards uncertainty produced by chronic ropinirole medication may explain why some PD patients treated with selective dopamine medication develop gambling and other risky and maladaptive behaviours. We intend to follow up these findings by determining the impact of chronic ropinirole in a dorsostriatal 6-hydroxydopamine (6-OHDA) lesion model of PD. These studies will help characterise the specific type of impairments experienced by PD patients taking dopamine agonist therapy and provide knowledge of the neurological mechanism underlying them.

Policy of full disclosure: None.

P-45. Biomarkers (incl. Pharmacogenomics and brain imaging) for diagnosis and treatment response C

P-45-001 Haplotype analysis of genetic polymorphism in antisocial alcoholism

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Objective: To evaluate the promoter region, exon 8 and exon 14 of MAO-A gene in antisocial alcoholism subjects (cases).

Methods: The normal control and cases were Thai males with more than 18 years old. The normal control subjects were screened using Alcohol Use Disorder Identification Test (AUDIT) (<8) and Tridimensional Personality Questionaire (TCI) and 77 subjects passed the criteria. For the cases, they were screened using Alcohol Use Disorder Identification Test (AUDIT) (>8), Mini-International Neuropsychiatric Interview (M.I. N.I) (type 1 and 2) and Tridimensional Personality Questionaire (TCI). There were 2 groups of the cases; type 1, the alcoholics who started to drink alcohol #25 years of age and had no antisocial behavior (n=125). Type 2 was the alcoholics who started to drink alcohol <25 years of age and had antisocial behavior (n=126).

Results: For MAO-A promoter study, genomic DNA was amplified in vitro, 3 alleles of 30-bp repeat polymorphism were detected for 3, 4 and 5 repeated polymorphisms. Three repeated polymorphisms of MAO-A promoter in normal control, type 1 and type 2 cases were 54.5, 53.6 and 51.6%, respectively. Four repeated polymorphisms of MAO-A promoter in normal control, type 1 and type 2 cases were 45.5, 45.6 and 48.8%, respectively. Five repeated polymorphisms of MAO-A promoter was detected only in type 1 cases (0.8%). However these results were non-significant different between controls and cases both type 1 and 2 by using X2-test. For exons 8 and 14 of MAO-A gene study using PCR and cutting amplicon of exons 8 and 14 with Fnu4HI and EcoRV, respectively.

Conclusion: The results showed that DNA polymorphism of exons 8 and 14 in control and cases both types 1 and 2 were non-significant different by using X2-test. Haplotype distribution of these 3 markers was studied and results were non-significant different between controls and cases.

Policy of full disclosure: None.

P-45-002 Clinical predictors of drug response in patients with obsessive-compulsive disorder

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Objective: The aim of this study was to evaluate which clinical variables might influence the antiobsessional response to proserotonergic drugs in a sample of patients with obsessive-compulsive disorder (OCD).

Methods: Two hundred forthy-nine patients with DSM-IV OCD underwent mean 13-month treatment with selective serotonin reuptake inhibitors. According to treatment response, defined as a reduction of the Yale-Brown Obsessive Compulsive Scale total score >35% and CGI 1 or 2, patients were divided into two groups.

Results: One hundred fourteen patients responded to treatment and one hundred thirty five patients did not. Responders had a significant high long duration of treatment, short duration of pre-treatment medication and higher frequency of drug naïve cases and lower baseline Y-BOCS scores.

Conclusion: The pre-treatment factors including pre-treatment period, drug naïve or not and baseline OCD symptoms and the factor of duration of treatment may influence drug treatment response in OCD patients.

Policy of full disclosure: None.

P-45-003 Plasma clomipramine levels in obsessive-compulsive disorder

D. Marazziti[1], S. Baroni[1], L. Dell´Osso[1]. [1]*Università di Pisa, Pisa, Italy*

Objective: The aim of this study was to explore the possible relationship between plasma clomipramine (CMI) and its major metabolite N-desmethylclomipramine (DMCMI) levels and related parameters, and clinical features in OCD patients.

Methods: Twenty-six OCD outpatients (13 men, 13 women), suffering from OCD were consecutively enrolled in the study. The severity of OCD was assessed by the Yale-Brown Obsessive Compulsive Scale (Y-BOCS). The measurements were carried out after four weeks and six months from the beginning of the treatment. The drug levels were measured by a HPLC method developed by us. The correlations between biological and clinical parameters were analyzed by means of the Spearman#s correlation coefficient. The Mann-Whitney test was used for comparing biological and clinical variables between men and women.

Results: The results showed that CMI levels were related to the doses at the two assessment times. A significant and positive correlation was detected at the beginning between the DMCMI ratio and the Y-BOCS total score, however this was true only for men, where the similar correlations were measured also with the Y-BOCS subscale. After six months of CMI, men showed a significant improvement of the compulsions.

Conclusion: These findings would highlight the potential impact of assessing CMI plasma levels and their relationships with specific symptoms, as well as the influence of the gender on the drug response.

Policy of full disclosure: None.

P-45-004 Abelson helper integration site-1 gene variants on major depressive disorder and bipolar disorder

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Objective: The present study aimed to explore whether 4 single nucleotide polymorphisms (SNPs) within the AHI1 gene could be associated with major depressive disorder (MD) and bipolar disorder (BD), and whether they could predict clinical outcomes in mood disorders.

Methods: One hundred and eighty-four (184) patients with MD, 170 patients with BD and 170 healthy controls were genotyped for 4 AHI1 SNPs (rs11154801, rs7750586, rs9647635 and rs9321501). Baseline and final clinical measures for MD patients were assessed through the Hamilton Rating Scale for Depression (HAM-D). Allelic and genotypic frequencies in MD and BD subjects were compared with those of each disorder and healthy group using the #2 statistics. Repeated measures ANOVA were used to test possible influences of SNPs on treatment efficacy.

Results: The rs9647635 A/A was more represented in subjects with BD as compared with MD and healthy subjects together. The rs9647635 A/A was also more presented in patients with MD than in healthy subjects. With regard to the allelic analysis, rs9647635 A allele was more represented in subjects with BD compared with healthy subjects, while it was not observed between patients with MD and healthy subjects.

Conclusion: Our findings provide potential evidence of an association between some variants of AHI1 and mood disorders susceptibility but not with clinical outcomes. However, we will need to do more adequately-powered and advanced association studies to draw any conclusion due to clear limitations.

Policy of full disclosure: This study was supported by a grant from the Korean Health Technology R&D Project, Ministry of Health & Welfare, Republic of Korea (A120004).

P-45-005 Reduction in serum brain derived neurotrophic factor concentration with subcallosal deep brain stimulation treatment for refractory depression

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Objective: Subcallosal cingulate (SCC) deep brain stimulation (DBS) is a promising experimental treatment for treatment resistant depression (TRD). Given the role of brain derived neurotrophic factor (BDNF) in neuroplasticity and antidepressant efficacy, we examined the effect of SCC-DBS on serum BDNF in TRD.

Methods: Four patients with TRD underwent SCC-DBS treatment. Following a double-blind stimulus optimization phase of 3 months, patients received optimal continuous stimulation in an open label fashion for 6 months. Clinical improvement in depressive symptoms was evaluated bi-weekly for 6 months using Hamilton Depression Rating Scale (HDRS). Mature serum BDNF levels were measured 1 week before and 9 months post-DBS.

Results: Out of four patients, three responded to SCC-DBS with two showing full clinical response (50% reduction in HDRS scores) and one showing partial response (35% reduction in HDRS scores) at the clinical endpoint. Interestingly, all 4 patients showed reduction in serum BDNF concentration from pre-DBS baseline.

Conclusion: SCC-DBS for TRD may be associated with decreased levels of serum BDNF. Longitudinal studies with multiple measurements in a larger sample are required to determine the role of BDNF as a biomarker of SCC-DBS and its antidepressant efficacy.

Policy of full disclosure: Supported by Hotchkiss Brain Institute (HBI), Calgary, Calgary Health Region, & Alberta Innovates and Health Solutions (AIHS).

P-45-006 Elevated serum amyloid a in depressive patients and its potential use as a clinical biomarker

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Objective: The biology of depression is becoming more understood, however, the need for reliable biomarkers remains evident. Studies have shown marked elevations in the cerebral spinal fluid (CSF) and plasma of inflammatory cytokine levels of depressed and suicidal patients. Serum Amyloid A (SAA) proteins are regulated in liver cells by the pro-inflammatory cytokines IL-1, IL-6, and TNF-α. These acute-phase SAAs (A-SAAs) are implicated in several chronic inflammatory diseases, and have also been shown to be elevated following administration of bacterial lipopolysaccharide (LPS) in mice. In this study, we show significant correlations with depressive symptoms and SAA levels in human plasma. These findings could implicate SAA as a potential biomarker for depression in the clinical setting.

Methods: 89 male and female patients, ages 18–67 with varying psychiatric histories were enrolled in this study. Plasma samples were analyzed utilizing the electrochemiluminescent technology of Mesoscale Discovery. Growth Factor 4-plex, Vascular Injury II 4-plex, Pro-inflammatory 9-plex, and Chemokine 9-plex assays were run on the SI6000 machine. Depressive symptoms and suicidality were evaluated using the Patient Health Questionnaire 9 (PHQ9), The Center for Epidemiological Studies Depression Scale (CES-D), Hamilton Depression Rating Scale (HAM-D), and SCID-1.

Results: Significant correlations between lnSAA and depressive symptoms were found. Crying spells, loss of appetite, feeling tired or having little energy, were among the positive correlations with peripheral SAA. Raw sampling also showed a positive correlation with suicidal intent and SAA levels. Furthermore, SAA levels correlate with IL-6 in these patients.

Conclusion: This study shows direct evidence of increased SAA levels in patients with depressive symptoms. Utilizing this protein for monitoring peripheral inflammation could prove advantageous in developing a panel of biomarkers for depression.

Policy of full disclosure: None.

P-45-007 QEEG biomarkers of sustained response to rapid antidepressant effect of NMDA antagonist in major depressive disorder

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Objective: A series of clinical studies demonstrated that QEEG (quantitative electroencephalography) prefrontal theta cordance value decreases after one week of treatment in responders to antidepressants and precedes clinical improvement. Ketamine, a non-competitive antagonist of NMDA receptors, has a unique rapid antidepressant effect but its influence on QEEG measures is still unknown. To date wasn't studied predictive value of cordance in response to single infusion of ketamine in depressive subjects.

Methods: In a double-blind, cross-over, randomized, placebo-controlled experiment we studied the influence of ketamine (0.54 mg/kg) on theta cordance in a group of 27 right-handed hospitalized depressive patients on stable antidepressant medication. QEEG cordance values in theta frequency band were calculated according to UCLA algorithm.

Results: Responders (n=11) to ketamine in compare to non-responders (n=16) showed significant difference in cordance values at the end of ketamine infusion (Spearman, p=0.039). The cordance decrease, measured between the end of infusion and next day, positively correlated with ketamine antidepressant response (MADRS decrease) fourth day after infusion (two-tailed Fisher's Exact test, df=1, p=0.0076) with NPV 90.9% (95% CI 64.3%–99.5%) and PPV 62.5% (95% CI 44.2%–68.4%).

Conclusion: Our data indicate that ketamine infusion immediately induces similar changes as monoaminergic-based antidepressants do gradually after a series of downstream signalling steps. The reduction in theta prefrontal cordance could serve as a biomarker of sustained antidepressant response, a hypothesis that should be tested in larger depressive population.

Policy of full disclosure: This study was supported by IGA MH CR: NT13403-4, NT12024-5; PRVOUK P34 and RVO-PCP/2012. The study was registered with EU Clinical Trials Register [EudraCT number 2009-010625-39].

P-45-008 Association of BDNF promoter methylation and genotype with suicidal ideation in elderly Koreans

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Objective: Brain-derived neurotrophic factor (BDNF) has been considered a risk factor for suicidal behavior in adult populations. BDNF secretion is influenced by epigenetic (DNA promoter methylation) and genetic (val66-met polymorphism) profiles. We investigated the independent and interactive effects of BDNF methylation status and val66met polymorphisms on late-life suicidal ideation.

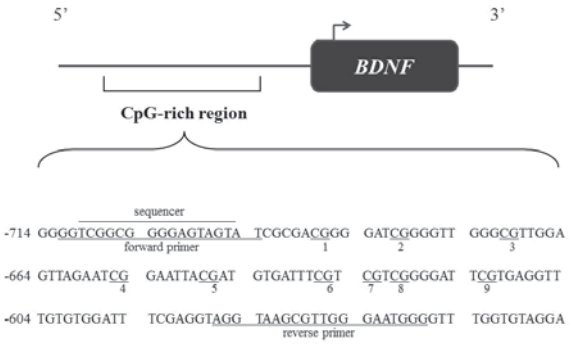
Methods: In total, 732 Korean community residents aged 65+ were evaluated; of 639 without suicidal ideation, 579 (90.6%) were followed up 2 years later. The prevalence and incidence of suicidal ideation were ascertained using the Geriatric Mental State Schedule. Socio-demographic and clinical covariates included age, gender, education, depressive symptoms, cognitive function, and disability. The independent effects of BDNF methylation status on the prevalence and incidence of suicidal ideation were investigated using multivariate logistic regression models. The two-way interactions of BDNF methylation status and val66met polymorphism on suicidal ideation were assessed using the same models.

Results: Higher BDNF methylation status was significantly associated with both prevalence and incidence of suicidal ideation, independent of potential covariates. No significant methylation-genotype interaction was found.

Conclusion: The BDNF hypothesis and the epigenetic origin of the suicidal behavior were supported, even in old age. BDNF promoter methylation status may be useful as a biological marker for suicidality in late life.

Policy of full disclosure: This study was supported by a grant of the Korean Health Technology R&D Project, Ministry of Health & Welfare, Republic of Korea (A120051). The Ministry of Health and Welfare of Korea had paper publication design; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

Figure1:



P-46. Attention deficit disorders C

P-46-001 Nicotine's effects on cognitive effort are dependent upon individual differences: Acetylcholine manipulation on a rodent cost/benefit decision-making task

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Objective: All individuals are confronted with choices that require weighing potential benefits against their associated costs. Animal models of such cost/benefit decision-making have typically focused on dopaminergic contributions to choice. Acetylcholine is heavily interconnected with the dopaminergic system, and has also been demonstrated to be essential element in many cognitive processes. Despite this, its contribution to cost/benefit decision making remains poorly understood, especially within the realm of effort.

Methods: Here we utilize a rat Cognitive Effort Task (rCET) to probe acetylcholine's contribution to effortful decision making. In the rCET, animals can choose either an easy trial, where the visuospatial attentional demand is low but the potential reward (sugar) is small, or a difficult trial on which both the attentional demand and available reward are greater. Following the establishment of baseline behaviour, four drug challenges were administered via intraperitoneal injection: nicotine, mecamylamine, oxotremorine, and scopolamine.

Results: As per previous studies, animals were divided by their baseline preferences, with "workers" choosing high-effort/high-reward options significantly more than "slackers". Nicotine dose-dependently caused slackers to choose even fewer high-effort trials than at baseline, but had no effect on the choice of workers, which was near ceiling. Despite these opposing effects on choice, nicotine greatly increased motor impulsivity for all animals. Interestingly, nicotine did not affect animals' ability to perform the task, i.e. did not benefit or impair their visuospatial attention.

Conclusion: Nicotine appears to exacerbate existing choice preferences for mental effort expenditure. Acetylcholine's contribution to decision making may therefore be best understood as a function of the individual differences in sensitivity to effort costs. As such, this research suggests novel therapeutic strategies based on individuals' underlying preferences.

Policy of full disclosure: None.

P-46-002 The effect of chronic atomoxetine treatment during adolescence on decision making and impulsive action in adulthood

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Objective: Atomoxetine, the first nonstimulant drug approved for the treatment of attention deficit hyperactivity disorder (ADHD), is a selective norepinephrine reuptake inhibitor (SNRI) that is efficacious in reducing the hyperactive, inattentive, and impulsive symptoms that characterize the disorder. Treatment for ADHD is administered chronically during adolescence, a time when the frontal brain regions necessary for executive function and impulse control are undergoing extensive maturation. Having previously shown that chronic atomoxetine treatment during adolescence decreases impulsive choice in adulthood, we set out to investigate its putative long-term effects on more complex decision-making processes using the rodent gambling task (rGT).

Methods: 24 Long-Evan rats were administered saline or 1.0 mg/kg atomoxetine daily from postnatal day 40–54, a time period reflecting rodent

adolescence. Two weeks following treatment, all animals were trained and assessed in the rGT. In this task, rats must choose between four response options that are each associated with the delivery of a different amount of reward, as well as different probabilities of receiving said reward. The rGT is also a sensitive measure of impulsive action, whereby premature responses made prior to stimulus onset are recorded.

Results: Regardless of the treatment administered during adolescence, rats learned to favour the advantageous options characterized by small, low penalty rewards in lieu of the larger, higher penalty reward options. rGT performance was then assessed following acute treatment with atomoxetine (0.1–1.0 mg/kg) or amphetamine (0.3–1.5 mg/kg). Across groups, the highest dose of atomoxetine decreased choice of the most advantageous choice option, and decreased premature responding at all doses tested. Amphetamine also impaired choice performance, but increased premature responding across groups.

Conclusion: These data suggest that chronic atomoxetine treatment during adolescence does not affect complex decision-making in adulthood, but that acute treatment with atomoxetine, while reducing impulsive action, can impair optimal decision-making.

Policy of full disclosure: None.

P-46-003 The efficacy of atomoxetine in treating adult ADHD: A meta-analysis of placebo-controlled trials

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Objective: To study the efficacy of atomoxetine in the treatment of adult attention deficit hyperactivity disorder [ADHD] compared to placebo.

Methods: We performed a Medline, search for English language publications of Randomized Controlled Trials (RCTs) comparing atomoxetine to placebo for adult ADHD using the keywords 'adult ADHD', 'atomoxetine' and 'placebo'. A total of 45 RCTs were returned of which we included eleven relevant RCTs reporting data on 2692 patients with adult ADHD in the analysis. Standardized mean difference between atomoxetineand placebo for the mean baseline-to-endpoint change in total ADHD scores, impulsivity/hyperactivity and inattention scores was calculated, with a 95% confidence limit.

Results: Atomoxetine had superior efficacy than placebo in treating adult ADHD [−0.40; 95% CI −0.48, −0.32; overall effect p<0.00001]. Atomoxetine was superior to placebo on both the domains of inattention [−0.39; 95% CI −0.47, −0.31; overalleffect p<0.00001] and impulsivity/hyperactivity [−0.34; 95% CI −0.42, −0.26; overall effect p<0.00001].

Conclusion: Atomoxetine is efficacious in treating adult ADHD compared to placebo, though the efficacy is marginally superior for inattention than hyperactivity/impulsivity.

Policy of full disclosure: None.

P-47. Gender and mental health

P-47-001 First onset postpartum psychosis and first line treatment: Series of five case studies remitted with olanzapine

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Objective: Postpartum psychosis [PPP] is rare disorder with an estimated prevalence in the general population of 1–2 per 1,000 childbirths. PPP is a psychiatric emergency that requires inpatient psychiatric treatment because it can have negative consequences for the mother, infant, and entire family.

Methods: We present five patients diagnosed with first onset PPP treated with olanzapine during the last year (2013th) in our Intensive care unit. All of our patients experienced clear phenomenological predominance of psychotic symptoms with no evidence of neither manic nor depressive symptoms.

Results: Median age of our patients was 31 years (range 27–40; interquartile range [IQR] 10), all of them were primiparous, and experienced some of the obstetrical complications during delivery. None of our patient had previous history of psychiatric illnesses, and only one had positive family history. The median onset of psychotic symptoms that led to hospitalization occurred at 12 days postpartum (range 8–25; IQR 10, 5). Median duration of hospitalization was 11 days (range 6–38, IQR 20.5). One patient was discharged prior to achieving full remission because of the infectious complications, although she showed clear response to treatment prior to demission. We treated all patients with olanzapine, and we used bromocriptine for every patient to achieve ablactation. Supplementary therapy was used according to symptomatology and the progress of treatment, namely low doses of typical antipsychotics (n=3), and benzodiazepines (n=4). Two of our patients had a typical antipsychotic still included in discharge therapy, and three of them had benzodiazepines.

Conclusion: According to out database search there are no clear guidelines regarding the treatment of first onset PPP in the patients with no prior history of psychiatric illnesses. According to our data, olanzapine proved itself as a valuable first line treatment. At this point there is a definite need for further investigations of preferably prospective design for the full understanding and possibly developing clear guidelines for PPP.

Policy of full disclosure: None.

P-47-002 The effect of depression on long-term risk incidence of cardiovascular diseases in female population aged 25–64 in Russia: Based on monica-psychosocial epidemiological study

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Objective: To explore the influence of depression (D) on relative risk of myocardial infarction (MI), arterial hypertension (AH) and stroke in female population of 25–64 years in Russia.

Methods: Under the third screening of the WHO "MONICA-psychosocial" (MOPSY) program random representative sample of women aged 25–64 years (n=870) were surveyed in Novosibirsk. D was measured at the baseline examination by means of test MOPSY. From 1995 to 2010 women were followed for 16 years for the incidence of AH, MI and stroke. Cox proportional regression model was used for assessment of relative risk (HR) of cardiovascular diseases.

Results: The prevalence of D in women aged 25–64 years was 55.2%. Over 16 years of study MI was developed in 2.2% of women, stoke - in 5.1%. 16-years risk of MI development in women having D was 2.53-fold (95% CI:1.26–24.34; p<0.05), HR of stroke was 4.63-fold (95% CI:1.03–20.89; p<0.05) higher compared to those without D. HR of AH in women with D over the first 5 and 10 years of study was 1.6-fold (95.0%CI:0.86–2.98; p<0.05) and 1.74-fold higher (95.0%CI:1.01–3.01; p<0.05) compared to those without D, respectively. MI, AH and stroke rates were more likely in married women having D with average educational level. Rates of AH was higher in first-line managers (chi-square=4.38 df=1 p<0.05) and easy manual laborers with D (chi-square=4.61 df=1 p<0.05). Similar tendencies in occupational class were typical for MI and stroke.

Conclusion: The prevalence of D in women aged 25–64 years is more than 50%. Over 16 years women with D have significantly higher risk of AH, MI and stroke than without D, especially in married women whose job positions were manager and physical worker.

Policy of full disclosure: None.

P-47-003 Maternal mental health: A prospective naturalistic study of the outcome of pregnancy in women with major psychiatric disorders in an African country - Update on fetal outcome

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Objective: There is a general consensus that mothers suffering from pre-existing mental illness are at an increased risk for pre-and post partum complications. The extent of the risk to the fetus has not been studied fully in Sub-Saharan Africa. A collaborative network of state and private practice clinics in Cape Town, South Africa monitor mothers suffering from mental illness. The aim is to address the paucity of data on the outcome of pregnancy in women with major psychiatric disorders in Sub-Saharan Africa.

Methods: This update reports on the first 75 pregnant female mental health users managed at the maternal mental health clinic at Stikland Hospital (one of the network of clinics) in this prospective study design. Data are collected as part of patient reviews during care-as-usual visits and for the purposes of this report we focus on fetal outcome (i.e. mortality).

Results: The 1st 75 participants (mean age 29 years) presented on average at 16 weeks pregnancy duration, with 20 of the cases being primigravida. The most common primary psychiatric diagnoses were major depressive disorder (n=25), bipolar mood disorder (n=21) and schizophrenia spectrum disorders (n=11). Pregnancy outcome data are available on 59 pregnancies (16 pregnancies ongoing at time of this report) at time of this report and shows 8 unsuccessful pregnancies including two voluntary abortions (8 and 10 weeks), four miscarriages (8, 21, 22 and 25 weeks),

one stillborn baby (>28 weeks), one death at day 5 post partum. Poor adherence to post partum follow-up was a common occurrence.

Conclusion: This update on fetal outcome in mental health users show a number of complicated pregnancies and this is compounded by irregular contact with psychiatric services. Effort should be made to improve adherence to regularly scheduled follow-up as the risk for a complicated pregnancy outcome is significant.

Policy of full disclosure: National Research Foundation of South Africa, Faculty of Health Sciences, University of Stellenbosch

P-48. History of neuropsychopharmacology

P-48-001 LSD treatment in Danish psychiatry, especially emphasizing the neurotoxic potentials of LSD. A follow-up study of 151 patients

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Objective: The purpose of the present study was to evaluate the long-term outcome of LSD-treatment in a population of Danish psychiatric patients. We aimed at estimating possible beneficial and damaging effects of the LSD-treatment. Finally the aim was to find evidence for the neurotoxic potentials of LSD.

Methods: From 1959 around 400 patients were treated with LSD in Denmark, the majority in the early and mid-1960'ies. In 1986 the LSD Damages Law was passed, and thereby patients treated with LSD could apply for compensation. Each application was dealt with in a tribunal under the Ministry of Social Affairs. The total material including hospital case records, applications, medical and psychiatric certificates and evaluation sheets of the tribunal was later on referred to the Danish State Archives. This material including 151 of the 154 applicants has been carefully studied.

Results: Already during the first years of treatment one homicide, two suicides and four attempted suicides were reported. However, a review published in 1964 of the first 129 patients within a broad spectrum of diagnoses found 45 % unchanged and 55 % improved. In total all 154 applicants being treated with LSD received economic compensation for LSD inflicted damages. In 151 applicants 5 % later on went through psychosurgery, 14 % developed a psychotic/schizophrenic breakthrough, 14 % developed recurrent or chronic depression, 69 % suffered from persistent flashback experiences and around 66 % reported increased chronic anxiety.

Conclusion: In the 1960'ies international warnings of the medical use of LSD were ignored. Even if the 154 applicants of this study are not representative of the total LSD material, the high incidence of serious damages in this subset is worrying. There is no conflict between the acute stimulating effect seen in a few patients and lasting serious damages observed in this sample. LSD is considered to possess neurotoxic potentials.

Policy of full disclosure: None.

P-49. Pharmacoeconomics

P-49-001 The importance of tardive dyskinesias in schizophrenia based on 21 cases. Tests run in psychiatry department of the military hospital of Marrakesh – Morocco

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Objective: We are going to analyze the occurrence processes according to incriminated therapeutic generation. We will also discuss the epidemiological and clinical features of tardive dyskinesia before focusing on therapeutical paharmaco-logics (and not pharmacologic) perspectives.

Methods: Through a retrospective study based on observations about 21 schizophrenic male patients suffering from a tardive dyskinesia of an iatrogenic origin, at the psychiatric department of the military hospital of Marrakesh between 2010 and 2012.

Results: In practice, tardive dyskinesias set up after many years of exposure to high antipsychotic dosages. However, they can occur – rarely indeed – rapidly and at low dosages (Correl CU et al, 2004). The late dyskinesias show resistance toward therapeutics causing social stigmatization by their « rabbit syndrome » aspect. They substantially decrease the quality of life and increase mortality and morbidity (Tarsy D et al, 2006). The extra pyramidal symptoms make the psychological suffering worse at the psychotic and depressive levels. The patients suffering from dyskinesia show more positive and negative psychotics symptoms compared to control schizophrenic patients. The tardive dyskinesias are associated to unsuccessful therapeutical prognosis in schizophrenia (Spivak B et al, 1997).

Conclusion: Dyskinesias induced by neuroleptics are a common side effect, regardless of the generation therapeutic complained, combining both classical neuroleptics that atypical antipsychotics. Prevention is the best prescription adequately carefully weighing the risk-benefit ratio, especially concerning the prescription of "hidden neuroleptics."

Policy of full disclosure: None.

P-49-002 Hyperprolactinemia and antipsychotic treatments: Screening and treatment strategy, based on 25 cases. Experiences run by the psychiatry department of the military hospital of Marrakesh-Morocco

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Objective: The study aims to analyze the discoveries circumstances, the clinical and biological features of hyperprolactinemia induced by those psychotropic drugs in addition to their evolving particularities, in order to set up recommendations about the neuroleptics prescription and the patients follow up procedures.

Methods: It is a retrospective study based on 25 cases of male patients suffering from hyperprolactinemia treated at the psychiatry department of the military hospital in Marrakesh, between 2005 and 2012, and who were put under antipsychotics.

Results: Clinical signs of sexual circumstance was the most common finding (Haddad PM et al, 2004). The average value of the PRL was 62±24 ng / mL. Pharmacological classes were encountered risperidone alone (07 cases), Olanzapine alone (03 cases), Haloperidol alone (07 cases), Olanzapine levomepromazine+(05 cases) and 03 cases of patients under neuroleptic treatment delay based Fluphenazine. Magnetic Resonance Imaging hypothalamic pituitairy was requested for all patients and no hypothalamic-pituitary abnormalities were detected. A combination with other therapeutics was revealed in 06 cases (antihypertensives and antihistamines). Dosages of psychotropic treatments were reduced in 18 cases, the change to other antipsychotic less hyperprolactinemia was observed in 07 cases. The normalization of the PRL was obtained on average in three months. No dopamine agonist therapy was prescribed in these cases. Treatment with injectable testosterone was required in two cases where a biological hypogonadism was confirmed.

Conclusion: The HPRL induced by antipsychotics is undervalued despite its frequency and yet not without clinical consequences. In addition to sexual disorders often factors of poor adherence to treatment, there is a potential long-term somatic development-related bone abnormalities and a possible increased risk of breast cancer or prostate cancer. For all these reasons, hyperprolactinemia must be careful research, through a pretreatment assessment and monitoring of patients, integrating in the analysis of risk / benefit ratio of antipsychotic treatment.

Policy of full disclosure: None.

P-49-003 Atypical Antipsychotic (AAP) use & cost trends in Indiana medicaid (MA) children & teens (2004–2012)

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Objective: The US Agency for Healthcare Research and Quality (AHRQ) and Rutgers U formed a 16-state consortium (including IN) to study the rapid escalation of antipsychotic (AP) use in MA youth. On average 1.6% (2007 data) were exposed to at least 1 AP (range 0.6–4%). Another key finding was the high rate (12%) of AP exposure in MA foster children. The goal of the present study was to replicate and extend the AHRQ/Rutgers study to include IN claims data from 2004 through 2012. Extension features included a primary focus on AAPs (vs all APs), analysis of both FFS and non-FFS groups, evaluation of cost trends, and the effect of recent IN MA program changes on AAP utilization and cost.

Methods: IN children (<19 years old) who had MA coverage for at least one month during any calendar year of the study period (January 2004 – June 2012) were eligible for inclusion (1.4 million unique cases). An exhaustive list of AAPs was used to search this data base. To evaluate the impact of several IN MA program changes on AAP utilization & cost, we examined 75 monthly time points over three time periods: before, during, and after key program changes.

Results: AAP utilization rates varied between 2–3%. We also observed high rates of AAP prescribing in MA Fosters (10–15%). MA program

changes occurring after 2007 were associated with plateauing AAP utilization from 2008–2012. There was a significant difference in utilization between pre-intervention and during-intervention (ANOVA $p<0.0001$), and between pre-intervention and post-intervention time periods ($p<0.0001$).

Conclusion: Our in-state AAP utilization trends were generally consistent with the earlier findings of the AHRQ-Rutgers consortium documenting rapid growth in AAP use and cost in MA youth. A series of containment strategies appeared effective in addressing these trends.

Policy of full disclosure: Professor Goddard: NAUREX clinical trial, site PI

P-50. Neuroimaging C

P-50-001 Differential effects of clozapine exposure compared to standard second-generation antipsychotics on hippocampal volumes in chronic schizophrenia

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Objective: Hippocampal volume deficits are one of a number of highly replicated observations in persons with schizophrenia. These volumetric deficits have been associated with memory impairment, negative symptom severity and deficits in executive functioning. The efficacy of current atypical antipsychotics in addressing functional deficits of the hippocampi is unestablished. Individual atypical antipsychotics on may exert differential effects on hippocampal volumes, particularly clozapine versus other standard second-generation antipsychotics. In a group of chronically treated patients, we investigated potential differential effects of clozapine versus standard atypical medications.

Methods: We examined total hippocampal volumes (L+R) using high-fi eld imaging in a cohort of 23 refractory schizophrenia and schizoaffective disorder patients, 13 who had received mainly clozapine treatment (mean dose 304.8 mg/d) and 10 who had received either 1 or more of aripripazole (mean dose 15 mg/), olanzapine (mean dose 12.5 mg/d), risperidone (mean dose 1.8 mg/d), quetiapine (mean dose 605 mg/d), loxapine (mean dose 80 mg/d), flupenthixol (mean dose 5.3 mg/d) or palliperidone (mean dose 83.3 mg/d).

Results: Total hippocampal volumes were significantly smaller in the mainly clozapine treated group ($F(1,22)=4.7$, $p.=0.044$. No group differences in age, length of illness, total PANSS score (Positive and Negative Syndrome Scale), ESRS score (Extrapyramidal Symptoms Rating Scale), CDS score (Calgary Depression Scale), HAMAS score (Hamilton Anxiety Scale) or WTAR score (Wisconsin Test of Adult Reading) were observed; all p-values >0.25.

Conclusion: Previous animal investigations on the effects of clozapine exposure on cell proliferation in the hippocampus were negative and did not induce neuroplasticity. The current results suggest that alternate atypical antipsychotics with higher D2 affinities may exert neurotrophic effects on the hippocampus, whereas clozapine does not.

Policy of full disclosure: None.

P-50-002 Autoradiographic characterization of [3H]JNJ-54235012, a radiolabelled allosteric potentiator of the M1 muscarinic acetylcholine receptor: A new tool for studying central cholinergic system

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Objective: Compounds activating the M1 muscarinic acetylcholine receptor (mAChR) may have therapeutic benefit in treating cognitive deficit associated with schizophrenia or dementia. Activation of the M1 mAChR by small molecules can be produced either by binding at the orthosteric acetylcholine binding site or by interacting with the allosteric site of this receptor. However, compounds belonging to the first category lack some selectivity and are causing cholinergic side effects whereas the allosteric potentiators of the M1 mAChR, showing a higher degree of selectivity, are expected to be better tolerated. Due to this reason, numerous drug discovery programs looking for positive allosteric modulators (PAM) of M1 mAChR have been initiated. In order to deepen our understanding of such molecule, a highly potent PAM of the M1 mAChR JNJ-54235012 was radiolabelled and characterized.

Methods: Binding properties of [3H]JNJ-54235012 were assessed on membranes prepared from human M1 mAChR-recombinant cell line and on rat brain sections.

Results: Initial binding experiments on membranes have shown a high acetylcholine dependency of [3H]JNJ-54235012 binding to the human M1 mAChR. In saturation experiment and in presence of 1 μM acetylcholine, Kd of [3H]JNJ-54235012 was equal to 4 nM. In rat brain sections, similar acetylcholine dependency was observed and the pattern of binding sites visualized by autoradiography was very similar to the known distribution of M1 mAChR. Due to the acetylcholine dependency of [3H]JNJ-54235012 binding, several experiments were initiated to evaluate the capacity of such radioligand to monitor ex-vivo the level of activation or blockade of M1 mAChR after in vivo administration of acetylcholinesterase inhibitors or muscarinic antagonists, respectively. Dose-dependent activation of M1 mAChR could be visualized after donepezil whereas scopolamine, clozapine and olanzapine were blocking the ability of acetylcholine to increase [3H]JNJ-54235012 binding.

Conclusion: Modulation of [3H]JNJ-54235012 binding by various drugs represents a new way for studying central cholinergic system.

Policy of full disclosure: All authors are employee of Janssen Research & Development.

P-50-003 In utero environment and function of fronto-limbic regions in adolescence: A study in a longitudinal sample of monozygotic twins

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Objective: Much work demonstrates an association between early adversity and brain development, with fronto-limbic regions being of particular interest given their involvement in emotion regulation. To disentangle the effects of the environment from genetic influences, we can address this question in monozygotic twins and thereby isolate the effects of early adversity on brain development and later functioning. We make use of birth weight as an index of the in utero environment and test the hypothesis that greater discordance in birth weight may be associated with greater discordance in brain activation in response to emotional stimuli in fronto-limbic regions including the amygdala, hippocampus, anterior cingulate cortex and prefrontal cortex.

Methods: Fifty-two healthy pairs of monozygotic twins from the Quebec Study of Newborn Twins, followed regularly since birth, were scanned in a 3 T Siemens Scanner at age 15. During the scan, they viewed happy, fearful, sad, angry and neutral faces from the Pictures of Facial Affect series (Ekman 1976), allowing us to determine brain activation in response to each of these emotions.

Results: Preliminary analyses demonstrated that greater BW discordance is associated with greater discordance in response to anger and sadness relative to neutral stimuli in frontal regions, but only in girls (Anger: pFDR-Corr=0.008, X=−22, Y=38, Z=8; Sadness: pFDR-Corr=0.043, X=−30, Y=50, Z=16). We will also present results accounting for the postnatal environment including income and parenting behaviors.

Conclusion: These findings support the idea that the in utero environment is associated with brain development in adolescence, and suggest that it is necessary to account for gender when studying brain function and emotion processing.

Policy of full disclosure: None.

P-50-004 Gender identity related regional brain activation assessed using 7 Tesla functional magnetic resonance imaging

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Objective: Studies aimed at defining brain regions associated with gender identity, or a person's subjectively experienced gender, have linked this phenomenon to the superior frontal cortex and reward regions. Due to their limitation to cissexual individuals, these studies may define sex, rather than gender identity specific phenomena. We aim to identify regions specifically linked to gender identity through inclusion of

transsexual subject groups using functional magnetic resonance imaging (fMRI).

Methods: 20 female-to-male (FtM, mean age±SD=26.50±7.58years) and 19 male-to-female (MtF, 30.47±8.55years) transsexuals naive to cross-sex hormone therapy, as well as 25 male (MC, 26.52±6.54years) and 26 female (FC, 25.61±6.31years) controls underwent an fMRI scan during which a paradigm invoking identification with one's perceived gender was performed. Functional data was acquired using a Siemens Magnetom 7 T scanner (EPI-sequence, TE/TR=0.023/1.4 s, 128×128 voxels, 32 slices). Standard preprocessing and statistics were carried out using SPM8. Statistics implemented 2-sample T-test (FtM and MC vs MtF and FC) to elucidate functional differences specific to male vs. female gender identity.

Results: In comparison to the FtM and MC group, MtF and FC showed greater activation in superior temporal (t=3.67), middle temporal (t=4.09), inferior temporal (t=4.04), middle frontal (t=3.83) and superior frontal regions (t=3.62) as well as the angular gyrus (t=3.46) and cuneus (t=4.73). However, no regions showed greater activation in the FtM and MC subject group. All T-values are $p<0.001$ uncorrected.

Conclusion: Our results allow not only for the isolation of brain activity related to reflection upon one's gender identity independent of biological sex, but also for differentiation of activity that may be distinctive to identification with a specific gender. However, further analysis must incorporate the consideration that gender identity may reflect a spectrum rather than two extremes. Further, analysis in larger subject groups is warranted.

Policy of full disclosure: This study is financed by a grant awarded to R. Lanzenberger by the FWF Austrian Science Fund (P 23021, 2010–2014) Without any relevance to this work, S. Kasper declares that he has received grant/research support from Eli Lilly, Lundbeck A/S, Bristol-Myers Squibb, Servier, Sepracor, GlaxoSmithKline, Organon, Dr. Willmar Schwabe GmbH & Co. KG and has served as a consultant or on advisory boards for AstraZeneca, Austrian Sick Found, Bristol-Myers Squibb, German Research Foundation (DFG), GlaxoSmithKline, Eli Lily, Lundbeck A/S, Pfizer, Organon, Sepracor, Janssen, and Novartis, and has served on speakers' bureaus for AstraZeneca, Eli Lilly, Lundbeck A/S, Servier, Sepracor and Janssen. R. Lanzenberger received travel grants and conference speaker honoraria from AstraZeneca, Lundbeck A/S and Roche Austria GmbH. M. Spies, and G.S. Kranz received travel grants from Roche and AOP Orphan Pharmaceuticals. S. Ganger, R. Sladky, M. Küblböck, A. Komorowski, R. Seiger, A. Hahn, C. Windischberger report no conflict of interest related to this study.

P-50-005 The norepinephrine transporter in adult attention deficit hyperactivity disorder quantified with (S,S)-[18F] FMeNER-D2 and PET

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Objective: The norepinephrine transporter (NET) is a central target for often prescribed medications in ADHD. Thus, the NET is suggested to be highly involved in the underlying neurobiological mechanisms in ADHD. The aim of this study was to quantify NET binding using positron emission tomography and the highly selective radioligand (S,S)-[18F] FMeNER-D2 in adult ADHD.

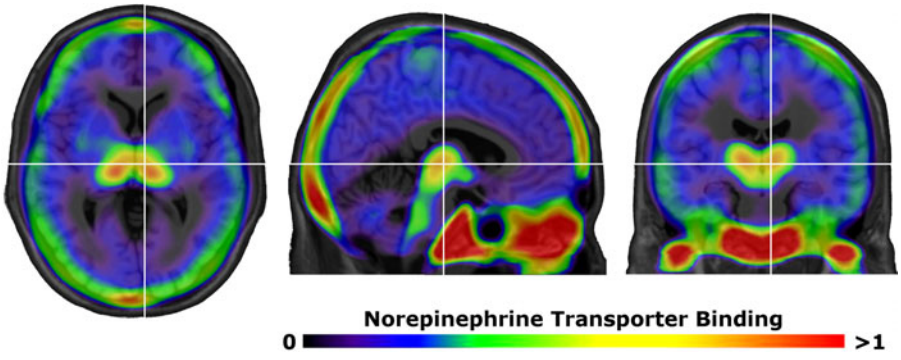
Methods: 22 medication-free ADHD patients (age: 32.16±10.86, mean± SD, 12males) without psychiatric comorbidities, and 22 age and sex matched healthy controls (HC, age: 32.00±10.56, 12males) underwent PET scanning once. The NET binding potential was compared between groups by means of a linear mixed model analysis including the hippocampus, putamen, pallidum, thalamus, midbrain with pons (including the locus coeruleus (LC)), and cerebellum (atlas-based ROIs). Additionally, we included thalamic sub-nuclei (13 atlas-based ROIs) and LC and thalamus (manually delineated ROIs) to the analysis. The 2-tailed significance level was set at 0.05.

Results: The results of this investigation revealed no main effect of subject groups ($F1,41<0.01$, $p=0.96$, Fig. 1) or sex ($F1,41<0.01$,$p=0.98$) and no interaction effects (all $p>0.1$). Further, we reveal no significant association between ADHD symptoms severity and regional NET availability. However, we found a significant negative correlation of NET BPND with age in the thalamus ($r=-.54$) and midbrain ($r=-.42$, $p<0.05$ corrected), but these correlations did not differ between HC and ADHD patients.

Conclusion: Our findings show no significant differences in the NET binding of (S,S)-[18F]FMeNER-D2 between ADHD patients and HC. Thus, results imply that NET BPND is not a major player in the pathogenesis of ADHD. However, different molecules of noradrenergic transmission might be altered, or the noradrenergic transmitter system might be affected on different levels, such as cortical regions, which cannot be reliably quantified with this radio-ligand.

Policy of full disclosure: Without any relevance to this work, S. Kasper declares that he has received grant/research support from Eli Lilly, Lundbeck A/S, Bristol-Myers Squibb, Servier, Sepracor, GlaxoSmithKline, Organon, Dr. Willmar Schwabe GmbH & Co. KG and has served as a consultant or on advisory boards for AstraZeneca, Austrian Sick Found, Bristol-Myers Squibb, German Research Foundation (DFG), GlaxoSmithKline, Eli Lily, Lundbeck A/S, Pfizer, Organon, Sepracor, Janssen, and Novartis, and has served on speakers' bureaus for AstraZeneca, Eli Lilly, Lundbeck A/S, Servier, Sepracor and Janssen. R. Lanzenberger has received travel grants and conference speaker honoraria from AstraZeneca, Lundbeck A/S and Roche Austria GmbH. T. Vanicek has received a travel grant from Sanova. M. Spies and G.S. Kranz received trave grants from Roche and AOP Orphan. W. Wadsak has received research support from Rotem GmbH, ABX, Iason, Advion and Raytest Austria and has served as a consultant/trainer for Bayer and THP. A. Kutzelnigg has received travel grants from Eli Lilly and Company, Affiris AG, Novartis Pharmaceuticals Corporation, and AstraZeneca, payment for lectures including service on speakers' bureaus from Eli Lilly and Company, Novartis Pharmaceuticals Corporation, AstraZeneca and Affiris AG and has served as a consultant and on advisory boards for the Austrian Federal Ministry of Health, Eli Lilly and Company, Biogen-Idec and Medice Arzneimittel GmbH. The authors N.D.Volkow, M. Mitterhauser, C. Rami-Mark and M. Savli report no financial relationships with commercial interests.

Images display (S,S)-[18F]FMeNER-D2 distribution in ADHD patients. NET BPND is found to be high in the thalamus and midbrain, and low in the basal ganglia. The colour table represent binding potential at each voxel, blue indicates lowest and red highest N:



P-50-006 **In vivo pet imaging of neuropeptide y2 receptors in diet-induced obesity in minipig**

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Objective: Neuropeptide Y (NPY) is a potent orexigenic agent expressed in both the central and peripheral nervous system. In the brain, NPY increases food intake and body weight leading to metabolic changes promoting energy storage. The activation of NPY Y2 receptors, the most prominent NPY receptor in the CNS, has been linked to the induction of satiety, and polymorphisms in this gene have been implicated in human obesity. We have recently developed a novel positron-emitting radioligand based on the NPY Y2 receptor antagonist, JNJ-31020028, and have used the radiotracer for positron emission tomography (PET) brain imaging in pigs. Here we examine changes in the binding potential (BPND) of NPY Y2 receptors in response to diet-induced obesity.

Methods: Four average weight (25 kg) adult female Gottingen minipigs were anesthetized and scanned at baseline with N-[11C]methyl-JNJ-31020028 in a Siemens PET/CT scanner. Minipigs were then fed an unlimited, high-fat, palatable diet for 10–12 weeks which resulted in doubling of their body weight (51 kg), prior to rescanning with N-[11C]methyl-JNJ-31020028. PET data were registered to an average minipig MRI atlas and processed using MINC tools. The BPND was obtained using the Logan graphical analysis, with corpus callosum as a region of non-displaceable binding.

Results: On average in the four pigs, JNJ-31020028 BPND was significantly reduced in the striatum, thalamus and amygdala after weeks with the high-fat diet.

Conclusion: Data demonstrate the use of this novel tracer in longitudinally examining physiological processes and reinforce the idea of NPY Y2 antagonism as a potential beneficial treatment of obesity.

Policy of full disclosure: None.

P-51. Others C

P-51-001 **Anxious and suicidal behaviors among relatives are associated with suicide attempts and hospitalizations in mood disorder subjects**

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Objective: - To examine the association between suicidal behavior in subjects with mood disorders and suicidal behavior in their relatives with psychiatric disorders - To examine the association between number of relatives with specific psychiatric disorders and clinical severity indicators in subjects with mood disorders - To begin to consider possible interventions for prevention of familial risk factors.

Methods: Participants were recruited from the Mood Disorders Program of the McGill University Health Center in Montreal, Quebec. Data was gathered using structured diagnostic interviews (SCID), family history of psychiatric illness questionnaire and patient clinical records. Ordinal and binary logistic regression analyses were to examine the association between type of diagnoses among relatives and suicide attempts and hospitalizations in the proband. Models were adjusted for age and gender.

Results: The greater number of relatives with suicidal behavior (attempts and completions), the greater the number of suicide attempts (OR=1.1, p=0.016) among mood disorder subjects. In addition, the greater number of relatives with anxiety (panic, worry), the less likely the mood disorder subject was hospitalized (adjusted OR=0.3, p=0.032).

Conclusion: These results indicate that individuals with family members who have a history of suicide attempts may be at risk for an increase in suicide attempts. Individuals with family members with an anxiety disorder are less likely to be hospitalized. To elucidate the mechanisms behind this association, future research should investigate the ways relatives with psychiatric illnesses may interact in families with mood disorders. The coping skills and the cognitive styles of mood disorder subjects and their family members may be targets for intervention to reduce clinical severity.

Policy of full disclosure: None.

P-51-002 **The association between contacts with relatives with psychiatric illness and cognitive distortions in mood disorder subjects**

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Objective: - To become better acquainted with the Types of Thinking questionnaire, a measure of cognitive distortions - To understand the effect of contact with sick relatives on cognitive distortions among mood disorder subjects - To understand the implications of specific cognitive distortions on mood disorder subjects.

Methods: 102 outpatients from the Mood Disorders Program of the McGill University Health Center in Montreal, Quebec completed the Types of Thinking Questionnaire as well as a Family History Questionnaire as part of a family study of mood disorders. Linear regressions were conducted, controlling for age and gender, to examine the associations between frequency of contact with sick relatives and cognitive distortions.

Results: The greater the contact with relatives with psychiatric illnesses was, the higher the levels of (1) Catastrophizing (unstandardized B=0.130, p=0.040), (2) All-Or-Nothing thinking (unstandardized B=0.157, p=0.012) and (3) Should Statements (unstandardized B=0.153, p=0.024) were reported. In addition, total level of negative cognitive style (unstandardized B=1.159, p=0.022) was higher as sick relative contact increased.

Conclusion: The mechanism by which contact with sick relatives renders its effect on the cognitive patterns of mood disorder subjects should be explored.

Policy of full disclosure: None.

P-51-003 **Factors influencing efficacy of specialized psychiatric help under conditions of primary care unit**

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Objective: Using clinical diagnostic criteria of course and outcome of mental disorders co-morbid with somatic pathology to distinguish basic treatment programs and to assess their efficacy.

Methods: Clinical-diagnostic, clinical-follow-up "scale of efficacy of therapy of patients with borderline states", SF-36, correlation and factor analyses. Material: 680 patients with mental disorders co-morbid with somatic pathology needing systematic therapy and dynamic observation by a psychiatrist.

Results: We have developed six rehabilitative programs with their gradual realization for patients with neurotic and somatoform disorders, organic mental disorders, personality disorders, affective mood disorders, alcohol dependence, for elderly. Basic therapeutic stages: initial, basic therapy and maintenance therapy. Basic and important method of therapy at all stages of treatment was medication. Most effective and used preparations were tranquilizers (sonval, radedorm, nozepam, phenazepam, grandaxin, sibazon, relanium); neuroleptics (sonapax, chlorprotixen, haloperidol, eglonil); antidepressants (amitriptiline, fluoxetin, azafen, pirazidol, anafranil). Conducted by us investigations during 25 years allowed distinguishing basic and obligatory principles of therapy providing its quality and efficacy, gradual character, complexity (treatment of somatic and mental pathology), sufficiency (necessary volume of therapy with minimum side-effects), individual-differentiated approach (along with other factors, account for financial possibilities), accessibility (not only territorial but also psychological), continuity (collaboration of psychiatrist and physicians at all stages of therapy), cooperativeness (possibility of concomitant curing by doctors of various specialties). According to data of follow-up and assessment of efficacy of treatment programs, recovery has been achieved in 46,2% of cases, stable clinical improvement - 44,1%,. Temporary disability decreased in patients with somatoform disorders as many as 1,8 times and number of not grounded seeking for help and examinations per 1 patient during the year as many as 2,3 times.

Conclusion: Integrative approach to medical help rendering as well as all-sided differentiated and grounded medication were enough effective according not only to clinical but also economic indices.

Policy of full disclosure: None.

P-51-004 **The functional role of the brain finger protein, Znf179, in learning and memory**

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Objective: The objective of this study was to reveal the physiological functions of Znf179 in the adult brain.

Methods: We generated Znf179 knockout mice to address Znf179 functions in vivo.

Results: Our data showed that most of the Znf179-/- embryos exhibited blood vascular defects and died in utero. Upon further investigation, we found that the survival rate of homozygous Znf179-knockout mice in 129/sv and C57BL/6 mixed genetic background was increased, providing opportunity to study the physiological function of Znf179 in the adult brain. The survived newborns of Znf179-/- mice manifested growth retardation as indicated by smaller size and a reduced weight. Although the overall organization of the brain did not appear to be severely affected in Znf179-/- mice, our data showed that the brain size and the thickness of cerebral cortex from the Znf179-/- mice were reduced. Moreover the Znf179-/- mice displayed impairment of brain functions including motor balance, and spatial learning and memory.

Conclusion: Our results revealed that deletion of both Znf179 alleles resulted in embryonic lethality associated with defects in embryonic vasculature. Moreover, the homozygous Znf179 knockout mice in 129/sv and C57BL/6 mixed genetic background can survive to adult, suggesting that the presence of modifier genes in different mouse strains could support survival of Znf179-/- mice. We also found that Znf179 deletion resulted in impairment of brain functions. Taken together, our results provide evidence for the important functions of Znf179 in embryo development and in adult brain.

Policy of full disclosure: None.

P-51-005 Transcriptional activation of non-LTR retroelements with age and in response to stresses

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Objective: Basic objectives were to analyze the transcriptional regulation of L1Rn elements in response to stresses.

Methods: Real time PCR analysis using RNA isolated from various brain regions and various tissues from old and young wistar rats was carried out to determine the change in L1 transcripts.

Results: There was no significant change in the expression of L1Rn in various brain regions of 2 month old and 18 month old rats except cerebral cortex. The heavy metals nickel, cadmium, lead, mercury and aluminum upregulates the expression of L1 in tissue specific and age dependent manner.

Conclusion: The results of this investigation conclusively prove that LINE1 retroelements are transcriptionally activated in response to stress.

Policy of full disclosure: None.

P-51-006 Intranasal erythropoietin with low sialic acid shows safety and tolerability: A phase I clinical trial

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Objective: The objective of this study was to evaluate safety and tolerability of NeuroEPO a neuroprotective candidate that has shown to be safe and beneficial in preclinical models of acute and neurodegenerative brain diseases.

Methods: We completed a randomized, open, two doses and parallel Phase I clinical trial. Thirty healthy volunteers with ages ranging from 18 to 40 years were included. All participants gave their written informed consent. Subjects from Group A and Group B received (1 mg or 0.5 mg NeuroEPO) respectively intranasal every 8 hours during 4 days. Participants were randomly allocated to each treatment group. Primary outcome of the study was adverse event. Vital signs, hematopoietic activity, blood biochemistry and local tolerance were evaluated.

Results: 25 subjects were analysed, 12 in group A and 13 in group B. No serious adverse event (AE) was reported. 95% of the AEs were mild, 2 (5%) were moderate. Most frequent AEs were headache (5; 11.3%), ALAT increase (5; 11.3%) and nasopharyngeal stinging (4; 9.1%). Hematopoietic activity and vital signs remain normal. No clinically significant laboratory abnormality was identified. Transient discreet redness of the nasal turbinate and slight congestion of the nasal mucosa was seen in only 1 patient each one. No significant difference was found between doses.

Conclusion: Intranasal administration of NeuroEPO is safe and well tolerated in healthy volunteers. This study warrant further trials in clinical conditions. Trial registration: RPCEC00000157

Policy of full disclosure: None.

P-51-007 Psychotropic drug utilization in geriatric psychiatry inpatients of a university hospital

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Objective: Psychotropic drug polypharmacy is common in elderly patients. A gender based difference in the prescription of potentially inappropriate psychotropic medication has been described with more use in elderly females. The objective of our study is to describe the psychotropic drug utilization pattern in elderly psychiatry inpatients of a university hospital in India and determine the presence of any gender difference.

Methods: Hospital records of all psychiatry inpatients more than or equal to 65 years of age admitted over a period of two years were studied. Drugs prescribed before hospitalization, during hospital stay and on discharge were recorded. The drug classes were delineated as follows - antidepressants, antipsychotics, mood stabilizers and anxiolytics/ hypnotics.

Results: Of the 51 patients admitted, 58.8% were males. The mean age was 73.67±5.8 years in males and 68.57±4.7 years in females ($p<0.05$). Unspecified dementia was the commonest psychiatric illness followed by bipolar affective disorder. 23.53% of the patients did not receive any psychotropic drugs. 41.2% were prescribed antidepressants, 29.4% antipsychotics, 7.8% mood stabilizers and 47.1% anxiolytics. Lorazepam was the most commonly prescribed drug followed by escitalopram (27.5% and 13.7% respectively). No gender difference was seen in the use of psychotropic medications. 45.1% of the patients were prescribed more than one psychotropic drug on discharge.

Conclusion: A larger percentage of the patients were males and were of significantly older age as compared to females. This is contrary to some of the data reported by other similar studies. Anxiolytics and antidepressants were the most commonly prescribed psychotropic drugs. No significant difference in the drug use was seen on admission and discharge. No gender difference was seen. Polypharmacy seen in our study is less than those reported by other studies although the appropriateness of the prescribed medications needs to be determined.

Policy of full disclosure: None.

P-51-008 The dopamine stabilizer (-)-OSU6162 reduces aggressive behaviour in mice at a dose affecting neither social interaction nor locomotion

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Objective: (-)-OSU6162 is a substance belonging to a new class of compounds named "dopaminergic stabilizers" and has been shown to be effective in several preclinical tests of schizophrenia as well as models of alcohol dependence. While its exact mechanism of action is still uncertain, it is assumed to maintain dopamine homeostasis mainly by exerting an atypical interaction with extrasynaptic and/or synaptic D2 receptors. Interestingly, it reduces stimulant-induced hyperlocomotion without inducing catalepsy even at high doses.

Methods: The effect of (-)-OSU6162 on aggressive behaviour and other social behaviours in the resident intruder test was evaluated in male mice of the outbred CD-1 strain. In addition, possible effects on spontaneous locomotion were evaluated in a separate experiment.

Results: (-)-OSU6162 dose-dependently reduced aggressive behaviour while not affecting other social behaviours and importantly, not by reducing spontaneous locomotion.

Conclusion: This study is the first to suggest that (-)-OSU6162 has potential as an anti-aggressive agent. Given the well-established influence of dopamine on aggression, we suggest the effect to be exerted by the dopamine-stabilizing properties previously attributed this compound.

Policy of full disclosure: None.

P-51-009 Types of suicidal self-harm in the individuals under investigation

E. Valzdorf. *BNUEL, Irkutsk, Russia*

Objective: To study and analyze the types of suicidal behavior in the individuals held criminally liable.

Methods: The clinical psycho-pathological and statistical.

Results: The research revealed that most of the 90 individuals who committed suicides and underwent the forensic psychiatric assessment. Among the suicidal individuals that were under the recognizance not to leave and proper behavior 1 and 2 self-harm acts were committed by 5; 3–3; 4–1 and 7 self-destructive acts-1 person under investigation. Among the persons whose measure of restraint was custody 1 self-harm

act in their life was committed by 19; 2–22; 3–11;5–7; and 4–5; 7,8,9 and 12 acts-2; and 6,19 and 11 self-injuries were committed by 1. 15 - under investigation that were under recognizance not to leave and proper behavior committed the following kinds of attempted suicide: self-hanging and self-cutting on the left forearm – 7; self-cutting on the right forearm – 5; abdominal self-cutting – 2; self-cutting on the neck and chest – 1; self-burning, poisoning with food, deliberate drug overdose – 1. 75 – under investigation whose measure of restraint was custody committed such attempted suicides as self-cutting on the right forearm – 29; poisoning with psychotropic medications - 16; poisoning with other medications – 13; abdominal self-cutting – 8; self-cutting on the neck – 5; self-shooting from firearms – 4; self-cutting in the groin area, deliberate road traffic accident – 3; self-cutting on the chest, jumps from the window, jumps from a height – 2; deliberate drug overdose, self-burning – 1.

Conclusion: The most popular type of self-harm among the suspects, who had the measure of restraint in the form of recognizance not to leave and proper behavior was self-hanging and self-cutting on the left and right forearms, and among those in custody - self-cutting on the left and right forearms, poisoning with psychotropic substances and other medications.

Policy of full disclosure: None.

P-51-010 Causes and objects for committing attempted suicides

E. Valzdorf. *BNUEL, Irkutsk, Russia*

Objective: To investigate a diversity of causes of deliberate self-destructive acts and objects for committing them in the individuals who have committed crimes and have undergone the primary inpatient comprehensive forensic psychological and psychiatric assessment.

Methods: The statistical, method of comparative analysis and clinical psychopathological.

Results: The research revealed the following causes of deliberate self-destructive acts in the suicidal individuals: conflict with their woman (parting, divorce, quarrel, unshared love) – in 21, conflicts (with mother, with administration of the pretrial detention center) – 17, sense of frustration – 15, protest against unfair sentence – 10, loss of life purpose, unwillingness to live – 8, conflict with a sister-3, rape – 3, psychological pressure from cell mates in the pretrial detention center – 2, fraternization with a friend – 2 individuals, a wish to be alone in the pretrial detention cell – 1, loss of a near relative – 1, conflicts with family – 1, effect of alcohol withdrawal hallucinations – 1, matricide – 1, for the sake of an experiment – 1, conflict with their aunt –1, an attempt to avoid quarantine in the pretrial detention center – 1, to be sent to the health center of the pretrial detention facility to have a less stricter custodial control – 1. The self-destructive acts were committed by the following objects: razor blade – 33, kitchen knife -11, washing line -10, medication – 4, glass – 3, psychotropic medication – 3, penknife – 3, belt – 3, firearm – 3, sheet – 2, undershirt – 2, telephone cord – 2, electrical wire – 2, laces – 1, petrol – 1, arch support from a boot – 1, syringe with a narcotic drug – 1, vinegar – 1, jumping rope – 1, sharpened coin – 1, mirror – 1, and a parachute line – 1.

Conclusion: The most frequent causes of the deliberate self-destructive acts were: Conflicts with woman, protest against unfair sentence, conflicts with relatives and administration of the pretrial detention center as well as the feelings of frustration and hopelessness. The most widely used objects included razor blade, washing line and medications including the psychotropic ones.

Policy of full disclosure: None.

P-51-011 Assessment of psychological and sexologic status of an individual with sadistic exhibitionism

E. Valzdorf. *BNUEL, Irkutsk, Russia*

Objective: To characterize and analyze the psychological and sexologic status of an inpatient of the forensic assessment department.

Methods: The clinical psychopathologic and pathopsychological methods.

Results: The sexologic and psychiatric research revealed the following: the individual notes that in the early childhood he expressed an interest in his own genitals and the genitals of other children. When in the first form of school, he found a magazine with pornographic photos. This was the first time he had felt arousal in the area of genitals. In the fourth form he started to manipulate his genital organ while looking through the pornographic magazine, he felt excitement. He made his first deliberate sexual intercourse at the age of 14 under alcohol intoxication. Until current arrest he has been going to the park to masturbate for two years. In terms of mental status the individual has clear consciousness. He is correctly oriented in all spheres. He is neat in appearance. His manner of walking is slow, during conversation he sits in one position and grows red when excited. During most of the conversation, he does not look at the conversation partner. Mimical responses are lively and correspond to the theme of conversation. He expresses an interest in the discussion and talks eagerly and sincerely. He is emotionally cold. The way of thinking is slow, of an average productivity. Intellect corresponds to the level of the received education.

Conclusion: All things considered the commission has arrived at the conclusion that the individual under consideration shows the signs of a mixed personal disorder (schizoid, emotionally-unstable) and a psychosexual disorder in the form of a true perversion, i.e. sadistic exhibitionism (according to ICD-10). This was revealed through the permanent inclination of the person to sudden exposure of his genital organs to strangers in a public place, without a proposal to have an intimate contact, which was accompanied by masturbation when a victim showed fear.

Policy of full disclosure: None.

P-51-012 The therapeutic principle in a structural biological organization

E. Venga. *Clinica Neuro Psichiatrica, Naples, Italy*

Objective: The execution of a Function is supported by a biochemical complement which has to be functional to the Function we represent.

Methods: We know that if a Function is physiologically modified, according to our syntomatologic diagnostic criteria, we name it Dysfunction. As any molecule expressing its own atomic organization can alter the atomic-molecular organization of a Function, we do not know if the transformation or alteration of the Function-Dysfunction is compatible with the other Functions-Disfunctions.

Results: And if we succeed in altering - transforming the Function, can we really have the scientific certainty of having cleared up the Disfunction of the Function?

Conclusion: Is it only a representative symptomatic remission that satisfies a therapeutic illusion?

Policy of full disclosure: None.

P-51-013 Water and ice: Using natural disasters to study prenatal maternal stress

S. King[1], D. P. Laplante[2], M. W. O'Hara[3], S. Kildea[4]. [1]*Department of Psychiatry, McGill University, Douglas Mental Health University Institute, Verdun, Quebec, Canada;* [2]*Douglas Hospital Research Centre, Montreal, Canada;* [3]*Iowa City, USA;* [4]*Brisbane, Australia*

Objective: Little is known about effects of prenatal maternal stress in humans, however, because it would be unethical to randomly assign pregnant women to stress conditions. Our objectives are to determine: (1) to what extent do objective hardship and subjective distress during pregnancy influence the cognitive, behavioural, physical and motor development of the unborn child? (2) Are these effects moderated by the timing in pregnancy and the child's sex? (3) What are the mechanisms of these effects? And (4) will more intensive prenatal care buffer these effects?

Methods: We are running three studies of pregnant women exposed to natural disasters. In each, we assessed objective exposure and subjective distress within weeks of the disaster (PTSD symptoms). We then evaluated pregnancy outcomes, and the cognitive, behavioural, motor and physical development of the children. We began Project Ice Storm in Quebec in 1998; The Iowa Flood Study in 2008, which added pre-disaster data from an on-going study of pregnant women; and The QF2011 Queensland Flood Study in Australia last year which included pre-trauma data on pregnant women, a pre-existing randomized controlled trial of two prenatal care programs, plus birth biological specimens that will reveal the mechanisms of action of prenatal stress in humans. We will give the background rationale for the research program, the methods of the three studies, and a sampling of results.

Results: We demonstrate strong and long-lasting effects of prenatal stress on children's cognitive outcomes (IQ, language, memory); behaviour (anxiety, depression, aggression, autistic-like traits); motor development (coordination, visual-motor integration); and physical development (brain, sexual dimorphisms, body composition, immune function, insulin secretion, obesity).

Conclusion: Using a natural disaster as a platform for studying prenatal maternal stress is a powerful approach for capturing the unique effects of objective and subjective aspects of stress exposure, as well as precise timing in utero effects.

Policy of full disclosure: None.

P-51-014 Iatrogenic aluminum and Moroccan children's memory

F.-Z. Azzaoui[1], H. Hami[2], S. Boulbaroud[2], M. El Hioui[2], A. Ahami[2]. [1]*Kenitra, Morocco;* [2]*Faculty of Science, Kenitra, Morocco*

Objective: The evaluation of the memory faculties among Moroccan schooled children (aged 6–8 years) living in the Gharb Plain (North-West of Morocco) and the study of the possible relationship between this faculty and the consumption of iatrogenic aluminum.

Methods: A cross-sectional study is conducted among 129 school-aged children living in the urban, periurban and rural region of the Gharb Plain (N-W of Morocco). The children suffering from cranial traumatism or neurologic disease are excluded. The memory faculties are measured by Memory Sub-test of WISC III (Wechsler Intelligence Scale for Children). The consumption of iatrogenic aluminum and the quality of children#s life are evaluated by the questionnaire. Statistical analyses are realized by ANOVA 1, LSD and Pearson correlation coefficient.

Results: The obtained results show that the high rate of working memory impairments (66.67%) is registered among rural children. Significant correlations between performance of working memory ($p<0.05$) and consumption of iatrogenic aluminum are also found.

Conclusion: The children's memory appears in connection with iatrogenic aluminum consumption. However, several factors (environmental, psychological, socio-economical, and nutritional factors) could influence this performance. So, deeper investigations are needed for studying all these factors.

Policy of full disclosure: None.

P-51-015 Atypical antipsychotics in the treatment of delirium

W.-M. Bahk[1], H. R. Wang[2], Y. S. Woo[2], B.-H. Yoon[3], S.-Y. Lee[4]. [1]*Yeouido St. Mary´s Hospital, Seoul, Republic of Korea;* [2]*Seoul, Republic of Korea;* [3]*Naju, Republic of Korea;* [4]*Iksan, Republic of Korea*

Objective: This study aims to review the efficacy and safety of atypical antipsychotics, comparing within class, placebo, or compared to another active treatment for delirium.

Methods: We conducted a literature search using PubMed, EMBASE, and the Cochrane database (January 1st in 1990-November 5th in 2012). Selection criteria for review were prospective, controlled studies (comparison studies), using validated delirium rating scales as outcome measures.

Results: A total of six prospective, randomized controlled studies were included in the review. The review showed that atypical antipsychotics are effective and safe in treating delirium, even though there seemed to be no difference between each agent. In particular, comparison studies with haloperidol showed that the efficacy of atypical antipsychotics was similar to that of low dose haloperidol.

Conclusion: This review found that atypical antipsychotics appear to be effective and tolerable in the management of delirium, even though the evidence is limited.

Policy of full disclosure: None.

Monday 23 June 2014

SA-01. New horizons in schizophrenia: Navigating the evidence at the frontier of patient care

supported by an educational grant from F. Hoffmann-La Roche Ltd.

SA-01-001 Charting advances in schizophrenia: Unmet needs and new targets

W. Honer. *University of British Columbia, Institute of Mental Health, Department of Psychiatry, Vancouver, BC, Canada*

Policy of full disclosure: None.

SA-01-002 Exploring the evidence: New treatment approaches in schizophrenia

W. W. Fleischhacker. *Medical University Innsbruck, Innsbruck, Austria*

Policy of full disclosure: None.

SA-01-003 Anchoring emerging evidence to real world clinical practice

C. Correll. *Psychiatry and Molecular Medicine, Hofstra North Shore-LIJ, School of Medicine, New York, USA*

Policy of full disclosure: None.

SA-02. Predictive pharmacology - reductionism and wishful thinking in antidepressant development

supported by an educational grant from Lundbeck

SA-02-001 Introduction

R. Lam. *University of British Columbia, Deptartment of Psychiatry, Vancouver, Canada*

Major Depressive Disorder (MDD) is a disabling neuropsychiatric disease linked to significant morbidity and premature mortality. The associated costs to patients, providers, and the public health are formidable, and underline the importance of successful long-term outcomes. Yet most patients do not achieve functional recovery, owing in part to the relative paucity of treatment options and to our limited understanding of disease mechanisms underlying this complex, heterogeneous disorder. Despite great progress, traditional preclinical and clinical studies have proved necessary, but not sufficient, to advance mechanism-based drug discovery programmes. Rather, a comprehensive approach, from first principles to patients, is essential for tailoring drug discovery to rigorously characterised biological correlates of depressive symptoms. Recent advances in the cognitive neurosciences are proving particularly important. An increasingly robust evidence base has demonstrated the functionally impairing effects of cognitive deficits in depressed patients. This patient population frequently experiences a range of cognitive symptoms including an impaired ability to think, concentrate, or make decisions that can adversely affect work, school, and relationships. Further, well-designed studies have documented cognitive impairment across the course of illness and its adverse impact on functional recovery. As interdisciplinary research programs continue to identify neural pathways underlying depressive symptomatology and novel targets for therapeutic intervention, new therapies will emerge from the clinic, providing physicians with additional options for individualized patient care. This symposium, chaired by Dr Raymond Lam, will address these and other important issues.

Policy of full disclosure: None.

SA-02-002 Antidepressant effects on cognitive function - From animal models to clinical trials

R. McIntyre. *University of Toronto, UHN – Toronto Western Hospital, Toronto, Canada*

The brain, operating hierarchically from gene to network, is not immediately tractable to experimental research. Reductionist preclinical models have therefore proved to be at once necessary, and limiting. While animal models have proved indispensable, no one model can fully elucidate complex, multidimensional neuropsychiatric disorders, particularly depression. The growing interest in endophenotypes—as with the Research Domain Criteria (RDoC)—lends well to deconstructing select facets of the depressed state. Using an array of animal models—genetic, pharmacological, environmental, and behavioural—can capture an agent's effects on well-specified clinical features, while improving success rates across all phases of early drug discovery. Dr Roger McIntyre will discuss the effects of antidepressants on cognitive dysfunction in MDD patients, which will in turn shape a discussion of the recently completed FOCUS study, a global, eight-week, randomised, double-blind, parallel-group, placebo-controlled, fixed-dose trial that evaluated the efficacy of vortioxetine on cognitive function in MDD patients. Consistent with preclinical studies that show important inter-relationships between brain areas critical for mood and cognition, results from the FOCUS study demonstrate that vortioxetine can significantly reduce depressive symptoms and independently improve executive function, attention, speed of processing, and memory.

Policy of full disclosure: None.

SA-02-003 The neurocircuitry behind depression

G. M. Goodwin. *Warneford Hospital, University Department of Psychiatry, Oxford, United Kingdom*

Non-invasive neuroimaging tools have provided important insights into the neurobiological abnormalities underlying cognitive as well as mood and sleep-related disturbances in MDD patients. Patterns of neural activity present an increasingly coherent picture of networks that govern cognition. Networks distributed across prefrontal and subcortical regions, in particular, have been implicated in the onset, progression, and clinical symptomatology of MDD. These networks and their neuropharmacological correlates are well-conserved, facilitating cross-species translational efforts. Critically, functional magnetic resonance imaging (fMRI) analysis in animal models can accelerate lead compound discovery and clarify the effects of an investigational antidepressant on neural networks in healthy, depressed, and remitted patients. Well-controlled studies before, during, and after cognitive tasks and sleep, and in other areas of interest can establish important mechanistic relationships across all levels of brain function, with important implications for drug development, pivotal study design, and patient care. Other modalities—including positron emission tomography (PET), single-photon emission computed tomography (SPECT), and electroencephalography (EEG)—are available to characterise an agent's in vivo receptor occupancy and fine-grained electrophysiological features. In Dr Guy Goodwin's presentation, case studies with agomelatine and vortioxetine will illustrate the benefits of human experimental studies in early drug development, leading to robust translation towards enriched patient populations, improved clinical endpoints, and other features of well-designed clinical trials.

Policy of full disclosure: None.

SA-02-004 Translating preclinical studies to improved clinical outcomes in depression

T. Robbins. *University of Cambridge, Department of Psychology, Cambridge, United Kingdom*

Clinical depression entails cognitive deficits often across a range of domains, including impairments of not only memory but also executive functioning, such as decision-making, sustained attention ('concentration') and working memory, although these deficits are frequently age-dependent and correlated with discrete brain pathology. I will review evidence of heterogeneous patterns of cognitive deficit across a number of studies focusing especially on decision-making and attention, measured

in a variety of ways. Depression is also associated with distinctive cognitive or affective biases evident in so-called 'hot' cognition settings, in which there is an emotional or motivational component. Examples include the tendency to say "no" in tests of memory recognition, to over-react to negative feedback when making decisions and also to respond more quickly to sad rather than happy words arising theoretically from more rapid access to, and retrieval from, semantic memory networks. These phenomena indicate the importance in depression of a motivational interface with respect to cognitive function that leads to the important distinction between 'hot' and cold' cognition. I will also consider how both 'cold' and 'hot' cognition can be modelled in experimental animals in preclinical studies, drawing upon the set of rich translational tests we already have available for assessing 'cold' cognition in experimental animals and their neural correlates, as well as 'hot' cognition, such as decision-making following negative feedback. Issues of validation, including sensitivity to 'cognitive-enhancing' effects of drugs will be addressed.

Policy of full disclosure: None.

Tuesday 24 June 2014

SA-03. Impact of maintenance treatment on the natural illness progression in schizophrenia

supported by an educational grant from Lundbeck/ Otsuka

SA-03-001 The nature of relapse in schizophrenia

A. Malla. *McGill University Douglas MHUI, Psychiatry, Montréal, Canada*

Patients with schizophrenia have a high rate of response to treatment after a first psychotic episode. During the course of schizophrenia, however - despite the prioritisation of relapse prevention as a treatment goal - most patients experience relapses of psychosis. Such relapses result in a negative trajectory of outcome in more than two thirds of patients. Relapse is also associated with considerable psychosocial consequences including physical harm, emotional distress, and strained relationships -social and professional. The fluctuating course of relapses and incomplete remissions in schizophrenia is associated with poor functional recovery. Treatment refractoriness may emerge, and time to treatment response may increase with successive psychotic episodes. Furthermore, longitudinal MRI studies have revealed that structural brain alterations in schizophrenia are, at least partially, related to the total length of relapses. These observations suggest that relapse carries a biological risk, and that active psychosis promotes disease progression. The risk of relapse following treatment for first-episode psychosis is significantly increased by non-adherence to antipsychotic medication, substance abuse, interpersonal stress, and poor pre-morbid adjustment. Patients can relapse very soon after treatment discontinuation, and the transition from remission to relapse may occur with or without warning signs. Many of the risk factors for relapse are malleable to intervention, and attention to these can help to prevent or attenuate relapses and the associated harm. Given the high frequency of remission of psychotic symptoms following the first episode of schizophrenia, and the high risk of relapse in the first few critical years, effective treatment to sustain remission during this phase of the disease is crucial for improving long-term outcome.

Policy of full disclosure: None.

SA-03-002 Comparative efficacy of LAIs versus oral antipsychotics in schizophrenia

C. Correll. *Psychiatry and Molecular Medicine, Hofstra North Shore-LIJ, School of Medicine, New York, USA*

Non-adherence is a major barrier to maximising the acute and long-term effectiveness of pharmacotherapy for schizophrenia. Long-acting injectable (LAI) antipsychotics, which release active ingredient gradually (over a period of weeks) from a deep-tissue injection, were developed to improve treatment adherence in schizophrenia, and thereby improve the long-term outcome for patients. Measuring such benefits can be challenging, however, since randomised controlled trials generally increase adherence compared with clinical practice, leading to an underestimation of any potential difference in effectiveness between treatments. Consequently, individual randomised controlled trials and meta-analyses have shown mixed results regarding the benefits of LAIs compared to oral antipsychotics, underscoring the relevance of appropriately considering design, population and treatment factors when interpreting these diverging results. Mirror image studies provide a better reflection of the real-world impact of schizophrenia treatment. In a mirror image study, each patient acts as his/her own control: historical treatment with an oral antipsychotic is compared with prospective treatment with an LAI. Such studies strongly and consistently favour the use of LAIs over oral antipsychotics, revealing significantly reduced rates of treatment discontinuation, relapse, and hospitalisation with LAIs. Important emerging data suggest that continuous antipsychotic treatment may exert the biggest preventive effect on treatment discontinuation, relapse and rehospitalisation when provided early in the illness course, at a time when each single relapse is associated with the greatest loss in social, educational, vocational and, possibly, biological reserve and functioning. Taken together, these real-world data indicate that appropriate use of LAIs early in the disease course is a valuable treatment option for patients with schizophrenia.

Policy of full disclosure: None.

SA-03-003 Differences among long-acting antipsychotics in the maintenance treatment of schizophrenia

J. Kane. *The Zucker Hillside Hospital, Glen Oaks, USA*

A number of different typical and atypical long-acting injectable (LAI) antipsychotics are currently available. Of the four atypical LAI antipsychotics (aripiprazole, olanzapine, paliperidone, and risperidone), aripiprazole once-monthly is the most recently approved (Canada, US, and EU). Aripiprazole once-monthly is an injectable, extended-release suspension which provides a new option for the maintenance treatment of schizophrenia in adults. Two large-scale, randomised, controlled clinical studies of aripiprazole once-monthly have been completed, both of which investigated prevention of relapse as the primary outcome. In a 52-week study, maintenance treatment with aripiprazole once-monthly statistically significantly delayed the time to relapse, reduced the proportion of patients experiencing relapse, and improved the symptoms of schizophrenia versus placebo. In a 38-week study, maintenance treatment with aripiprazole once-monthly was non-inferior to oral aripiprazole, and statistically significantly superior to a low reference dose of LAI aripiprazole, in terms of the proportion of patients experiencing relapse. Other studies, completed and ongoing - including a mirror image study - complement these findings. The safety profile of aripiprazole once-monthly is favourable and similar to that of oral aripiprazole. It is important to place in perspective the various characteristics of available LAI medications, so that clinicians, patients and families have the information necessary to make informed decisions. Having a new option that is effective and safe will be valuable in the maintenance treatment of schizophrenia.

Policy of full disclosure: None.

SA-04. Challenges in the management of bipolar disorder: Focus on unmet needs

supported by an educational grant from Sunovion

This symposium reviews important challenges in the diagnosis and treatment of bipolar disorder and highlights current unmet needs. Bipolar disorder is one of the most challenging psychiatric disorders to treat, with multiple diagnostic complexities, frequent medical and psychiatric comorbidities, and high use of healthcare resources. The presentation of bipolar disorder is dominated by the depressive phase, as patients spend two-thirds of symptomatic time depressed. Cognitive impairment is common during both mood episodes and euthymia and strongly predicts the functional impairments that reduce quality of life. While many treatment options exist for the debilitating effects of mania and hypomania, the development of medications for bipolar depression has been fraught with difficulty, leading to a number of failed and negative trials. High placebo rates have contributed the challenge of conducting successful clinical trials in bipolar depression. However, the several agents that have been successful in the treatment of bipolar depression may share an important mechanism of action. Commonalities in the select agents that have proven efficacious in clinical trials of bipolar depression in addition to preclinical data highlighting its role in mood regulation and cognition suggest that the serotonin receptor 5-HT7 may provide a new research target in bipolar depression. This symposium also considers Level 1 evidence for available treatments for bipolar depression, including mood stabilizers, traditional antidepressants, and atypical antipsychotics, as well as treatment guidelines. Both approved treatments and those more recently investigated for bipolar depression are reviewed. In addition, the issue of the effect of various agents on metabolic parameters in this population is examined as an important limitation of current therapies. The program also discusses several nonpharmacologic approaches, such as psychoeducation and cognitive behavioral therapy, that can contribute to improved

outcomes in patients with bipolar disorder. The symposium concludes with a presentation of both short- and longer-term clinical trial data of Latuda® (lurasidone HCl), which demonstrated efficacy both as monotherapy and as adjunctive therapy with lithium or valproate in patients with major depressive episodes associated with bipolar I disorder (bipolar depression).

Policy of full disclosure: None.

SA-04-001 Challenges in the management of bipolar disorder

L. Yatham. *Vancouver Coastal Health and Providence Healthcare, Department of Psychiatry, Vancouver, Canada*

Policy of full disclosure: None.

SA-04-002 Management of bipolar depression: Current practice

E. Vieta. *University of Barcelona, Hospital Clinic, IDIBAPS, CIBE, Department of Psychiatry, Barcelona, Spain*

Policy of full disclosure: None.

SA-04-003 New data regarding the efficacy of Lurasidone in bipolar depression

J. Calabrese. *USA*

Policy of full disclosure: None.

Wednesday, 25 June 2014

SA-05. Stepping up to the challenge of cognitive dysfunction in major depressive disorder

A Medscape Education program supported by an educational grant from Lundbeck

This independent Medscape Education program is an interactive live symposium for an audience of non-US psychiatrists, neurologists and primary care physicians. It has four learning objectives: 1) to discuss the impact of cognitive dysfunction in patients with major depressive disorder (MDD); 2) to identify potential methods for measuring cognitive dysfunction in clinical practice; 3) to describe the mode of action of antidepressants with respect to cognition and MDD; and 4) to discuss treatment strategies for MDD patients with cognitive dysfunction. The program is supported by an unrestricted educational grant from Lundbeck. MDD has a significant deleterious effect on patients' work, social interactions, and quality of life. Many MDD patients report slowed thoughts, poor concentration, distractibility, and reduced capacity to process information. Both the Diagnostic and Statistical Manual of Mental Disorders, 5th edition, and the International Classification of Diseases, 10th edition, include reduced concentration as a criterion for an MDD diagnosis. Some questionnaires are being developed for potential use in clinical practice, such as the Perceived Deficits Questionnaire - Depression. Even after treatment with conventional antidepressants, patients frequently report cognitive problems, such as poor concentration and memory. Some trials that primarily aim to improve measures of cognitive function are underway with some conventional and newer antidepressants. Vortioxetine has been approved in the US and Europe for the treatment of adults with MDD. In a randomized, double-blind, placebo-controlled phase 3 study in MDD patients aged 18-65 years, and with cognition as the primary endpoint, vortioxetine 10 and 20 mg/day was suggested to have a direct effect on cognition compared to placebo. The live symposium will discuss the above in detail and will include a question and answer session. The program will subsequently be available online on Medscape Education. Note: Vortioxetine is not currently approved for use in Canada.

Policy of full disclosure: None.

SA-05-001 Recognizing cognitive impairment and its impact on functional outcome in patients with major depressive disorder

G. M. Goodwin. *Warneford Hospital, University Department of Psychiatry, Oxford, United Kingdom*

Policy of full disclosure: None.

SA-05-002 Targeting cognition and depression in major depressive disorder

R. McIntyre. *University of Toronto, UHN – Toronto Western Hospital, Toronto, Canada*

Policy of full disclosure: None.

SA-05-003 Therapeutic options to address cognitive impairment in patients with major depressive disorder

D. Nutt. *Imperial College, London, United Kingdom*

Policy of full disclosure: None.

Monday 23 June 2014

SC-01. Stem cells and related epigenetic factors in alcoholism

supported by an unrestricted educational grant of Suntory

SC-01-001 Altered retinoic acid homeostasis and microglial activation: Implications for neuropsychiatric disorders and therapeutic approaches

J. Hellmann-Regen. *Germany*

Microglial (MG) activation represents a hallmark of many neuropsychiatric disorders, including alcohol abuse-related pathologies. MG activation results in a variety of microenvironmental changes that eventually lead to altered stem cell differentiation, neuronal proliferation and survival. The underlying mechanisms appear to be of complex nature and remain subject to discussion. Here, we suggest a potential role for retinoic acid (RA) in mediating MG activation-associated effects on the microenvironment. RA acts as a potent morphogen, endogenous neuroprotectant and inhibitor of MG activation in the adult CNS. Altered RA homeostasis has previously been implicated in alcohol-related pathologies. Using primary mouse microglia, we demonstrate strongly increased protein expression of RA-degrading cytochromes CYP26A1, CYP26B1, CYP3A4 and CYP2C in lipopolysaccharide (LPS) activated vs. resting MG. Correspondingly, activated MG showed increased RA catabolism as determined by reversed phase-high performance liquid chromatography (HPLC). As expected, RA-administration attenuated LPS-induced MG activation. Furthermore, the inhibitory actions of RA on MG activation were found to be mimicked by the administration of liarozole, an inhibitor of RA-metabolism. In summary, our findings indicate that activation of microglia results in increased breakdown of RA, which is an endogenous inhibitor of MG activation. Increased turnover of RA may constitute a 'vicious cycle' of MG activation and contribute to MG activation-associated microenvironmental changes. Finally, our results on the RA-metabolism blocking agent liarozole suggest RA homeostasis as a potential therapeutic target in neuropsychiatric disorders.

Policy of full disclosure: None..

SC-01-002 Our liver regeneration therapies using autologous bone marrow derived cells for liver cirrhosis

T. Takami[1], S. Terai, I. Sakaida. [1]*Department of Gastroenterology and Hepathology, Yamaguchi University, Yamaguchi, Japan*

In our murine model, we have confirmed that GFP-positive bone marrow cells (BMCs) infused via a tail vein efficiently repopulated cirrhotic liver induced by repeated carbon tetrachloride treatment. Repopulated GFP-positive BMCs were also seen to produce collegenases including matrix metalloproteinase 9. As a result, reduced liver fibrosis, elevation in serum albumin levels, and then a significant increase in survival rate were confirmed. On these evidences, we have started "Autologous bone marrow cell infusion (ABMi) therapy", which was a method of liver regeneration using non-cultured autologous whole BMCs for patients including alcoholic liver cirrhosis, and reported the efficacy and safety of this approach. Moreover, we recently confirmed that frequent BMCs infusion contributed to suppressed tumor initiation during stages of hepatocarcinogenesis through the stabilization of redox homeostasis in hepatocarcinogenic mice with liver cirrhosis. On the other hand, our ABMi therapy involves bone marrow (BM) aspiration under general anesthesia, and is not indicated for patients for whom general anesthesia is difficult. We therefore developed a less-invasive liver regeneration therapy in which cells having curative effects on liver cirrhosis are isolated and cultured from a small amount of autologous BM aspirated under local anesthesia and infused back into the same patient. We revealed that the infusion of cultured human BM derived mesenchymal stem cells (BMSCs) under normal culture condition could reduce hepatic fibrosis in the immunodeficient NOD-SCID cirrhotic mice, consistent with the lower levels of reactive oxygen species from hepatocytes co-cultured with BMSCs in vitro. For the clinical trial using cultured BMSCs, we are now preparing safety evaluation guidelines and a system conforming to Standard Operating Procedure at the cell processing facility in our university hospital. Here, we present the current status and prospects for our liver regeneration therapy using autologous BMCs.

Policy of full disclosure: None.

SC-01-003 The role of neurogenesis in alcohol dependence and metabolic disease

D.-J. Kim. *Department of Psychiatry, Seoul St. Mary's Hospital, Catholic University, Seoul, Republic of Korea*

Alcohol has deleterious influences on glucose metabolism which may contribute to the development of type 2 diabetes mellitus (T2DM). Insulin-like growth factor I (IGF-I) and growth hormone (GH), which interact with insulin to modulate metabolic control, have been shown to be related to impaired glucose tolerance. Furthermore Brain-Derived Neurotropic Factor (BDNF), a potent regulator of neuronal activity and neurogenesis, is also an important regulator of glucose metabolism, so it may be associated with an increased risk for T2DM in alcoholism. This study was conducted to assess the possibility that altered circulating IGF-I, GH and BDNF levels related to T2DM by alcohol use in type 2 diabetic Otsuka Long-Evans Tokushima Fatty (OLETF) rats and non-diabetic Long-Evans Tokushima Otsuka (LETO) rats. To investigate effect of chronic alcohol consumption, rats were fed a liquid diet containing ethanol as 36% of calories or pair-fed a control diet. An Intraperitoneal Glucose Tolerance Test (IP-GTT) was performed and IGF-I, GH and BDNF levels were evaluated. Prior to an IP-GTT, OLETF-Ethanol (O-E) group had significantly a decrease in the mean glucose levels compared to OLETF-Control (O-C) group. At 120 min post IP-GTT, the O-E group had significantly an increase in the mean glucose levels compared to O-C group. The serum IGF-I and BDNF levels were significantly lower and the serum GH levels were significantly higher in the O-E group than in L-C group. These results suggest that IGF-I, GH and BDNF are prominent in defining the risk and development of T2DM, and may be adversely affected by heavy alcohol use, possibly mediating its diabetogenic effects. Thus, the overall glucose intolerance in the setting of alcoholism may be attributable to inappropriate alteration of IGF-I, GH and BDNF levels.

Policy of full disclosure: None.

SC-01-004 Stem cell therapy as a candidate treatment approach for neural plasticity change in alcohol-induced brain damage and depression

W. Ukai[1], Y. Kigawa, E. Hashimoto, T. Ishii, K. Fuluse, H. Tsujino, T. Saito. [1]*School of Medicine, Sapporo Medical University, Japan*

In alcoholism and fetal alcohol spectrum disorder (FASD) research, alcohol disruption of neuron development and alcohol-induced neurodegeneration is central to the pathology and clinical expression of these disorders. The active role of neurogenesis in neurodegeneration and regeneration processes has emerged at the front topic of adult central nervous system (CNS) disorders and therapy. A number of in vitro and in vivo studies demonstrate the impact of neurogenesis impairment as the common mechanism in pathophysiology of alcoholism and other psychiatric disorders such as depression. Many researchers has suggested that antidepressant increased neurogenesis which was required for the behavioral effects and alcohol treatment decreased this function. Stem cell-based regenerative therapy promises great benefits for patients with incurable brain diseases. We studied the involvement of corticolimbic GABAergic interneuron disruption in cognitive and social impairment in FASD and the effect of stem cell treatment. We used an animal model of FASD created in fetal rats by the binge-like administration of ethanol during the peak of GABAergic cell generation of dams (E11-E14). We show that aspects of cognitive and social dysfunction are reversed by intravenous administration of fetal rat brain-derived neural stem cells (NSCs) at 45 days, a time point when neural developments are already completed. We also show that alterations of PV-containing GABAergic interneurons and synaptic density protein levels are essential

for the therapeutic efficacy of intravenous NSC treatment in this animal model. Moreover, in our recent study, we created new rat model of refractory depression by combination of fetal (alcohol) and adolescent (corticosterone) period stress exposures. We have indicated that depressive behavior described in this model could be recovered by combined treatment of antidepressant with stem cells but not by antidepressant treatment alone. Our results suggest that alterations of neurogenesis function, especially GABA neuron production underlie the pathogenetic mechanism of alcohol-induced brain damage and depression and possible therapeutic mechanism of stem cell treatment combined with drug for these disorders.

Policy of full disclosure: None.

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