

## AsCNP I-001 (P1-001)

## Aripiprazole for the Treatment of Psychotic Symptoms in Patients with Dementia with Lewy Bodies: A Case Series

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Dementia with lewy bodies (DLB) is commonly considered the second most common form of dementia. The core features of DLB are fluctuations in cognition, visual hallucinations, and parkinsonism. Other supportive features are neuroleptic sensitivity, repeated falls, syncope, transient loss of consciousness, depression, delusions, and nonvisual hallucinations. Neuroleptic sensitivity has been reported with the use of both typical and atypical antipsychotic medications, little is known about the treatment effects of aripiprazole in patients with DLB.

We used a 10-week, open label study design. We present the clinical outcomes of aripiprazole treatment of 7 patients with probable DLB who manifested moderate to severe psychotic symptoms. Patients had experienced persistent or intermittent delusions, hallucinations or both for at least one month. The presence of psychotic symptoms was confirmed by scores of 6 or higher on either the delusions or hallucinations items of the NPI score. Aripiprazole could be titrated to higher doses at 2-week intervals or more rapidly based on investigator's judgment, if the patient showed insufficient clinical response. Reductions from higher doses were permitted for tolerability. NPI, BPRS and CGI-S were performed at baseline, 2, 4, 6, 8, and 10 week. CDR and MMSE were carried out at screening and week 10.

BPRS and NPI score showed a marked decrease in psychosis and agitation at week 2, and 5 of 7 responded at week 10. Aripiprazole was safe and well tolerated for treatment of psychotic symptoms with DLB.

## AsCNP I-003

## Comparison on the Efficacy of Quetiapine Versus Haloperidol in the Treatment of Delirium

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Haloperidol has been the medication of choice in most deliriums. But due to fewer side effects atypical antipsychotics are becoming the first line drugs in various neuropsychiatric conditions, and also increasing in delirium treatment. The purpose of this study was to compare the clinical efficacy of quetiapine with haloperidol in the treatment of delirium.

Seventy-seven subjects completed the study receiving a flexible-dose of quetiapine (n=40) or haloperidol (n=37). Memorial delirium assessment scale (MDAS) was administered as a specific tool to rate the severity of delirium and Neurobehavioral rating scale (NRS) to rate neuropsychiatric symptoms and Mini-mental state examination (MMSE) to assess cognitive status, specifically. The symptoms were checked at baseline, on day 3 and day 7 of treatment and compared between the two groups.

In both quetiapine and haloperidol groups, MDAS and NRS scores improved significantly on day 3 and day 7 compared to baseline. There is significant interaction between drug and time for the NRS score (p=0.074) and the interaction is likely due to the difference in scores between the groups on day 3 with the quetiapine group having a trend toward significantly higher (worse) score (p=0.07) than haloperidol, and not on day 7. For MMSE scores, compared to baseline, quetiapine group improved significantly on day 3 and day 7, whereas haloperidol group showed no improvement on neither day 3 nor day 7.

This study demonstrated that quetiapine is efficacious as haloperidol in the treatment of delirium. In particular, behavioral problems decreased faster with quetiapine than haloperidol and cognitive impairments improved with quetiapine and not haloperidol. Thus, it is possible that quetiapine can be used as a first-line treatment in delirium.

**Keyword: Delirium, Quetiapine, Haloperidol**

## AsCNP I-002

## A Case Report of Delirium Induced by Quetiapine

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Antipsychotic drug is the choice of treatment for delirium. Quetiapine, an atypical antipsychotic drug, was also used in the treatment of delirium in some studies. However, we report a 58 year-old male, victim of major depressive disorder with psychotic features, suffered from delirium induced by 600 mg quetiapine before sleep two days later. In the beginning, the total scale score of the Delirium Rating Scale-Revised-98 (DRS-R-98) and the 17-item Hamilton Depression Scale (HAM-D17) were 41 and 34 respectively. Two days after we stopped quetiapine use, the delirium subsided. The total scale score of the Delirium Rating Scale-Revised-98 (DRS-R-98) in the first and second night after tapering quetiapine were 25 and 0. This is the first case report about quetiapine-induced delirium. Balit et al. (2003) reported a case series of quetiapine intoxication. Delirium happened in 3 of 18 patients but the dose of intoxication did not be mentioned in his report. In our case, delirium symptoms were developed in a physically health man right after addition of quetiapine to previous antidepressant medications (venlafaxine) and improved soon after quetiapine stopped. We attribute the mechanism of delirium to the anticholinergic effect of quetiapine and we consider the dose of treatment and speed of titration are all the possible factors of delirium. We consider the use of 600 mg quetiapine without stepwise titration is most important cause of delirium developed. The appropriate doses of quetiapine used in the treatments of delirium and depression were also reviewed in our discussion. Here, we emphasize the importance of "low dose" and "short-term" principles about quetiapine use for both delirium and depression.

## AsCNP I-004 (P1-002)

## Identifying Capable Raters for Global Alzheimer's Disease Clinical Trials in Japan: Challenges and Potential Solutions

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Clinical trials in Alzheimer's disease have become global in nature, and increasingly include Japan. Identifying raters with relevant clinical experience and familiarity with the efficacy instruments is often challenging. Raters required enriched training if their experience fell below a level agreed upon by both the sponsor and rater training company. Prior to the Investigators' Meeting (IM), those designated raters received enhanced training on the co-primary efficacy measures (ADAS-Cog and ADCS-ADL) and completed a scoring assessment of both measures. During the IM, they completed a scoring assessment on a different set of videos required for certification of all raters. The performance of Japanese raters was analyzed and compared to all global raters. Sixteen percent (16%) of global raters required enriched training, and of those, 7% were Japanese. After the enriched training, all of the Japanese and 93% of the global raters met the enriched training scoring criteria on the initial assessments. Raters who successfully completed enriched training, went on to meet the ADAS-Cog qualification scoring criteria more often than experienced raters. The ADCS-ADL qualification scoring percentages were similar between both experienced and enriched training groups. The program described above proves that less experienced raters can be successfully trained to score efficacy instruments in global Alzheimer's trials. This has been shown both for global raters and Japanese raters in particular. Further analysis is needed to assess their performance over the course of a trial.

## Antipsychotics Prescribing Pattern for Geriatric Patients with Delirium in Thailand

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**Objective:** The aim of this study is to find out antipsychotics prescribing pattern for hospitalized older patients with delirium, comparing to the younger patients in consultation-liaison service in Thailand.

**Methods:** All psychiatric consultations performed upon hospitalized patients at Siriraj Hospital during a one-year period were studied. The data were collected from consultation request forms and medical records.

**Results:** Among all 840 patients referred for psychiatric consultation, 656 of them had complete medical records available for studying. 172 (26.2%) of them were diagnosed with delirium. After 16 patients with delirium tremens were excluded, data on antipsychotics prescription of 156 (23.8%) patients were analyzed. The mean age was 62.3 years old (22-95); 91 (61.9%) were 60 years old or more, and 103 (70.1%) were male. 94.2% of all patients were prescribed with antipsychotics. Regarding the type of antipsychotics, atypical antipsychotics were prescribed for 54.9% of the aged VS 35.4% of the younger. Antipsychotics used in the elderly were haloperidol (45.1%), risperidone (44.0%), quetiapine (5.5%), and olanzapine (2.2%). The younger patients were prescribed haloperidol (53.8%), risperidone (22.7%), quetiapine (4.6%), olanzapine (3.1%), and perphenazine (1.5%).

**Conclusion:** To our knowledge, this is the first study on current antipsychotics prescribing practice for the hospitalized elderly with delirium in consultation-liaison service in Thailand. Although the current evidence show no superiority for atypical antipsychotics over haloperidol, and limited evidence of their efficacy and safety in managing delirium, most doctors had tendency to prescribe atypical antipsychotics for the hospitalized patients, in particular the seniors. The results suggest the need to implement evidence-based guideline recommendations.

## Antiepileptic Medications and Emotional and Behavioral Problems in Children and Adolescents with Epilepsy

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**Background and Objectives:** Children with epilepsy tend to experience more emotional and behavioral problems compared with healthy controls. The objective of this study was to elucidate the clinical factors influencing anxiety and depressive symptoms in children and adolescents with epilepsy.

**Subjects and Methods:** Subjects were 90 epilepsy patients between the ages of 6 and 17 years (mean 11.8±3.9 years) and their parents. We administered the Revised Children's Manifest Anxiety Scale (RCMAS) and the Children's Depression Inventory (CDI) to children and adolescents with epilepsy.

We administered the Impact of Childhood Illness Scale (ICIS) and the State-Trait Anxiety Inventory (STAI) to the parents of these children and adolescents. Parents also provided behavioral informations on their children and adolescents through a Childhood Behavior Checklist (CBCL) and Conners scale.

We compared the differences across patient groups according to the clinical factors such as seizure frequency, epilepsy types and duration, and mono- or polytherapy, etc.

**Results:** ICIS, QRS, CBCL and Conners scores were higher when patients still had poor seizure control ( $p=0.011$ ,  $0.027$ ,  $0.047$  and  $0.075$ , respectively) than when patients had good seizure control.

ICIS, QRS, CBCL and Conners scores were higher when patients took more than one antiepileptic drugs ( $p=0.008$ ,  $0.003$ ,  $0.022$  and  $0.033$ , respectively) than when patients took only one antiepileptic drug.

RCMAS scores were higher in patients with epilepsy within the first 2 years and longer than 4 years than another group ( $p=0.023$  and  $0.043$ , respectively).

Parents' STAI scores were correlated with patients' ICIS, RCMAS, CDI, and Conners scores ( $p=0.002$ ,  $0.002$ ,  $0.009$ , and  $0.004$ ).

**Conclusions:** Epilepsy patients in childhood and adolescence have significant impacts on their emotion and behavior if they have poorly controlled seizures and/or more antiepileptic medications.

Key words: Anxiety, Depression, Epilepsy, Childhood, Adolescent

## The Effect of Psychosocial Stressor Towards the Prevalence of Depression Among Epilepsy Patients

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**Background:** The prevalence of epilepsy has been increasing annually with 80% itself occurring on developing countries (WHO, 2001). Currently the WHO estimation on its prevalence is up 8,2 per 1000 people per year. Epilepsy patient and their families are often burdened by its condition. Occurring burdens are related to various media, psychological aspects, social aspects and economical aspects, thus causing depression on epilepsy patient. The estimation of depression prevalence, according to Barry et al. (2000) is between 11-62%. Bad management will decrease the quality of life of epilepsy patient (Johnson et al., 2003) and increase the risk of suicide (Jackson et al., 2005). Many factors contributing on the occurring of depression are: psychological factors, seizure and its location, age, onset, therapy, and genetic (Branget et al., 2003), also stress disorder and emotional and environmental factors (Gribz et al., 2005).

**Objective:** To discover the effect of psychological factors towards the prevalence of depression among epilepsy patients.

**Method:** This study used cross sectional with descriptive-analytic method. This study has been held at Dr. Sardjito central Hospital between January -April 2008. The population of this study is all outpatient epilepsy went to neurology clinic at Dr. Sardjito central Hospital with fulfill inclusion requirements. By using Snedector and Lochran's formula, the number of sample is counted to become 96 subjects. The technique of sampling was using consecutive sampling system. Data processing was done using chi square and then multivariate regression counting was done by using SPSS-15.

**Result:** The result of chi square analysis shows the significant correlation between psychosocial stressor and the occur of depression among epilepsy patients ( $p<0,05$ ). From multivariate regression analysis, it was known that psychosocial stressor was affecting the depression occur among epilepsy patients.

**Conclusion:** There was a significant correlation between psychosocial stressor and occur of depression among epilepsy patients.

## Cognitive Function Disorder as a Reflection of Immunological Status in People Living with HIV/AIDS

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**Background:** Comorbidity of psychiatric disorders has been linked with HIV (human immunodeficiency virus) since the early epidemics of AIDS (acquired immunodeficiency syndrome), and until recently there have been many literatures focusing on psychiatric problems in relations with HIV seropositive patients (Morrison 2002). Among these patients, 72.3% have psychiatric problems (Cohen et al. 2002). The existing psychiatric problems may exist as dementia, delirium, anxiety, adjustment disorders, depression, substance abuse, and even suicide (Saddock 2003). Data from AIDS treatment house in the United States showed that 65% of the patients had psychiatric disorders other than substance dependency and neurocognitive disorders. If the last two diagnoses are included, the prevalence rate becomes 99.8% (Cohen 1998). In addition, regardless of its correlation with disease progressiveness, the presence of psychiatric disorders may influence one's quality of life, social functions, and general health conditions of the patients with HIV seropositive (Sherbourne et al 2000).

**Objective:** This study identify the disturbance of cognitive functions and the correlation with immunological status of HIV seropositive patients. **Method:** This is an observational-analytical research using cross sectional design conducted against 34 patients with HIV seropositive in HIV unit in Dr. Soetomo Hospital Surabaya, Indonesia. **Results:** This study examined the cognitive functions of 34 patients with HIV seropositive, correlated with their immunological status. We found 22 samples in MMSE test who had cognitive disorders (64.7%), and the remaining 12 samples were in normal condition (35.3%). Short memory disorder was found in 19 samples (55.9%) and the other 15 samples were normal (44.1%). The reduction of CD4 immunological status to less than 200 was found 23 respondents (67.6%) and the others had CD4 of more than 200. Significant correlation was found between cognitive function disorder and immunological status of individuals with HIV seropositive ( $p = 0.021$ ). **Conclusion:** The cognitive function disorder may reflect immunological status of HIV patients. Therefore, regular testing of cognitive function may be a practical and cost-saving marker of CD4 reduction.

**Keywords:** Cognitive function - Immunological status - HIV/AIDS patients

## Depression on Seropositive HIV/ AIDS Patients

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**Objectives:** To describe the depression among seropositive HIV/AIDS patients and its relationship to the stage of HIV progression, family support, ARV medication, and the understanding of the disease.

**Methods:** Seropositive HIV/AIDS patients (n=34) were enrolled into this research. They were outpatient and inpatient patients in HIV/AIDS clinic in Surabaya Dr. Soetomo general hospital. The samples were assessed using Beck's Depression Inventory. Statistical analysis were assessed by chi-square and cross tab.

**Results:** It was found that borderline depression was 17.6%, mild depression was 29.5%, moderate depression was 8.8%, severe depression was 5.9%, very severe depression was 2.9%. An amount of 35.3% was normal. There were significant relationship between depression and understanding of the HIV/AIDS disease and also ARV medication.

**Conclusion:** There was a large amount of depression (64.7% including borderline depression) among HIV/AIDS patients. This findings underscore the importance of depression screening, since it is known that the comorbidity of depression will worsen the disease progression.

## Comparative Assessment of Clinical Efficacy Between the Naive and the Switching Group to Donepezil: 12 Months Prospective Study

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**Objectives:** The purpose of this study was to compare the efficacy between switching patients with Alzheimer's disease (AD) from galantamine or rivastigmine to donepezil because they were not responding adequately, and naive patients with AD who initiated therapy with donepezil. **Methods:** Eighty-six patients with mild to moderate AD were recruited for this 52-week study. The effect of donepezil on cognitive function was measured using Preliminary Korean version of Alzheimer's Disease Assessment Scale-Cognitive subscale (K-ADAS-Cog). Patients' activities of daily living using the Seoul-Instrumental Activities of Daily Living (S-IADL) and Seoul-Activities of Daily Living (S-ADL); behavioral symptoms using the Neuropsychiatric Inventory (NPI) were measured at baseline, 13-weeks, 26-weeks, 39-weeks and 52-weeks. **Results:** Sixty-six naive patients and twenty switching patients were enrolled in the study. Fifty patients completed the study and thirty-six discontinued their treatment before week 52. There was no significant difference between two groups in demographic data, baseline characteristics and dementia severity except duration of illness. The total K-ADAS-Cog scores were not significantly different from baseline after 52 weeks of treatment in both groups ( $p>.05$ ). Switching group demonstrated deterioration of S-ADL ( $p=.034$ ) and S-IADL ( $p=.010$ ), whereas a decline in only S-ADL ( $p=.008$ ) was observed in the naive group. The NPI scores did not significantly change in both groups ( $p>.05$ ). When the degree of change from baseline in test scores at each post treatment assessment was compared, there was no significant difference between two groups for any of the outcome measures except S-IADL at 26 weeks. S-IADL mean scores in switching group was higher than naive group at 26 weeks ( $p=.001$ ). **Conclusions:** Switching patients had similar levels of efficacy with naive patients who initiated therapy with donepezil. These results suggest that patients not responding adequately to rivastigmine or galantamine may improve or stabilize after switching to donepezil and prior medication does not effect donepezil's efficacy. This study was supported by a grant of the Korea Health 21 R&D Project, Ministry of Health, Welfare, and Family Affairs, Republic of Korea (A050079). **Key Words:** Alzheimer's disease, Donepezil, Naive group, Switching group, Treatment response

## Comparative Assessment of Clinical Efficacy after 12-Month Clinical Trial of Donepezil between the Patients with Alzheimer's Disease and Mixed Dementia

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**Objective:** To investigate the comparative assessment of clinical efficacy, we examined the clinical response to donepezil between the patients with Alzheimer's disease (AD) and mixed dementia (MD) during a 12-month trial. **Methods:** Sixty-nine AD and nineteen MD were recruited for this 52-week study. All patients met the following inclusion and exclusion criteria. Subjects were eligible to enter the trial if they met all of the following criteria: Korean version Mini-Mental State Examination (K-MMSE) scores between 10 and 26; History of cognitive decline that had been gradual in onset and progressive over at least 6 months; A caregiver who could assist the patient with medication, attend the assessment and provide information about the patient. The effect of donepezil on cognitive function was measured using the Preliminary Korean version of Alzheimer's Disease Assessment Scale-cognitive subscale (K-ADAS-cog). Patients' activities of daily living using the Seoul-Instrumental Activities of Daily Living (S-IADL) and Seoul-Activities of Daily Living (S-ADL); behavioral symptoms using the Neuropsychiatric Inventory (NPI) were measured at a given point of time. The prespecified group with an individual response was defined. A responder was defined as 'no change or any improvement (decrease in the total K-ADAS-cog scores)' on the K-ADAS-cog at 26-weeks in comparison with baseline. **Results:** A total of 88 patients were enrolled. 39 patients dropped out, and 49 completed the study. A significant worsening was not observed for the total K-ADAS-cog, S-IADL, S-ADL, and NPI scores in both AD and MD patients at 52-weeks. Generally AD patients (60%) revealed higher responsiveness than MD patients (42.9%). AD patients had highest responsiveness at 26-weeks and MD patients had highest responsiveness at 39-weeks. **Conclusions:** In this study, AD and MD patients were treated with donepezil for 52-weeks. Both patient groups were similar in their scores for K-ADAS-cog, S-IADL, S-ADL, and NPI after 52-weeks. These results show that donepezil is effective in both AD patients and MD patients, and support that donepezil seems to be well tolerated in AD patients with vascular comorbidity. **Key words:** Donepezil, Alzheimer's disease, Mixed dementia

## Effectiveness of Aripiprazole Oral Solution for Delirium: A Case Report

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[Introduction] Recently, risperidone has been a first-line compound in the treatment of delirium. Although risperidone has a beneficial effect on delirium, adverse effects such as extra-pyramidal symptoms and sedation may occur. We experienced a patient with delirium who was treated successfully with aripiprazole oral solution (OS).

[Case] A 61-year-old man had a 1-month history of major depressive disorder. He had a medical history of diabetes mellitus. He was admitted into the intensive care unit after self-injuringly cutting his chest, abdomen and neck with a knife. On the first day of the administration, midazolam was started by drip infusion continuously and then gradually tapered. On third day, instillation of midazolam was discontinued. Afterwards, he was disoriented about time and place, and developed lack of attention, sleep-wake cycle disturbance and disturbance of mood. He fulfilled the DSM-IV criteria for delirium. His delirium rating scale (DRS) score was 13. After obtaining informed consent, we prescribed aripiprazole OS at a daily dose of 6mg. Within 2 days, symptoms of delirium disappeared promptly except mild disturbance of sleep-wake cycle, and his DRS score decreased to 2. The improvement was maintained until his discharge. No serious adverse event was observed.

[Conclusion] Our case suggests that aripiprazole may be effective for delirium.

## A Randomized Controlled, Pilot Study of Aripiprazole in the Treatment of Delirium

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**Purpose:** Aripiprazole has less extrapyramidal, sedative and anticholinergic side effects, So it can be one of the effective drugs for the treatment of patients with delirium. Therefore, this study is purposed to investigate whether aripiprazole has the effectiveness for treatment of delirium and whether there is a difference between risperidone and aripiprazole. **Methods:** All subjects were randomized to receive either risperidone or aripiprazole with fixed dose at the first day of treatment. Risperidone group (12 patients) was given 1 mg and aripiprazole group (8 patients) was given 5 mg on the first day of treatment at night. Then, all subjects received flexible doses of either aripiprazole or risperidone according to the clinicians' assessment and clinical status of patients with delirium. The effectiveness was evaluated by Clinical Global Impression-Severity (CGI-S), Korean version of Delirium Rating Scale (K-DRS), and Korean Mini Mental Status Examination (K-MMSE). The side effects were evaluated by Extrapyramidal Symptom Rating Scale (ESRS). One psychiatrist, blind to the status of treatment, measured the symptom at the baseline and repeated that seven days later. Statistical analysis was performed using Mann-Whitney Test, Wilcoxon Signed Ranks Test, chi-square test; a level of  $p < 0.05$  was considered significant. **Results:** There were no significant differences between risperidone and aripiprazole groups in age (risperidone group  $64.75 \pm 3.31$ , aripiprazole group  $65.38 \pm 5.37$ ) and sex (risperidone group, male: female 9:3, aripiprazole group male: female 5:3). There were no significant differences between two groups by Mann-Whitney Test in the baseline K-DRS ( $p=0.18$ ), K-MMSE ( $p=0.57$ ) and CGI scores ( $p=0.27$ ). After the treatment, K-DRS ( $p=0.018$ ), CGI scores ( $p=0.004$ ) of aripiprazole group were more significantly decreased from the baseline scores than those of risperidone group, but there were no differences in K-MMSE ( $p=0.29$ ), ESRS scores ( $p=0.15$ ) between two groups by Wilcoxon Signed Ranks Test. **Conclusion:** These results suggest that Aripiprazole is seemed to be as effective as risperidone for the treatment of delirium.

## Coping Strategy of Children with Acute Lymphoblastic Leukemia

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**Objectives:** To study the coping strategy of children with acute lymphoblastic leukemia (ALL), including the features of coping strategy and aspects which influence the coping strategy, by observing the relationship of social support, biological factor, aspects of the parents, perception of the illness, children's response of the illness, psychosocial and cognitive development. **Methods:** It was field study using triangular method by applying the qualitative approach. Qualitative data collection was performed cross sectionally. The subjects are children with age 3-6 years old (early childhood) who have induction phase with their parents, children with age 3-6 years old who have maintenance phase with their parents, children with age 6-12 years old (middle childhood) who have induction phase with their parents, and children with age 6-12 years old who have maintenance phase with their parents. **Results:** The children have various coping strategies. They have emotional focused coping and problem focused coping strategy. Younger children tend to show emotional focused coping than the older who show rationalisation and sublimation. The older children have significant problem focused coping in cured seeking behavior. Children's perception of the illness influence cured seeking behavior. Social support and coping strategy of the parents influence the strategy coping of the children. Strategy coping from mothers is more significant than fathers. Temperament of the children also influence the children to perceive and respond to the illness. Cognitive and psychosocial developmental of the children influence the strategy coping to handle the illness. The parents' effective coping behavior increased along with their rising spirituality. The presence of the child in family who suffers from ALL can cause not only problems that is directly related to the problem of the treatment, but also the complexities impact which include the change of the parental model of the children, whether they were ill or not, the change of interaction of husband and wife, the change of interaction model of the big family, and school problems of the children, family financial and works. **Conclusion:** Children's temperament influence coping strategy significantly. Age and cognitive developmental influence the children how to perceive the illness and the treatment. Younger children (early childhood) have acting out and regression to lower level of the developmental. Social support from parents, big family, medical staff and others children who suffer ALL influence the strategy coping of the children. ALL has a big impact for the family life. The problem focused coping is not better than emotional focused coping but, in person who less adapt just use emotional focused coping. **Keywords:** Leukemia, qualitative, coping strategy, children, emotional and problem focused coping, impact

## Comprehensive Review of Neuropsychiatric Aspects on Mutation Zoonosis Diseases

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**Background:** The outbreak of mutation zoonosis diseases is like Avian Influenza and Swine Influenza which beginning attack animals then mutation and capable attack human, its makes fidgety in all countries of the world. The deviations from this zoonosis diseases appears many differential diagnoses, one of them is neurology diseases and psychiatry. The necessary of comprehensive review from neuropsychiatric aspects includes classification, epidemiology, biochemical, diagnosis, therapy and related diseases with neurology and psychiatry.

**Aim:** The aim from this literatures study is to explanation comprehensive review of neuropsychiatric aspects on mutation zoonosis diseases.

**Methodology:** This literatures study using descriptive analytic.

**Result:** The expectation from this literatures study is comprehensive review of neuropsychiatric aspects on mutation zoonosis diseases.

**Benefit:** This literatures study may explanation comprehensive review on mutation zoonosis diseases not only from emergency physical aspect, but from neuropsychiatric aspects either.

**Kata Kunci:** Neuropsychiatric Aspects – Mutation Zoonosis Diseases.

## Plasma Homocysteine Levels and Apathy in Alzheimer's Disease

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**Background:** Apathy is common in Alzheimer's disease (AD) and leads to great disability. Thus far, it is still unclear about the etiologies of apathy in AD. Homocysteine affects brain in various pathophysiology and has been proposed to increase risk to develop AD. The main aim of this study was to investigate if higher homocysteine is associated with apathy among the patients with AD.

**Methods:** Consecutive 93 patients with AD and 70 controls recruited by advertisement were enrolled. Apathy was assessed using Apathy Evaluation Scale (AES) and was defined as scores of 41 and above. Fasting plasma homocysteine levels were examined. Scores of vascular risk were measured using Framingham stroke risk scale (FSRS).

**Results:** Homocysteine levels were higher in AD patients compared to the controls ( $14.5 \pm 6.7 \mu\text{mol/L}$  vs.  $10.6 \pm 5.2 \mu\text{mol/L}$ ;  $p < 0.0001$ ). Sixty-nine (74.2%) of AD patients presented apathy. Higher homocysteine levels occurred in patients with apathy than those without ( $15.9 \pm 7.3 \mu\text{mol/L}$  vs.  $11.6 \pm 4.8 \mu\text{mol/L}$ ;  $p < 0.0001$ ). Positive association was found between homocysteine and apathy (OR=1.14,  $p=0.046$ ), controlling for age, sex, MMSE and FSRS. In secondary analysis, plasma homocysteine levels were correlated with total score of AES (pearson  $r=0.33$ ,  $p=0.022$ ) and its subdomains of apathy in cognition (pearson  $r=0.34$ ,  $p=0.017$ ) and behavior (pearson  $r=0.34$ ,  $p=0.016$ ) in the women patients only.

**Conclusion:** Our findings support higher homocysteine level is associated with apathy in AD, and their relationship is independent of vascular risks. AD patients with higher level of homocysteine will present more cognitive and behavior dimensions of apathy, especially for the women. Further prospective study is warranted to support the cause-effect, and intervention study may provide more information about treatment of prevention of apathy in AD.

## Study of G1/S Control Protein Failure in Patients with Alzheimer's Disease by using Peripheral Lymphocytes

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Extensive neuron death occurring in the Alzheimer's disease is related to apoptosis. The control failure of cell cycle is involved in the apoptosis. Cell cycle elements play an important role in neuronal death-apoptosis.

Cell cycle is controlled CDK-Cyclin complexes and E2F- Rb pathway and CDKI (cyclin-dependent kinase inhibitor) play a major role in cell cycle.

Recent studies have suggested that the regulatory failures of cell cycle appear to be early events of AD pathogenesis in lymphocytes as well as in neuron.

Therefore we confirmed the G1/S regulatory proteins and their roles, and examined whether the G1/S control failure in lymphocytes affects the apoptosis in AD patients.

CDKs (Cyclin Dependent Kinases) - 2, 4 and 6 were increased in AD patients and significantly CDK2 was elevated in AD patients after using PHA. Also the increasement of CDK 2,4 and 6 occurred in AD patients with rapamycin.

We also investigated the expression of E2F, Rb and p27 that proteins closely related to cell cycle. Lymphocytes in AD group showed that the increase of phosphorylation of Rb and expression of E2F.

Expression of p27 was more decreased in lymphocytes of AD than age matched control by western blot.

Our findings could provide the basis for new clinical tests that identify the pathogenesis of AD-apoptosis in lymphocytes.

Therefore we hope that these results could be relied on the preventive measures for AD.

## Polymorphisms in Phospholipase A2 (PLA2) and Cyclo-Oxygenase 2 (COX2) Genes Predict Risk of Depression and Polyunsaturated Fatty Acids Levels in Patients Receiving Interferon-Alpha for Chronic Viral Hepatitis

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**Background.** Phospholipase A2 (PLA2) and cyclo-oxygenase 2 (COX2) are the two key enzymes in the metabolism of polyunsaturated fatty acids (PUFAs), which in turn may play an important role in mechanisms underlying cytokine-induced depression and sickness behaviour. **Methods.** Patients with chronic hepatitis C viral (HCV) infection (n=132) were assessed to examine the effects of single nucleotide polymorphisms (SNPs) of COX2 and PLA2 genes on the development of depression and on the erythrocyte levels of three main PUFAs, docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA) and arachidonic acid, during interferon-alpha therapy. A second "replication" group of patients (n=82) with major depression was used to replicate the effects of genotypes on specific clusters of depressive symptoms. **Results.** 28% of participants developed interferon-alpha-induced depression. Participants with PLA2 BanI GG or COX2 rs4648308 AG genotypes had a higher risk of IFN-alpha-induced depression (odds ratio=3.1 and 3.5, respectively). The "at risk" PLA2 polymorphism was associated with lower EPA levels, and the "at risk" COX2 polymorphism was associated with lower DHA levels, during IFN-alpha therapy. The PLA2 BanI GG was also associated with more somatic symptoms, both in patients with interferon-alpha-induced depression and the replication sample of patients with major depression. **Conclusions.** Genetic variations in the COX2 and PLA2 genes have effects on IFN-alpha-induced depression, possibly by affecting the levels of EPA and DHA. PLA2 genotypes is associated with somatic symptoms in depression, hence it may be a potential biomarker to understand clinical subtypes of depressive disorders.

## Blood Serotonin Level, Depression and Neurocognitive Condition in Six Months Post Brain Injury

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**Background:** Brain injury still becomes serious public health issue resulting in death and prolonged disability. A patient with brain injury undergoes a significant change in cognition, behaviour and other psychiatric symptoms. Depression is the most common psychiatric symptom, accounting for about 14-77% of the patients post-brain injury. Serotonergic system possibly takes a role in the brain injury condition. Neurocognitive deficits, emotional and behavioural changes occurring after brain injury most likely will resolve within the first six months, while 10-15% of the patients have the established and persistent symptoms. **Objective:** This research is to analyse a relationship between blood serotonin level and depressive and neurocognitive condition following six months post-brain injury. **Method:** This is an observational-analytical research using cross sectional design conducted against 34 patients with moderate brain injury who were ever hospitalised at neurosurgical unit in Dr. Soetomo Hospital Surabaya in six months ago. **Results:** From 34 patients, 17 (50%) of them underwent mild depression, 12 (35%) moderate depression, 2 (6%) severe depression and 3 (9%) patients without depression. The Hamilton Depression Rating Scale (HDRS) test indicated that depression was significantly correlated with serotonin level ( $p<0.05$ ). Regarding the cognitive functions test using Batere Neurocognitive Test, particularly Verbal Fluency (VF), Rey Auditory Verbal Learning Test-Immediate (RAVLT-I) and RAVLT-Delayed (RAVLT-D) had significant correlation with blood serotonin level ( $p<0.05$ ). The Inspection Time Task (ITT), Continuous Performance Task-Identical Pairs (CPTIP) and Continuous Performance Task-Degraded Stimuli (CPTDS) had no significant correlation with blood serotonin level. **Conclusion:** The blood serotonin level of six months post-brain injury patients significantly correlated with depressive condition and neurocognitive conditions particularly with verbal fluency (VF), immediate and delayed memories (RAVLT-I and RAVLT-D). **Keywords:** Serotonin - Depression - Neurocognitive

## Varenicline Did Not Increase Serum BDNF Levels in Patients with Nicotine Dependence: A Preliminary Study

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**Objective:** Varenicline acts as a partial agonist with affinity and selectivity for alpha4beta2 nicotinic acetylcholine receptors. This activity help patients achieve smoking cessation by reducing withdrawal symptoms and smoking satisfaction. Recent animal studies have suggested an association between nicotine and alterations in brain-derived neurotrophic factor (BDNF) expression levels. However, the role of BDNF in humans with nicotine dependence treated with varenicline has not yet been investigated. **Aim:** We investigated the effects of varenicline on serum BDNF in patients with nicotine dependence treated with varenicline.

**Subjects and Methods:** Nine were male and 4 were female. Their age ranged from 30 to 66 (51±12) yr. All participants were met DSM-IV criteria for nicotine dependence. The mean of age of first use, duration of smoking use and amount of use were 19.0±2.7 yr, 31.5±11.3 yr and 27.3±14.5 cigarettes/day. Fagerstrom test for nicotine dependence (FTND) were evaluated, and serum BDNF levels and CO levels were measured before and 8 weeks after varenicline treatment. The protocol of this study was approved by the Ethics Committee of the UOEH.

**Results:** All patients have stopped smoking in 12 weeks treatment. The mean of FTND and CO levels before treatment were 6.5±2.5 and 22.6±12.9. Serum BDNF levels were not increased from baseline to 8 weeks after varenicline (before: 5.90±2.69 ng/ml, 8W: 6.39±2.50 ng/ml).

**Conclusion:** Treatment with varenicline for 8 weeks combined with 12 week's smoking cessation did not increase serum BDNF levels in smokers.

## Neuronal Nicotinic Acetylcholine Receptor Alpha 4 and Beta 2 Gene (CHRNA4B2) Polymorphisms and Nicotine Dependence in Japanese Workers

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Neuronal nicotinic acetylcholine receptor is a specific binding site of nicotine, which normally bind the acetylcholine. The binding of nicotine to nicotinic acetylcholine receptors mediates the feeling of reward. CHRNA4 and CHRNB2 genes were previously reported as an important role in nicotine dependence. To investigate the difference between CHRNA4 and CHRNB2 SNP and nicotine dependence in Japanese, we collected 673 workers with 558 male workers and analyzed 5 SNPs in CHRNA4 gene and 3 in CHRNB2. We assessed nicotine dependence by a score of 4 or more on the Fagerstr m Test of Nicotine Dependence (FTND). In the current smokers, there are 168 nicotine dependence smokers and 116 non-nicotine dependence smokers in our subjects. We found a significant difference between genotype frequency in CHRNA4 rs1044397 SNP and the nicotine dependence ( $\chi^2=7.84$ ,  $df=2$ ,  $p$ -value=0.02). In the CHRNB2 gene, there are differences in both genotype and allele frequencies (rs4845652, genotype:  $\chi^2=2.99$ ,  $df=1$ ,  $p$ -value=0.08; allele:  $\chi^2=3.78$ ,  $df=1$ ,  $p$ -value=0.05), although both of the result did not achieve the significant level. Our data suggests that CHRNA4 and CHRNB2 gene polymorphism may correlate to nicotine dependence in our sample. The gene-gene interaction data will be presented.

## Chinese Version of the Severity of Dependence Scale as Screening for Benzodiazepine Dependence in Taiwan

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**Aims.** To assess the validity of Chinese version of the Severity of Dependence Scale (SDS[Ch]) as a screening test to measure benzodiazepine dependence among regular benzodiazepine users in Taiwan. **Method.** 164 regular benzodiazepine users, attending the Psychiatric Outpatient Department of Kaohsiung Municipal Hsiao-Kang Hospital or Kaohsiung Medical University Hospital in Taiwan, were administered the SDS[Ch] and responses were compared with the Mini-International Neuropsychiatric Interview diagnosis of benzodiazepine dependence. Receiver Operating Characteristic (ROC) analysis was used to determine which cut-off score on SDS[Ch] allowed the best cut-off between sensitivity and specificity. **Results.** The SDS[Ch] was showed to have high diagnostic utility, and a score higher than 6 on the scale appears to be an appropriate threshold for problematic benzodiazepine users. SDS[Ch] was noted to have a specificity of 83.9% and a sensitivity of 89.5%, and the area under the curve was of 0.833. **Conclusion.** The findings support that the SDS[Ch] is a valid brief self-report questionnaire for assessment of benzodiazepine dependence among regular benzodiazepine users in Taiwan.

## The Human Mu-opioid Receptor OPRM1 Gene Polymorphism and Nicotine Dependence in Japanese Workers

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The mu-opioid receptor has been implicated in the pathogenesis of substance dependence including nicotine dependence. Studies examining the association of the mu-opioid receptor gene (OPRM1) with substance dependence have focused on the Asn40Asp (A118G) single nucleotide polymorphism (SNP). In the present study, we tested association between the functional OPRM1 A118G polymorphism (rs1799971) and nicotine dependence in its each stage (e.g., smoking initiation, dependence development, and smoking cessation). Smoking status was confirmed by in-person structured interviews. We have recruited the present sample from one of the Japanese major manufacturing company (total N = 673), with advantage of relatively homogeneous background. Among our sample, we identified 233 never smokers (who reported never having smoked a single cigarette in their lifetime) and 167 heavy smokers (who smoke  $\geq 20$  cigarettes daily). We found a non-significant difference in allele frequency ( $\chi^2 = 3.54$ ,  $df = 1$ ,  $p = 0.06$ ) between never smokers and heavy smokers. Our data suggests that OPRM1 gene may confer the risk for nicotine dependence in our sample.

## Pharmacotherapy and Clinical Characteristics of Korean Pathological Gamblers in Admission Treatment

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**Purpose:** The pathological gambling (PG) is a disabling impulse control disorder. The patients with PG may be responsive to the treatment with serotonin specific reuptake inhibitors (SSRIs), opioid antagonist and mood stabilizers. We investigated the psychopharmacotherapy and clinical characteristics in patients with PG.

**Methods:** From Jan 2008 to May 2009, 40 patients with PG (39men and 1 woman) who applied to a specialized in-patient treatment were included. We obtained the clinical characteristics of the patients and investigated their pharmacological treatments.

**Results:** The mean age of the patients with PG was 42.9 (SD 9.0, range 27 - 68) years. The mean IQ was 109.7 (SD 10.4, range 81 - 132) and the mean Beck's Depression Inventory score was 22.4 (SD 12.3, range 0 - 62). The mean State Trait Anxiety Inventory I and II scores were 48.3 (SD 12.5, range 12 - 68) and 49.3 (SD 11.1, range 27 - 76), respectively.

Twenty nine (72.5%) patients were treated with medications including antidepressants (26 patients), opioid antagonist (10), anxiolytics (12), atypical antipsychotics (6), hypnotics (3) and mood stabilizers (2). In 26 patients treated with antidepressants, 20 patients were treated with various types of SSRIs (escitalopram 7, paroxetine 7, sertraline 4, fluoxetine 2) and the others with bupropion (4) and mirtazapine (3). Single antidepressant was used in 19 patients (73.1%) and 7 patients (26.9%) were treated with a combination of two antidepressants. The naltrexone was administered to 10 (25%) patients.

**Conclusions:** 29 (72.5%) patients with pathological gamblers in admission treatment

were treated with various medications including antidepressants, opioid antagonist, anxiolytics, antipsychotics, hypnotics and mood stabilizers. Pharmacological treatment should target all symptoms in individual patients and should be considered in PG patients.

## The Norepinephrine Transporter (NET) Gene is Not Associated with Heroin dependence

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**Running title:** NET Gene is not associated with Heroin Dependence.

**Key words:** heroin dependence; norepinephrine transporter gene; hSLC6A2; polymorphism, duration.

To examine whether the norepinephrine transporter gene (*NET*, *hSLC6A2*) is a susceptibility factor for the development of heroin dependence (HD) or its clinical subgroups. A total of 601 male Han Chinese subjects in Taiwan (364 HD, 237 healthy controls) were recruited for this study. Individuals with HD were classified into several subgroups to reduce the clinical heterogeneity. All subjects were interviewed using identical methods, and HD was diagnosed according to DSM-IV criteria. The polymorphisms of *rs28386840*, *rs2242446*, and *rs5569* in the *hSLC6A2* gene were analyzed by using polymerase chain reaction and restriction fragment length polymorphism methods. Genotyping was confirmed using bidirectional sequencing. Statistical associations between *-3081 T/A (rs28386840)*, *-182 T/C (rs2242446)*, and *1287 G/A (rs5569)* gene polymorphisms and various subtypes of HD were analyzed using the Pearson  $\chi^2$  test, multiple logistic regression, and Estimating Haplotypes software. No statistically significant difference in genotype and allele frequencies of *hSLC6A2* polymorphisms were found between patients with HD and healthy controls, or between its subgroups with HD and controls. In addition, in analyses of haplotype frequencies and multiple logistic regression analyses, the *hSLC6A2* polymorphisms (*rs28386840*, *rs2242446*, and *rs5569*) were not associated with HD and its subgroups. This study suggests that the promoter polymorphisms (*rs28386840*, *rs2242446*), and exon 9 variants (*rs5569*) in the *hSLC6A2* gene are not major risk factors in increasing susceptibility to either HD or its clinical subgroups.

## NMDA Receptor Subunit 2B Gene (GRIN2B) and Nicotine Dependence in Japanese Workers

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Preclinical research findings in laboratory animals indicate that the glutamatergic system may be involved in nicotine dependence. In animals, N-methyl-D-aspartate (NMDA) receptor antagonists decreased nicotine self-administration or reinstatement of nicotine-seeking behavior. NMDA receptor dysfunction may be involved in the pathophysiology of smoking behavior. The human gene coding for the 2B subunit of the NMDA receptor (GRIN2B) is thus considered a candidate gene for nicotine dependence. To examine the hypothesis, we examined the association between smoking behavior and three GRIN2B polymorphisms, G-200T (5'UTR), C2664T (exon 13) and T5072G (3'UTR), using a sample of Japanese healthy workers (N = 673). This study was approved by the Ethics Committee of the University of Occupational and Environmental Health, and informed consent was obtained from all subjects prior to participation to the study. Among smokers, the -200G allele, which has been associated with lower gene activity, was associated with having smoking cessation histories (for more than 1 month) with non-significant trend (P=0.09). Our results suggest that GRIN2B G-200T polymorphism may play a role in smoking cessation in our sample. Details of association analyses for other markers as well as marker haplotypes will be presented.

## The Psychological Problems Among Injecting Drug Users (IDUs) in Bandung, West Java, Indonesia

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**Background** Until recently, the most common view was that drug addicts are weak and/or bad people, unwilling to control their behavior and gratifications. However, the addictive drugs affect the brain circuitry controlling the motivated and learned behavior. Some of drug users start using drug to "cure" their psychological problems. This make psychiatric disorders and addiction are often dubbed 'dual disorders'. This present study was conducted to explore the common psychological problems among injecting drug users (IDUs) in Bandung, West Java, Indonesia. **Methods** A cross-sectional, non-experimental study using respondent driven sampling was conducted from June to September 2008 at a primary health centre in Bandung, Indonesia. A total of 197 IDUs were interviewed using EuropASI to screen their psychological problems. **Results** The psychological problems, such as depression, anxiety, trouble in remembering, hallucination, and/or controlling violent, which were not a direct result of their drug use, were experienced by 50% of IDUs in the last 30 days and by 80% of IDUs in the life time. The psychological problems with the highest percentage in the last 30 days and also in the life time are trouble in remembering and anxiety. Thirty seven percent of all IDUs have ever had serious thought of committing suicide and more than 50% of them have attempted suicide. However, only 26 IDUs (13%) have ever sought for help for their psychological problems. **Conclusion** This study suggests that providing information about psychological problems and their treatment is needed by IDUs. Furthermore, addressing psychological problems in the general community can reduce the chance to become a drug user. Last, those who deliver addiction care also have to be aware about the psychiatric comorbidity in order to have a better outcome. **Key words:** Psychological Problems, Injecting Drug Users

## BDNF Val66Met Polymorphism and Nicotine Dependence in Japanese Workers

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It has been reported that BDNF and dopamine (DA) systems interact within a number of neurobiological processes (Guillin et al., 2001). BDNF's influence on DA responsiveness might be an important factor in the etiopathology of substance abuse including nicotine dependence, which is implicated in DA reward system (Guillin et al., 2001, 2007). Recent reports showed an association between smoking behavior and the BDNF Val66Met polymorphism (Lang et al., 2007). We have recruited the present sample from one of the Japanese major manufacturing companies (total N = 673), with advantage of relatively homogeneous background. Among our sample, we identified 233 never smokers (who reported never having smoked a single cigarette in their lifetime) and 167 heavy smokers (who smoke  $\geq 20$  cigarettes daily). We could not find an association between smoking and the BDNF Val66Met polymorphism in our sample. Our data suggests that BDNF gene may not confer the risk for nicotine dependence in Japanese workers.

## Possible Association Between the Ala72Ser Polymorphism of the Catechol-O-methyl Transferase Gene (COMT) and Nicotine Dependence in a Sample of Japanese Workers

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Catechol-O-methyl transferase gene (*COMT*) is one of the enzymes involved in the degradation and inactivation of catecholamine transmitters including dopamine, which is present in dopaminergic brain regions. Nicotine stimulates dopamine release and activates dopaminergic reward neurons. The dopaminergic reward system may be a key mechanism in nicotine dependence. Recently, new functional single nucleotide polymorphism (SNP) Ala72Ser in the *COMT* gene, which accounts for the enzyme activity, was found. The purpose of our study is to examine the association between the *COMT* Ala72Ser polymorphism and nicotine dependence in its each stage (e.g., smoking initiation, dependence development). Smoking status was confirmed by in-person structured interviews. We have recruited the present sample with advantage of relatively homogenous background (total N=673). Among them, we defined 435 smoking initiators (SI) and 234 non-initiators (never having smoked a single cigarette: NI). Among SI, 417 were high nicotine dependent smokers (having smoked>100 cigarettes or total smoking duration>6 months in their lifetime: HND), and 16 low nicotine dependent smokers (LND). Although there was no significant difference in both genotype and allele frequencies between SI and NI, we found a significant difference in both genotype ( $p=0.019$ ) and allele frequencies ( $p=0.038$ ,  $OR=0.34$ ,  $95\%CI=0.14-0.81$ ) of the *COMT* Ala72Ser between HND and LND. These data suggest that the *COMT* Ala72Ser polymorphism is possibly associated with the degree of nicotine dependence in Japanese workers.

## Association between NTNG1 Gene and Schizophrenia in the Chinese Northern Han Population

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**Objective:** To investigate the role of the NTNG1 gene susceptibility in schizophrenia, Three SNPs (rs4132604, rs2218404, rs1373336) and haplotypes were detected using Chinese case-control samples. **Method:** DNA was obtained from 316 Chinese northern Han schizophrenia patients and 311 healthy controls. Three SNPs were detected by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). In addition, the association between three SNPs and clinic symptoms in the first-episode schizophrenia patients were examined. **Results:** The allele and genotype frequencies for rs2218404 rs1373336 were not significantly different between the schizophrenia patients and the healthy controls. However, rs4132604 showed significant association with schizophrenia ( $G > T$ ,  $\chi^2 = 7.858$ ,  $P = 0.0051$ ,  $OR = 1.379$ ,  $95\%CI: 1.101-1.727$ , genotype  $P = 0.022$ ). Strong pairwise linkage disequilibrium was found between the three SNPs tested, (all  $|D'| > 0.60$ ). The 3 loci were therefore designated as a LD blocks. Significant haplotype differences between case and control groups was observed. It include GG, TG between rs4132604 and rs2218404, GT, GC between rs1373336 and rs2218404 and GGT, TGT between three SNPs. There were significant difference between rs4132604 allele frequencies and personality ( $\chi^2 = 13.186$ ,  $P = 0.010$ ). There were also significant difference between rs4132604 and some clinic symptoms. It include delusion of relation ( $\chi^2 = 20.328$ ,  $P = 0.000$ ), delusion of being revealed ( $\chi^2 = 8.531$ ,  $P = 0.014$ ), delusion of persecution ( $\chi^2 = 11.105$ ,  $P = 0.004$ ), delusion of jealousy ( $\chi^2 = 8.334$ ,  $P = 0.015$ ). Significant difference between rs1373336 and some clinic symptoms were detected. It include delusion of relation ( $\chi^2 = 15.905$ ,  $P = 0.000$ ), delusion of persecution ( $\chi^2 = 14.367$ ,  $P = 0.001$ ), delusion of jealousy ( $\chi^2 = 11.716$ ,  $P = 0.003$ ). **Conclusions:** Rs4132604 variations in NTNG1 may play a role in schizophrenia in the Chinese Northern population. The frequencies of haplotypes between the three SNPs have difference between cases and controls. There were associations between rs4132604, rs1373336 and clinic symptoms.

## Genome-wide Analysis of Gene Expression Profile and Transcript Isoform Variation in Schizophrenia

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Multiple genes and environmental exposures have been demonstrated to be involved in the etiology of schizophrenia, but its biological underpinnings remain largely unknown. Alternative pre-mRNA splicing (AS) generates variation in mRNA and protein isoforms and plays an important role in phenotypic diversity and genetic disorders. To explore the differences in gene expression profiles and AS patterns in schizophrenia, we compared the genome-wide transcriptome expression profiles of lymphoblastoid cell lines derived from 30 schizophrenic patients and 30 healthy controls by using the Affymetrix GeneChip Human Exon 1.0 ST Array. In the gene-level analysis, we found 11 differentially expressed genes, which also displayed >1.5-fold or <0.67-fold change between the case and control samples ( $p < 0.05$ , without correction). A quantitative real-time PCR analysis was also conducted to confirm these findings. To investigate the genetic contribution to differentially expressed genes and transcript isoform variations, next, we performed the combination approach with the genome-wide association profiles by using the Genome-Wide Human SNP Array 5.0. We are doing the exon-level analysis by using Exon Array and the combination approach with genetic profiles. This study was approved by the Ethics Committee of the Nagoya University Graduate School of Medicine. Written informed consent was obtained from each subject and personal information was totally anonymized.

## Effects of the DRD3 Ser9Gly Polymorphism on Aripiprazole Efficacy in Schizophrenic Patients as Modified by Clinical Factors

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Aripiprazole, a novel antipsychotic agent, has a unique pharmacological action (partial agonist) on the dopamine neurotransmission system. Aripiprazole has high affinity for dopamine D2 and D3 receptors (DRD2 and DRD3). We investigated whether the efficacy of aripiprazole can be predicted by a functional DRD3 gene polymorphism Ser9Gly (rs6280) as modified by clinical factors in Han Chinese hospitalized patients with acutely exacerbated schizophrenia. After hospitalization, the patients ( $n=128$ ) were given aripiprazole for up to four weeks. Patients were genotyped for DRD3 Ser9Gly polymorphism by Restriction Fragment Length Polymorphism (RFLP) method. Clinical factors such as gender, age, duration of illness, education level, diagnostic subtype and medication dosage were recorded. Psychopathology was measured biweekly with the Positive and Negative Syndrome Scale (PANSS). The effects of genetic and clinical factors on PANSS performance after aripiprazole treatment were analyzed by a mixed model regression approach (SAS Proc MIXED). We found that, although the Ser carriers have numerically larger score reductions when compared with non-carriers in almost all PANSS dimensions, the difference of their effects are statically not significant. However, the clinical factors, including dosage of aripiprazole, age, duration of illness, and diagnostic subtype could influence PANSS performance after aripiprazole treatment. This study suggests that DRD3 Ser9Gly polymorphism may not contribute significantly to inter-individual differences in therapeutic efficacy of aripiprazole, but some clinical factors may predict treatment efficacy.

**Keywords:** DRD3 Ser9Gly polymorphism, dopamine D3 receptor, aripiprazole



### Lack of Association between Glutathione S-transferase -M1, -T1, and -P1 Polymorphisms and Olanzapine-induced Weight Gain in Korean Schizophrenic Patients

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**Objective:** Oxidative stress may be an important pathogenic mechanism in the obesity and metabolic syndrome. The aims of this study was to assess the possible association between the oxidative stress related Glutathione S-Transferase genes (GST-M1, GST-T1, and GST-P1) variants and the olanzapine-induced weight gain in the Korean schizophrenic patients.

**Methods:** We categorized the seventy-eight subjects into two groups the more than 7% weight gain from baseline ( $\geq 7\%$  weight increase) and the less weight gain ( $< 7\%$  weight increase) groups according to weight change between before and after long-term olanzapine treatment. All participants were genotyped for the GST-M1, GST-T1 and GST-P1 genes. Differences in allele frequencies between cohorts with different body weight changes were evaluated by a chi-square analysis and Fisher's exact test.

**Results:** There was no difference in the null genotype distribution of GST-M1 and -T1 between weight gainers (weight gain  $\geq 7\%$ ) compared to non-weight gainers (weight gain  $< 7\%$ ) ( $p > 0.05$ ). No significant difference in GST-P1 genotype and allele frequencies were observed between the groups ( $p > 0.05$ ).

**Conclusion:** These findings do not support a relationship between the genetic variants of three GST genes (GST-M1, -T1 and -P1) and weight gain in Korean schizophrenic patients receiving olanzapine treatment.

**Keywords:** weight gain, olanzapine, polymorphism, glutathione-S-transferase

### Lack of Association between Val158Met Polymorphism of Catechol-O-Methyltransferase Gene and Cognitive Functions in Schizophrenia Patients and Controls

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**Objectives:** Catechol-O-methyltransferase (COMT) gene has been identified as a positional and functional candidate gene of schizophrenia. Although specific mechanism of increasing schizophrenia susceptibility by this gene has not been well described yet, recent studies suggest that the valine allele of COMT Val158Met polymorphism may contribute to cognitive decline in schizophrenia. The present study investigated the association between this polymorphism of COMT gene and cognitive markers related to schizophrenia in both schizophrenia patients and normal controls.

**Methods:** The subjects were 78 patients with schizophrenia diagnosed by DSM-IV and 97 normal controls. Comprehensive neurocognitive tests for which performance deficits have been reported in schizophrenia were administered. Genotyping for COMT Val158Met polymorphism was done with SNaPShot method. Association analyses between genotype and cognitive functions were performed using ANCOVA and MANCOVA.

**Results:** In the comparison of allele frequencies between patient and control groups, no significant association between the polymorphism and schizophrenia was observed. Significant differences of cognitive performance among genotype groups were not identified in control group. This trend was also observed in the patient group. In the combined analysis of both patient and control groups, there was no significant genotype or genotype-by group effect on any cognitive function measure.

**Conclusion:** These findings do not support a major role of COMT gene in the regulation of the cognitive processes of schizophrenia.

### ADRA1A Gene is Associated with BMI in Chronic Schizophrenic Patients Exposed to Antipsychotics

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Obesity is an outcome of low energy expenditure and high energy intake, and a major side effect of antipsychotic medication in schizophrenic subjects. Noradrenaline and adrenaline are neurotransmitters in the sympathetic nervous system that interacts with various adrenergic receptor (ADR) subtypes, and these actions regulate the basal metabolic rate, thermogenesis, and efficiency of energy utilization. Here, we examined a possible role of the gene coding for ADRA1A receptor in weight gain in schizophrenic subjects exposed to antipsychotic medications. Four hundred and one schizophrenic inpatients treated with antipsychotics for more than two years were recruited and a final 394 DNA samples were genotyped. Their BMIs were recorded for 12 months (13 visits, i.e., baseline and once per month) and parameterized to be correlated in regression. Among 60 SNPs genotyped, 44 SNPs which had minor allele frequency  $\geq 0.03$  and followed Hardy-Weinberg Equilibrium were analyzed in statistics. Linear regression model with age, gender, diabetes and type of antipsychotic medication as covariates, with or without gender interaction, demonstrated evidences of associations between the ADRA1A gene and BMI, either by genotype or allele distribution. Most of the SNPs associated with BMI are located in promoter and intron region, and being female appeared to enhance the effect of the gene. Our study suggests that the ADRA1A gene is involved in the weight gain among schizophrenic patients treated with antipsychotics. Further molecular dissection of the ADRA1A gene, especially on the promoter and intron region, warrants better understanding on the weight gain mechanisms in schizophrenia (248 words).

### Association Study of Antipsychotics-induced OC Symptoms and Polymorphism of COMT, Serotonin Transporter and BDNF Gene

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Since the introduction of atypical antipsychotics (AAP) to treatment of schizophrenia, emergence of obsessive-compulsive (OC) symptoms has been numerously documented. The authors have reported 12.4% of patients developed OC symptoms among 209 schizophrenic patients treated with atypical antipsychotics. However, there has been no systematic investigation on the pathogenesis of antipsychotics-induced OC symptoms. According to the results of genetic association studies and other biological studies, genes involved in dopaminergic and serotonergic systems and neurodevelopment could be promising candidate genes of AAP-induced OC symptoms. This study aims to investigate whether Val-158-Met polymorphism of *Catechol-O-methyltransferase* (COMT), polymorphism of 23 tandemly repeated sequence region in serotonin transporter gene (5-HTT) promoter region (5-HTTLPR; Short, Long(A), Long(G)), which includes rs25531 (A>G), and Val-66-Met polymorphism of *brain-derived neurotrophic factor* (BDNF) are associated with AAP-induced OC symptoms. Among schizophrenic patients who are treated with atypical antipsychotics, 40 patients with treatment-emergent OC symptoms (OC group) and 54 patients without development of OC symptoms during treatment for more than 2 years (non-OC group) were recruited. Genotyping of three genes was done with SNaPShot assay, Sequencing assay and PCR-RFLP. None of the polymorphisms investigated showed significant differences in allele or genotype frequencies between the OC and non-OC groups. Considering insufficient power of the current analysis to identify genetic associations with minor effects, further studies with larger sample size and more SNPs for each gene to cover all of the coding sequences are needed to elucidate the involvement of these genes in the development of AAP-induced OC symptoms. **Keywords:** Schizophrenia, atypical antipsychotics, OCD, COMT, Serotonin transporter, BDNF

## Association of COMT Gene with Prolactin Elevation Induced by Olanzapine

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**[Introduction]** Hyperprolactinemia as an adverse effect induced by antipsychotics brings on sexual dysfunctions and treatment non-adherence. Establishing genetic markers associated with prolactin elevation during treatment would be useful on predicting clinical response of antipsychotics. We studied association between prolactin levels in olanzapine treatment and COMT gene, with only male subjects in order to eliminate the confounding effect of sex differences on prolactin levels.

**[Methods]** The subjects were 32 male patients with schizophrenia and taking antipsychotic monotherapy of olanzapine. The mean  $\pm$  SD of age and daily olanzapine dosage were  $39.7 \pm 14.0$  years and  $20.2 \pm 9.0$  mg. The dosage of olanzapine was maintained for at least four weeks and blood sampling for prolactin concentration was performed in early morning. We consulted HapMap database and selected 14 'tagging SNPs' that covered the COMT gene region. The study was approved by the Ethics Committee on Genetics of the Niigata University School of Medicine, and written informed consent was obtained from all subjects.

**[Results]** The mean  $\pm$  SD of prolactin concentration was  $25.7 \pm 14.8$  ng/ml. The prolactin concentration was not correlated with daily olanzapine dosage, age and BMI. The prolactin concentration was significantly associated with rs5993882 ( $P < 0.001$ ), rs4633 ( $P = 0.030$ ), rs4680 ( $P = 0.020$ ) and rs165774 ( $P = 0.038$ ) in COMT gene.

**[Conclusions]** The present study suggests that COMT gene have some impacts on regulation of dopamine functions in olanzapine treatment.

## Polymorphism of CYP2D6 Gene Related to Therapeutic Outcome of Schizophrenia Patients

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Objective:

Schizophrenia is one of the main problem in psychiatric disorders in Indonesia. Long term of treatment and disadvantage could be caused by respond of drugs and the psychopharmacogenetic background. CYP2D6 enzyme metabolism involves in many antipsychotic drugs. CYP2D6 enzyme encoded by CYP2D6 gene and polymorphism of cyp2d6 gene its was reported in many ethnics population.

Method

The current studies was undertaken by using PCR-RFLP technique to determine whether a relationship exists between CYP2D6 alleles \*3, \*4, \*5, and whether these alleles are related to therapeutic outcomes in schizophrenia patients treated with antipsychotics metabolized at least in part by CYP2D6.

We also investigated the influence of CYP2D6 genotype on psychopathological symptoms in inpatients with schizophrenia, receiving long-term maintenance antipsychotic treatment by using BPRS score in schizophrenic meet the DSM IV criteria for poor metabolizers (PMs) and extensive metabolizers (EMs).

Result

The result of determining Allele \*3 and Allele \*4 showed that there was no polymorphism (mutant allele) found. BPRS score changing are not correlated in Cyp2d6 gene.

Conclusion

- There is no polymorphism for cyp2d6 alleles \*3 and \*4 in our case
- We can not conclude whether response of treatment influenced by polymorphism cyp2d6 gene.
- Its seems that response of treatment is not related to cyp2d6 polymorphism
- BPRS score are not related to cyp2d6 alleles \*3 and \*4.

## Effects of the CYP2D6\*10 Allele on the Steady-state Plasma Concentrations of Aripiprazole and Its Active Metabolite, Dehydroaripiprazole in Japanese Patients with Schizophrenia

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The CYP2D6\*10 (\*10) allele that causes decreased CYP2D6 activity is present in Asians with a high frequency of about 50%. We studied the effects of the \*10 allele on the steady-state plasma concentrations (C<sub>ss</sub>) of aripiprazole (ARI) and its active metabolite, dehydroaripiprazole (DARI). The subjects were 39 Japanese schizophrenic patients who had only the wild-type or \*10 alleles. All patients had been receiving the fixed doses (24 mg, n=24; 12 mg, n=11) of ARI for at least 2 weeks. Plasma concentrations of ARI and DARI were measured by LC-MS/MS. This study was approved by the Ethics Committee of Faculty of Medicine, University of the Ryukyus, and all patients gave informed consent to participate in this study. 15 patients were homozygous for the wild-type allele, 23 were heterozygous and 1 was homozygous for the \*10 allele. The mean  $\pm$  SD values of ARI concentration/dose (C/D) ratio in the patients with 0, 1, 2 \*10 allele were  $9.7 \pm 3.2$ ,  $13.4 \pm 4.8$ ,  $30.0$  ng/mL/mg, respectively, and those values for DARI were  $4.8 \pm 1.6$ ,  $6.0 \pm 1.8$ ,  $8.0$  ng/mL/mg, respectively. Those values for the active moiety (ARI plus DARI) were  $14.5 \pm 4.7$ ,  $19.4 \pm 6.4$ ,  $38.0$  ng/mL/mg, respectively. The mean C/D ratios of ARI and the active moiety were significantly ( $p < 0.05$ ) higher in the patients with 1 \*10 allele than in those with 0 \*10 allele. The patient with 2 \*10 allele had the highest values of the C/D ratios of ARI and the active moiety. This study suggests that the \*10 allele plays an important role in controlling the C<sub>ss</sub> of both ARI and the active moiety.

## Cerebral White Matter Changes on Combined Structural MRI and Diffusion Tensor Imaging in First Episode Schizophrenia

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Previous studies have revealed volumetric abnormalities of white matter in patients with schizophrenia but the corresponding white matter dysconnectivities are less studied in tandem. The aim of this study is to examine white matter integrity in the region of white matter volume deficit in patients with first-episode schizophrenia (FES). A cross-sectional, case-control design was adopted and we used empirically-defined region of known white matter volume deficit to interrogate diffusion tensors. The participants included 103 subjects comprising of 39 patients with FES and 64 age-, sex-, and handedness-matched healthy controls. The main outcomes were gray and white-matter partial volumes, fractional anisotropy, trace and geometric diffusion indices. Structural voxel-wise analyses revealed that patients with first episode schizophrenia had lower gray matter volumes in bilateral hippocampi ( $P < .01$ ) and lower white matter volume in the right temporal-occipital region ( $P < .005$ ) corresponding to the inferior longitudinal fasciculus. Further analyses of diffusion anisotropy in the right temporal-occipital region revealed lower planar anisotropy, cp, and higher linear anisotropy, cl ( $P = 0.012$ ) in patients with first episode schizophrenia. However, no differences were found for fractional anisotropy and trace in the implicated white matter region between the two groups. Patients performed poorer in digit span, spatial working memory and executive functioning, compared to healthy controls. To the best of our knowledge, this is the first study to employ geometric diffusion measures in interrogating the nature of diffusion tensor in schizophrenia. We confirmed previous findings of white matter volume deficit in the region of inferior longitudinal fasciculus. The presence of changes in geometric diffusion indices in the implicated white matter region suggests that pathophysiological processes which underlie cerebral white matter volume reduction may not be reflected by changes in fractional anisotropy. Further research is needed to better understand the nature of these white matter changes and its progression in schizophrenia over time.

## Differential Brain Volume Correlates of Trait Anhedonia in Patients with Schizophrenia: A Voxel-Based Morphometric Study

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The aim of this study was to characterize the association between trait anhedonia and regional gray matter volume in patients with schizophrenia. Forty-six patients with schizophrenia and 56 age-matched and sex-matched healthy controls underwent magnetic resonance imaging (MRI) to acquire high-resolution T1-weighted images. Anhedonia was measured using the Chapman Revised Physical Anhedonia Scale. Voxel-based morphometry was performed to investigate brain volume correlates of anhedonia. The gray matter regions of the patient group that were significantly more affected by anhedonia than those of the control group were the temporal pole, the right premotor cortex, the right superior parietal lobule, the left superior frontal gyrus, the right superior temporal gyrus, the right uncus, the left precentral gyrus, and the right middle frontal gyrus. The right superior temporal gyrus, the right insula, the right hippocampus, the precuneus, the right lingual gyrus, the left ventromedial prefrontal cortex, and the right posterior cingulate cortex were the gray matter regions of the patient group which were significantly less affected by anhedonia than those of the control group. These findings suggest that anhedonia in patients with schizophrenia may be reflected by volume reduction in the regions related with self-referential mental activities. However, anhedonia in the control group may be mediated by depressive symptoms. Taken together, different brain volume correlates of anhedonia between both groups suggest that anhedonia has a distinct neural mechanism in both groups.

## Asymmetric Alternation of Prefrontal Hemodynamic Response During ECT in Schizophrenia

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**OBJECTIVE:** Although electroconvulsive therapy (ECT) is a well-established treatment, the mechanism of action remains unclear. To investigate a hemodynamic marker for clinical efficacy, we measured the change of regional cerebral blood flow (rCBF) at the prefrontal cortex (PFC) during ECT by using near infrared spectroscopy (NIRS). **METHOD:** The participants were ten patients with schizophrenia and ten patients with mood disorders. Normalized tissue hemoglobin index (nTHI) was used as a parameter of relative change of rCBF at bilateral PFC, and was measured every 0.5 seconds for 7 minutes during ECT by utilizing a two channel NIRS. We assessed the efficacy of ECT by several clinical rating scales such as GAF, PANSS and HAM-D before and after the full session of ECT. **RESULTS:** 1. Levels of bilateral nTHI showed a transient decrease during electrical stimulation and immediately increased at both ictal and post ictal phases by approximately 20%. 2. Patients with schizophrenia, but not mood disorders, showed asymmetric alternation of nTHI (left>right) levels during both ictal and post ictal phases. 3. Although the change of nTHI did not correlate with scores of all three rating scales, the asymmetric index (maximal change of nTHI between left and right) of schizophrenia was negatively correlated with the period of illness. **CONCLUSION:** Our data demonstrated that ECT caused hemodynamic changes in bilateral PFC, and that asymmetric alternation was found only in schizophrenia. The asymmetrical hemodynamic response by ECT might be a novel marker for schizophrenia in early stages.

## Reduced Functional Connectivity of Anterior Cingulate Cortex in Schizophrenia

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**Background:** We previously reported reduced microstructural integrity of the white matter underlying anterior cingulate cortex (ACC) as measured by fractional anisotropy (FA) in schizophrenia, specifically in the right hemisphere. Moreover, lower FA in the white matter underlying the anatomical components of the right-hemisphere dominant network for spatial attention and volitional saccades – ACC, frontal frontal eye field, and posterior parietal cortex – predicted longer saccadic latency. Here, we evaluate whether patients also show compromised functional connectivity (FC) of right ACC. **Methods:** Twenty-seven patients and 21 matched healthy controls underwent fMRI scans while performing intermixed pro- and antisaccade trials. Right and left ACC seeds were defined as spheres around peak activation in the correct trials vs. fixation contrast in all participants. We created ACC FC masks based on positive correlations of low frequency fMRI fluctuations using the averaged data of all participants. To identify regionally specific group differences in FC, we compared groups at each voxel in the brain. **Results:** In both hemispheres ACC FC masks included canonical regions for volitional saccades: bilateral frontal eye fields, posterior parietal cortex and dorsolateral prefrontal cortex. Patients showed reduced FC specifically of right ACC, but FC did not correlate with saccadic latency in either group. For right ACC, patients showed regionally specific significant reductions in the FC of left pulvinar, right pre-SMA and right anterior insula. **Conclusions:** Along with our prior study, these findings suggest reduced structural and functional connectivity of the right-hemisphere dominant network for spatial attention and volitional saccades in schizophrenia. The measure of functional connectivity may provide a good neural marker for psychopharmacological research in the future.

## A Simulation Study Using Raclopride PET in New Antipsychotic Development

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To find appropriate doses of YKP1358, a candidate antipsychotic drug, for further clinical trials, we measured the dopamine receptor occupancy induced by YKP1358 and simulated the dopamine receptor occupancy according to the doses of concern. We intended to provide an example on practical applications of a simulation study using raclopride positron emission tomography (PET) in the development of a new antipsychotic drug.

Eight patients completed the present study. According to a repeated oral dose, dose escalation, open-label study design, YKP1358 was administered orally twice a day for 15 to 24 days. The YKP1358 dosage was escalated to between 50mg bid and 400mg bid. After the escalation, the dosage was maintained for 6±1 days. PET scans for the measurement of dopamine receptor occupancy were obtained 12 h after the last administration at each step in the dose escalation. Blood samples for the measurement of YKP1358 were obtained just before the PET scan and at 0 (pre-dose), 0.5, 1, 2, 3, 4, 8, 12 h after the last administration at the last step in the dose escalation.

The relationship between the plasma concentration and the dopamine receptor occupancy was examined using non-linear mixed effects modeling. In the simulation based on the modeling, we predicted the concentration of YKP1358 and receptor occupancy using NONMEM®.

In the simulation, the dopamine receptor occupancy by YKP1358 was projected to be above 60% at the dosage of 200mg bid; 400mg bid of YKP1358 induced over 80% receptor occupancy. Compared with conventional approaches, the simulation method can provide clinical investigators with more information regarding pharmacokinetic and pharmacodynamic characteristics, and it also enables researchers to evaluate many different clinical designs and strategies before conducting the actual trial. It is anticipated that the simulation approach using raclopride PET will raise productivity and efficiency in the development of new antipsychotic drugs.

## Antipsychotic Medication Affects the GABA Concentration in Schizophrenic Patients: A Proton Magnetic Resonance Spectroscopy Study

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Gamma-amino butyric acid (GABA) is thought to play a role in the pathophysiology of schizophrenia. High magnetic field proton magnetic resonance spectroscopy (1H-MRS) has permitted a reliable measurement of GABA in specific regions of the brain.

This study measured GABA concentration in the anterior cingulate cortex (ACC) and in the left basal ganglia (ltBG) in 38 patients with chronic schizophrenia and 29 healthy control subjects.

The GABA concentration did not significantly differ between the schizophrenic patients and the healthy controls either in the ACC (1.36 ± 0.45 mmol/l, schizophrenics; 1.52 ± 0.54 mmol/l, controls) or in the ltBG (1.13 ± 0.26 mmol/l, schizophrenics; 1.18 ± 0.20 mmol/l, controls). Among the right handed schizophrenic patients, the GABA concentration in the ltBG was significantly higher in patients taking typical antipsychotics (1.25 ± 0.24 mmol/l) than in those taking atypical antipsychotics (1.03 ± 0.24 mmol/l,  $p=0.010$ ). The GABA concentration was negatively correlated with the dose of the antipsychotics in the ACC ( $r_s=-0.347$ ,  $p=0.035$ ).

Our results suggest no difference in the GABA concentration of schizophrenic patients and healthy controls either in the ACC or in the ltBG. Antipsychotic medication may cause changes in the GABA concentration and the pattern of changes differed between atypical and typical antipsychotics. Medication effects possibly concealed the essential difference in GABA concentration between schizophrenic patients and the healthy controls.

## Neurocognitive Function and Diffusion Tensor Imaging Study in First-episode Schizophrenic Patients

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**Objectives:** To evaluate cognitive deficits as well as to investigate whether abnormalities were present in the white matter integrity in first-episode schizophrenic patients with early adulthood onset; to explore relationship between neuropsychological performance and white matter integrity in first-episode schizophrenic patients of early adulthood onset. **Methods:** Forty-two first-episode schizophrenic patients with early adulthood onset (16-28 yrs old) and forty six healthy individuals, matched with sex, age and education, underwent neuropsychological testing and diffusion tensor imaging. Patients' neurocognitive performance was evaluated via an neuropsychological test battery, which assessed 4 cognitive domains including learning and memory, speed of processing, motor skills and executive function. **Results:** Patients showed a generalized neurocognitive deficit of 0.6-2.5 SDs compared with controls, with verbal learning, working memory, and visual learning being the most affected areas. But there are no significant difference between drug-naïve patients and those treated by atypical drugs in all neurocognitive domains. Reduced fractional anisotropy was seen in right posterior limb of the internal capsule ( $t=2.510$ ,  $p=0.014$ ) and left cerebral peduncle ( $t=2.318$ ,  $p=0.023$ ) in the first-episode schizophrenic patients with early adulthood onset. Compared with drug-naïve patients, those treated by atypical drugs were observed higher fractional anisotropy in genu of corpus callosum ( $t=-2.199$ ,  $p<0.05$ ). The relationship between cognitive performance and DTI in first-episode schizophrenic patients with early adulthood onset was different from that in healthy individuals. **Conclusion:** Cognitive deficits across almost all domains exist in the first-episode schizophrenic patients with early adulthood onset compared to healthy individuals, especially in auditory working memory, verbal learning and visual learning; Our finding suggests that structural disconnections in right posterior limb of the internal capsule and left cerebral peduncle in the first-episode schizophrenic patients with early adulthood onset. Atypical drugs may have neuroprotective effects. The location of cognitive function in first-episode schizophrenic patients of early onset might be different from that in healthy individuals. **Keywords:** schizophrenia; first episode; early adulthood onset; neurocognition; diffusion tensor imaging

## Differential Neural Processing of Social Conformity to Group Pressure in Patients with Schizophrenia in Day Hospital Programs

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**Background:** Patients with schizophrenia are minimally responsive to social pressure for conformity due to paranoid tendency in active symptoms or lack of need for social interaction. Despite impairment in social conformity, group environment provided by day hospital programs help patients with schizophrenia make social adjustments. Recently reinforcement learning has been suggested as the underlying cognitive neural mechanism behind social conformity. This study investigated the difference in the neural mechanism of group conformity in patients with schizophrenia. **Methods:** Twelve patients with schizophrenia attending day hospital programs in two university hospitals, one general hospital, one community mental health center and one psychiatric clinic, and 15 healthy controls from the same group in work places or graduate schools participated in this study. Blood-Oxygen-Dependent (BOLD) signals were measured using a 3T MRI scanner while participants decided on the more-frequently-used meaning of a homograph after being shown photographs of their group members or strangers and each of their supposed opinions. **Results:** Patients with schizophrenia had significantly lower Working Alliance Inventory scores than healthy participants. Although both groups did not show significant differences in the conformity rates to group opinion in the homograph meaning decision task, healthy participants were significantly faster in disagreeing with their group than with strangers while patients with schizophrenia were significantly faster in agreeing with their group than with strangers. The tendency of conforming to one's group while opposing opinions of strangers were associated with activities in the anterior cingulate gyrus and the middle temporal gyrus in the healthy participants and activities in the putamen and the pulvinar in patients with schizophrenia. **Conclusions:** These findings suggest that patients with schizophrenia fail to recruit neural process of monitoring deviations from the expected and may rely on the process of reward association during group conformity.

## The Relationship between Motor Coordination in Neurological Soft Signs and Neurocognitive Performance and Brain White Matter Structure in First-episode Schizophrenic Patients

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**Background:** Neurological soft signs are found to be abnormal and considered as one of candidate endophenotypes in schizophrenia. They are also thought to be correlated with neurocognitive performance and structural abnormalities in schizophrenic patients. **Objective:** To investigate the correlation between motor coordination in neurological soft signs and neurocognitive function and brain white matter structure in early stage of schizophrenia. **Methods:** A total of 47 first-episode schizophrenic patients with onset in their early adulthood (16-28 years old) were recruited from February 2008 to February 2009, and were administered with diagnostic screening by SCID-I/P, neurological examination with excerpt of Cambridge neurological inventory (CNI), neurocognitive examination by a neurocognitive batteries, psychopathological evaluation by PANSS and diffusion tensor imaging (DTI). A total of 46 controls matched with age, gender and education level were recruited and administered with the same tools. **Results:** Data of 42 first-episode schizophrenia (age: 20.5 ± 3.37 years old, education: 12.6 ± 2.57 years, Male: Female 12:30) were included in analysis (4 excluded because they are mix-handed, 1 excluded for lack of effort in neurocognitive test). Compared to normal controls, there were both significant increase in the score of the whole group of soft signs and of motor coordination soft signs. Motor coordination signs were not significantly correlated with PANSS scores, but they were correlated with information processing ( $p<0.01$ ,  $r=-0.408$ ), verbal learning and memory ( $p<0.05$ ,  $r=-0.309$ ), visual learning and memory ( $p<0.01$ ,  $r=-0.426$ ), working memory and attention ( $p<0.05$ ,  $r=-0.312$ ), inhibition ( $p<0.05$ ,  $r=-0.367$ ) and right prefrontal white matter FA value ( $p<0.05$ ,  $r=0.354$ ) in patients with first-episode schizophrenia. In controls they were only correlated with information processing ( $p<0.05$ ,  $r=-0.305$ ) and left corticospinal tract FA value ( $p<0.05$ ,  $r=0.338$ ). **Conclusion:** Motor coordination in neurological soft signs is significant abnormal in first-episode schizophrenia, and is independent of clinical state. It is correlated with many neurocognitive function domains impaired in first-episode schizophrenic patients as well as with frontal white matter integrity. While in normal controls it is only correlated with information processing and corticospinal tract integrity. It is indicated that motor coordination is involved in brain function and structural impairments in first-episode schizophrenic patients. **Keywords:** schizophrenia; first-episode; neurocognition; neurological soft signs; motor coordination; diffusion tensor imaging

## Social Cognition and Neurocognition Deficits in Individuals at High Risk of Developing Psychosis

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**Background:** While deficits in social cognition and neurocognitive functions are frequently reported in psychotic disorders, it is unclear whether these deficits antedate the onset of psychosis. The aim of present study was to examine the performances on social cognition and neurocognition of subjects at ultra-high risk for schizophrenia who converted later.

**Method:** The investigators studied 36 subjects at ultra-high risk (UHR) for psychosis and 36 sex- and age- matched healthy control (HC) subjects. Of the ultra-high risk group, 13 subjects later developed psychosis over the course of the investigation. Two types of theory of mind (ToM) tasks and a neuropsychological test battery were measured. Analyses compared the ultra-high risk patients who developed psychosis later (UHR-P), those who did not develop psychosis (UHR-NP), and the control subjects.

**Results:** At baseline, the UHR-P group had significantly lower performance than the HC group on the executive and visual memory, verbal memory tests. The UHR-P group had significantly lower verbal memory scores at baseline compared with the UHR-NP group. Furthermore, compared to the HC group, the UHR-P group performed significantly worse for two verbal tasks of ToM tasks, false belief task and strange story task.

**Conclusions:** These findings suggest that deficits in social cognition and verbal memory impairment were apparent prior to psychotic illness onset. These deficits may be an important risk marker for the development of psychosis.

## Relationships Among Age of Onset, Psychopathology, Cognition, Quality of Life and Prescription in Schizophrenia Inpatient

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Recently, schizophrenia is classified as 4 very early (VEOS<20 years old), early (EOS 20-40), late (LOS 40-60) and very late-onset schizophrenia (VLOS >60) subgroups. In this study, we investigated relationships among age of onset, psychopathology, cognition and quality of life in schizophrenia patient. Using subjective and objective measurements, 406 patients were investigated during inpatient treatment. More male, younger, longer duration of illness and hebephrenic subtype characterize VEOS. VEOS and EOS are often medicated by nonstandard pharmacotherapy (chlorpromazine equivalent  $\geq 1000$  or antipsychotic polypharmacy), using conventional neuroleptics with more antiparkinsonian and mood stabilizer drugs. Although BPRS total, thinking disturbance and tension scores are high in VEOS and low in VLOS, these differences disappeared by ANCOVA with covariate as duration of illness. While DIEPSS score is high in LOS, AIMS score is high in VLOS. HDSR score was significantly lower in LOS and VLOS. JSQLS motivation/energy score is highest in LOS. In regression analysis, age at onset was negatively correlated with duration of illness, BPRS total, thinking disturbance, tension and HDSR scores. Duration of illness was positively correlated with BPRS and DIEPSS scores. In conclusion, male, younger age, and being treated by conventional, multiple dose, polypharmacotherapy characterize VEOS. Their longer duration of illness leads to serious levels of psychopathology, resulting in non-standard treatment with serious level of EPS and low level of QOL.

## Relationship between Basic Symptoms & Self-esteem and Delusion in Patients with Schizophrenia

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Basic symptoms are subjectively experienced subtle change in thought, emotion, and perception, which may be a key pathology in schizophrenia. Poor self-esteem or self-appraisal in schizophrenia is known to be as a maintaining factor and a consequence of the illness. We aim to investigate the relationship between the basic symptoms and poor self-esteem, and delusion in people with schizophrenia. Twenty-five clinically stabilized people (M 14, F 11) with schizophrenia and 23 normal controls (M 11, F 12) were recruited. The basic symptoms were measured using the self-reported Frankfurt Complaint Questionnaire. Negative self-evaluation was indexed by a composite, which were calculated by the z-transformed scores of Rosenberg self-esteem scale, Sherer self-efficacy scale, Connor-Davidson resilience scale, self-perception scale. The severity of delusion measured by Positive and Negative Syndrome scale was correlated with negative self-evaluation ( $r=.56$ ,  $p=.002$ ), state anxiety ( $r=.40$ ,  $p=.047$ ), depression severity ( $r=.44$ ,  $p=.029$ ), and basic symptoms ( $r=.39$ ,  $p=.053$ ). The regression analysis revealed that the severity of delusion was related to negative self-evaluation. These findings suggest that self-appraisal may be a key component for treatment intervention of delusion.

## Relationship between Cognitive Function and Clinical Symptoms in People with Schizophrenia

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(Aims/Objective) The aim of the present study is to investigate the relationship between cognitive function and clinical variables in people with schizophrenia. (Methods) The subjects were 61 stabilized outpatients with schizophrenia (DSM-IV). Their mean age was 40.1 (SD=12.2) years. All subjects gave written informed consent to participate in the research. Cognitive function was evaluated using the Brief Assessment of Cognition in Schizophrenia (BACS). Clinical symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS), the Calgary Depression Scale for Schizophrenia, and the Drag-Induced Extrapyramidal Symptoms Scale (DIEPSS). (Results) Dose of neuroleptics was not significantly correlated with the BACS scores. The PANSS negative syndrome score was significantly correlated with Verbal Memory score ( $r=-.37$ ,  $p<.01$ ), Working Memory score ( $r=-.38$ ,  $p<.01$ ), Attention score ( $r=-.51$ ,  $p<.01$ ), Verbal Fluency score ( $r=-.39$ ,  $p<.01$ ), and Composite score ( $r=-.54$ ,  $p<.01$ ). In addition, the DIEPSS score was significantly correlated with Verbal Fluency score ( $r=-.45$ ,  $p<.01$ ), and Composite score ( $r=-.41$ ,  $p<.01$ ). (Conclusion) These results suggest that cognitive function of people with schizophrenia might be associated with negative symptom, and extrapyramidal symptom. Minimizing negative and extrapyramidal symptoms is important in the maintenance pharmacotherapy.

## Quality of Life and Cognitive Dysfunction in People with Schizophrenia

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**Objective:** The main purpose of the present study was to examine the relationship between quality of life (QOL) and cognitive dysfunction in people with schizophrenia. **Methods:** Subjects were 61 stabilized outpatients with schizophrenia. Quality of life and cognitive function were assessed using the Quality of Life Scale (QLS) and the Brief Assessment of Cognition in Schizophrenia (BACS), respectively. Clinical symptoms were evaluated with the Positive and Negative Syndrome Scale (PANSS), the Calgary Depression Scale for Schizophrenia (CDSS), and the Drug-Induced Extrapyrimal Symptoms Scale (DIEPSS). **Results:** No significant correlation was found between dose of antipsychotics and the QLS scores. The BACS composite score and the BACS verbal memory score were positively correlated with the QLS total score and the two subscales. The BACS attention score had positive correlation with the QLS total and all the subscales scores. Some clinical indices including the PANSS positive and negative syndrome scores and the CDSS score also had significant correlations with the QLS total score and some of the subscales. Stepwise regression analysis showed that the BACS attention score was an independent predictor of the QLS total score but it had less impact on the QLS than the PANSS negative syndrome score and the CDSS score. **Conclusion:** The results suggest that treatment effort should be mainly paid to negative and depressive symptoms in order to improve patients' QOL.

## Attention-Capturing Properties of Happy and Sad Faces in Schizophrenia

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**Objective:** Patients with schizophrenia show increased distractibility and deficits in social functioning. To better understand patients' attention in social situations, it would be helpful to estimate the attention-capturing properties of emotional faces, one of the most common social stimuli. The objective of the present study was to explore the attention-capturing properties of emotional (happy, neutral, and sad) faces in patients with schizophrenia and controls. **Method:** Nineteen schizophrenia patients and twenty-one healthy control subjects completed AX-CPT with Emotional Face as Background (AX-CPT EFB), which presented natural numbers with emotional faces as the background. Subjects were required to attend to the number stimuli. Sensitivity ( $A'$ ) and reaction time were measured. The attention-capturing properties of happy and sad faces were estimated by comparing  $A'$  and reaction time between blocks in patients and controls. **Results:** Patients performed worse than control subjects on the AX-CPT EFB. The decline of  $A'$  over time was more evident in patients. The attention-capturing property of sad faces was greater than that of happy, and the difference between the attention-capturing properties of happy and sad faces was greater in patients than in controls. The attention-capturing property of sad faces was more resistant to habituation than that of happy faces. **Conclusions:** These findings can be interpreted as showing patients' 'negativity bias' in the level of attention attracted by emotional faces. These findings cautiously suggest that patients are more attracted to sad faces than happy faces, even though patients have more deficits in recognizing sad faces.

## Aberrant Visual Form Perception without Thought Disturbance in Clinical High-Risk for Psychosis: Rorschach Findings

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Psychotic disorder is associated with deficits in visual perception and cognitive processing, but before the onset of psychosis these deficits are unclear. This study investigated the visual perception and thought disturbance characteristics of clinical high-risk for psychosis by using the Rorschach Comprehensive System. 11 individuals at clinical high-risk for psychosis, 12 individuals with Schizophrenia patients and 14 normal controls participated in this study. Rorschach test results to them are as follows. Perceptual aberrant among those 3 groups of clinical high-risk group, schizophrenia patients and normal group showed significant difference. All those 3 indexes (X-%, WSum6, SCZI) of Schizophrenia group were higher than normal group, while it appeared only X-% was increased in high risk group comparing to normal group and there were no significant difference in WSum6 and SCZI. These findings suggest that aberrant visual form perception in clinical high-risk for psychosis exist as a risk factor before the onset of psychosis. In contrast thought disturbance is expressed after the onset of psychosis. Finally we discussed clinical implication in relation to characteristics of high-risk population and suggestions for the further investigation.

## Contempt Bias and Impairment in Facial Emotion Recognition in People with Clinical High-Risk for Psychosis and with Schizophrenia

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The purpose of this study is to examine whether people with clinical high-risk for psychosis show bias to the threatening facial stimuli as well as impairments in recognition of the facial emotional stimuli, which is well-established findings in people with schizophrenia. Twenty-five people (M 14, F 11) with clinical high-risk for psychosis (CHR), 46 people (M 24, F 22) with schizophrenia (SPR) and 52 normal controls (M 28, F 24) were asked to recognize the emotional valences of facial emotional photographs. The stimuli were selected from the standard emotional photographs of Japanese and Caucasian Facial Expressions of Emotion (JACFEE), which depicting the basic emotions of happiness, disgust, sadness, anger, surprise, fear, and contempt. The unbiased hit rates of and the error biases to each emotion were calculated using the confusion matrix. People with CHR and SPR showed not only generalized deficits of emotion recognition, encompassing almost all emotional valences but also bias to contempt. In CHR, the negative symptoms were associated with the unbiased hit rates of fear and these associations were found in other various emotional valences in SPR. The contempt bias was correlated with the threatening bias scores of the Korean Version of the Ambiguous Intentions Hostility Questionnaire (K-AIHQ) in both CHR and SPR groups. These findings suggest that the social threatening bias and deficits of emotional recognition may be already present in the (putative) prodromal stages of schizophrenia.

**Key Words:** Clinical High-Risk for Psychosis, Schizophrenia, Emotion, Contempt, Bias, Deficit, Prodromal Stage

## Coping Strategies and its Contribution Factors in People with Clinical High-Risk for Psychosis and with Schizophrenia

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Based on stress-vulnerability model, coping with stressors could influence on the course of schizophrenia. It is well established that schizophrenia patients adopt ineffective coping strategies, but the relationship between the coping and onset of psychotic disorder is not fully understood yet. In this study, we investigated the coping style and its potential contribution factors - personality traits, self-esteem, attributional bias and neurocognitive impairments - in people with clinical high-risk (CHR) for psychosis and schizophrenia (SPR). Thirty-three people (M 16, F 17) with CHR for psychosis, 22 people (M 11, F 11) with SPR and 33 normal controls (M 18, F 15) participated in this study. To measure coping strategies, the Ways of Coping Questionnaire (WCQ-S) was used. Personality traits, self-esteem and attributional bias were assessed by Eysenck personality questionnaire, Rosenberg self-esteem scale and Ambiguous Intentions Hostility Questionnaire (AIHQ) respectively. Five domains of neurocognition were assessed - verbal memory, visual memory, verbal fluency, sustained attention, and executive function. CHR and SPR group were more likely to adopt a tension-reduction strategy and CHR group was less likely to adopt a problem focused coping than normal controls. In CHR group, lower scores of self-esteem predicted reduced adoption of problem-focused coping and higher scores for blaming index of AIHQ predicted increased adoption of tension reduction. Lower levels of extroversion predicted increased adoption of wishful thinking and reduced adoption of social support seeking. In SPR group, higher scores of self-esteem and sustained attention predicted increased adoption of problem-focused coping, and lower scores of verbal fluency predicted increased adoption of wishful thinking. Our data suggest that CHR and SPR groups adopt more ineffectual coping strategies. In prodromal phase (CHR group), way of coping seems to be influenced by personality, self-esteem or attributional bias, and after onset of psychosis (SPR group), neurocognitive impairment seems to become more influential on coping strategies.

Key Words: Coping, Clinical High-Risk for Psychosis, Schizophrenia, Neurocognition, Personality, self-esteem, Attributional Bias

## Neurocognitive Effects of Aripiprazole in Adolescents and Young Adults with Schizophrenia-Spectrum Disorders

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Objective: Cognitive deficits are among the core features of schizophrenia. Improvement in cognition may lead to improvement in functional outcome. Aripiprazole is a novel antipsychotic with a unique mechanism of action that differs from previous antipsychotics. The purpose of this study was to evaluate the neurocognitive effects of aripiprazole in adolescents and young adults with schizophrenia-spectrum disorders.

Methods: This was a 24-week prospective study. A total of 42 patients who had clinical diagnosis of DSM-IV of schizophrenia-spectrum disorders were treated with aripiprazole. Neurocognitive function was evaluated by the change from baseline in Continuous Performance Test (CPT) and Wisconsin Card Sorting Test (WCST). Clinical Efficacy was evaluated by the change from baseline in Clinical Global Impression Scale (CGI), Brief Psychiatric Rating Scale (BPRS) and the World Health Organization Quality of Life questionnaire (WHOQOL). Patients with baseline assessment and at least one follow up assessment were included for efficacy analyses. Missing data were accounted for using the last observation carried forward method.

Results: Primary diagnoses included schizophrenia (n = 30), schizoaffective disorder (n = 2) and psychotic disorder not otherwise specified (n = 10). There were 25 males and 17 females. Mean (SD) age was 18.1 (3.7) years. The mean dosage of aripiprazole was 8.3 (4.6) mg/day. The CGI severity, BPRS total score and WHOQOL improved significantly from baseline to the 24<sup>th</sup> week. The subjects had significant improvements in detectability (p=0.015) of CPT, and total errors (p=0.001), perseverative errors (p=0.004) and perseverative responses (p=0.002) of WCST, but not non-perseverative errors (p=0.072).

Conclusion: Adolescents and young adults with schizophrenia-spectrum disorders had significant improvements in some areas of attention and executive function after treatment with aripiprazole. A double-blind controlled design is suggested to replicate these findings.

## Patients with Schizophrenia Might Have Some Difficulties in Perceiving Emotional Nuance of Music

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Emotion perception deficit has long been suggested to be one of the core features of schizophrenia. There have been several studies examining responses to facial expressions but studies investigating auditory emotion perception have been rare. The aim of the present study was to investigate the difference in auditory emotion perception in music between normal subjects and patients with schizophrenia.

24 pieces of music were presented to 14 patients with chronic schizophrenia and 18 healthy controls. The set of music consisted of 12 pieces of sad music and 12 pieces of cheerful music. When the subjects were asked to answer whether each piece of music was sad or cheerful, we found that the percentage of correct answer was lower in patients with schizophrenia (73.50%) compared to healthy controls (93.75%).

This preliminary study results suggest that patients with schizophrenia might have some difficulties in recognizing emotional nuance of music.

## Neurocognitive Effects of Quetiapine in Patients with Treatment-resistant or -Intolerant Schizophrenia

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Background: Cognitive dysfunction is regarded as a core symptom of schizophrenia. Quetiapine (QTP) is thought to have a potential to enhance cognitive functioning because of its fast dissociation feature for D2 receptor and its favorable effects for 5HT receptors. Objective: To determine how QTP is useful for improving the cognitive dysfunction of the patients with treatment resistant schizophrenia or the patients who were intolerant to antipsychotics. Methods: Thirteen subjects with schizophrenia who did not respond or were not tolerate current mono-therapy of antipsychotic were switched to QTP, and assessed at baseline, 3, 6 months. Outcome measures included, the brief assessment of cognition in schizophrenia (BACS), positive and negative syndrome scale (PANSS), drug Induced extrapyramidal symptoms scale (DIEPSS), HbA1c, prolactin and body weight. Results: Quetiapine was well tolerated, reduced extrapyramidal side effects, and normalized the prolactin level without any worsening of clinical symptoms or abnormal elevation of HbA1c and weight. It also improved subjects' performance on verbal fluency and executive function as well as composite score of BACS. Conclusion: QTP may have specific cognitive enhancing properties in subjects with schizophrenia who did not respond or were not tolerate current mono-therapy of various antipsychotics.

## Effects of Switching to Long-Acting Injectable Risperidone on Cognitive Function in Schizophrenia

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**Objective:** To investigate changes in cognitive function and clinical features following a switch from oral atypical antipsychotics (AAPs) to long-acting injectable risperidone (LAIR) in patients with schizophrenia.

**Methods:** Thirty-six patients with schizophrenia treated with oral AAPs participated in this open-label, 26-week study. Cognitive functions were measured at baseline and at 12 and 26 weeks. The secondary outcome measures included the Positive and Negative Syndrome Scale (PANSS), Social and Occupational Functioning Assessment Scale (SOFAS), Scale for Unawareness of Mental Disorder (SUMD) and measurements for extrapyramidal symptoms.

**Results:** Significant improvements in cognitive function were observed in the backward Digit Span Test, Verbal Learning Test, Wisconsin Card Sorting Test, correct responses on the Continuous Performance Test, and Trail Making Test Part B following a switch to LAIR. Scores on the PANSS, SOFAS, SUMD, and the Simpson-Angus Rating Scale also improved significantly. Most improvements in neurocognitive function were not correlated with clinical measures. Weight gain and hyperprolactinemia were the most common adverse events.

**Conclusions:** Switching from oral AAPs to LAIR improved cognitive function including vigilance, verbal learning and memory, executive function, sustained attention, and visuomotor speed in patients with schizophrenia. It was also effective for improving psychotic symptoms, social functioning, and insight.

## The Influence of Haloperidol and Risperidone to the Cognitive Function in Schizophrenic Patient

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Antipsychotic drugs therapy can effect cognitive function in schizophrenic patient. The first line of antipsychotic leads to minimal effect in repairment of cognitive function, but instead can damage it. Whereas the new line of antipsychotic can improve all aspect of cognitive, although some controversy still occur.

The aim of the research is to find out the influence of haloperidol and risperidone to the cognitive function in schizophrenic patient which treated in Dadi Hospital, Makassar, South Sulawesi, Indonesia. The research is a observational study with prospective cohort study design involving 85 samples followed for 6 weeks from the 15 of September 2007 to the 16 of April 2007 in Dadi Hospital, Makassar. The assessment of cognitive function using the Mini mental state examination (MMSE). Data processing using the SPSS program 11,5 version and Kruskal-Wallis statistic test in order to find out the difference of cognitive function and MMSE subscore point between schizophrenic patients who is using haloperidol or risperidone. The result show that the cognitive function in patients using haloperidol have no response, while the patients using risperidone show some improvement. In MMSE subscore, the main difference is only in attention.

**Keyword :** schizophrenia, haloperidol, risperidone, MMSE.

## Second Generation Antipsychotics Induce Cognitive Impairment and Deficit Symptoms in Healthy Volunteers

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**Objective:** This study was undertaken to investigate the effects of single administration of conventional and second generation antipsychotics on cognitive function and deficit symptoms in healthy volunteers. **Method:** Seventy-eight subjects (mean age, 28.28±2.57) were randomized to 5 group (haloperidol (HPT) 3 mg, risperidone (RIS) 2 mg, amisulpride (AMS) 400 mg, aripiprazole (ARP) 10 mg, and placebo (PL)). For the evaluation of cognitive function, computerized neuropsychological test (CNT), digit span test, auditory continuous performance test, stroop test, verbal learning test, Trail marking test, Wisconsin card sorting test, and word fluency test, was performed. For deficit symptoms, Neuroleptic induced deficit syndrome scale (NIDSS), Subjective deficit syndrome scale (SDSS) were used. In addition, extrapyramidal symptom related scales (SAS, BAS) and visual analogue scale (VAS) for mental and physical sedation and calming effect were used. All assessments were conducted at baseline, 1 week before the ingestion of the drugs and 4 hr after the administration by blind rater. All observed or volunteered adverse events were recorded at any time and 4 hr after administration. **Results:** In CNT, all groups including PL group showed improvement of memory function at 4 hr after the administration which may be related to practice effects, compared to baseline. However, significant impairment of attention was only observed in 4 antipsychotic groups. In deficit symptoms, all antipsychotics except AMS, showed increased avolition in NIDSS and RIS and ARP increased SDSS score meaning greater deficit symptoms. In SANS, only RIS showed increased affective blunting. In VAS, all 5 groups showed increased mental sedation but RIS and ARP only showed increased physical sedation compared to baseline. For adverse events, RIS and ARP showed higher frequency of sedation and cognitive slowing compare to other antipsychotics. **Conclusion:** Single administration of second generation antipsychotics impede attention and produced deficit symptoms. These findings should be considered in choosing antipsychotics for patients.

## Cognitive Effects on Paliperidone in Schizophrenia Patients Previously Treated with Risperidone

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**Objective:** To evaluate the cognitive effects of direct switching from risperidone to paliperidone extended-release (ER) in patients with chronic schizophrenia.

**Method:** This was a prospective, open-label, 24-week pilot study in patients treated with paliperidone ER 3-12 mg/day. Patients who had been treated with fixed-dose risperidone ≥ 4 weeks and able to complete cognitive evaluations were included. Assessments were done including the Positive and Negative Syndrome (PANSS), Extrapyramidal Symptom Rating Scale (ESRS) and adverse event reports. Cognition was measured by the Cognitive Abilities Screening Instrument Chinese version (CASI C-2.0).

**Results:** 13 patients (100%) completed the 24-week treatment course with mean age (SD) 48.3 (7.8) years, onset age 23.1 (8.7) years, and 8.1 (3.4) formal educational years. The duration of prior risperidone treatment and dose were 34.0 ± 27.7 months and 4.62 ± 1.45 mg/day. The baseline doses of paliperidone ER were 5.3 ± 1.3 mg and 6.0 ± 1.7 mg at endpoint (p = .0821). There was no clinically significant change in PANSS scores (74.8 ± 20.1 at baseline and 71.6 ± 17.9; t = 2.35, p = 0.0369). No significant difference on ESRS. For all ten CASI C-2.0 measures, significant improved category fluency subscale was noted. 11 patients (84.6%) showed improvements at endpoint. There were no significant differences in other cognitive performance. No significant correlations between clinical symptom, ESRS and cognitive changes were found.

**Conclusions:** This was the first study examining the effects of paliperidone ER on cognition in schizophrenia. Significant improvement in category fluency after 24 weeks directly switching from risperidone to paliperidone ER. Further controlled trials with larger numbers of patients were necessary to clarify the cognitive effects of paliperidone ER.



## Tandospirone Improves Neurocognitive Function and Clinical Status in a Patient with Schizophrenia; Effect on Mismatch Negativity

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The case was a 37-year old woman suffering from schizophrenia. She had been ill for 19 years, and was treated at a psychiatric hospital. She continued to be in a good condition after being switched to treatment with olanzapine at the time of admission. However, frequent prescription of lorazepam (in 0.5 mg tablets) was required as an occasional use (40 times per month) to treat anxiety. Therefore, the addition of tandospirone (30 mg/day as an initial dose) was started, which was subsequently increased to 60 mg/day. Psychopathology, cognitive function, as measured by the Brief Assessment of Cognition in Schizophrenia (BACS), and event-related potentials (ERPs) were evaluated before and after treatment with tandospirone.

Six-months after the start of augmentation therapy with tandospirone, the patient experienced less anxiety, and the chance of lorazepam use was decreased to only 0-3 times per month. Verbal learning memory and working memory, as measured by the BACS, were improved. The amplitude of mismatch negativity at the Fz lead was increased (-2.7 $\mu$ V  $\rightarrow$  -5.3 $\mu$ V), which was evident as early as 3-month after the start of tandospirone.

These observations provide the first suggestion for the ability of tandospirone to improve electrophysiological activity, which may precede amelioration of cognitive function and clinical status, in subjects with schizophrenia.

## Aripiprazole Combination with Divalproex in Patients with Acute Manic and Mixed Episode: A Multi-Center, Prospective, Open-Label Study

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**Objective:** The goal of this study was to assess the efficacy and tolerability of aripiprazole in combination with divalproex in patients with acute manic and mixed episode. **Method:** This study was a large, multicenter, 6-week, open-label, combination, prospective investigation of Korean patients with an acute manic and mixed episode of bipolar disorder. A total of 100 patients were recruited from 21 hospitals. Aripiprazole 20mg/day was given in combination with flexible dose of divalproex for 7 days. The aripiprazole dose was titrated flexibly (10-30mg/day) according to the clinical response and tolerability after day 7. The data collected included treatment efficacy using the Young Mania Rating Scale (YMRS), Montgomery-Asberg Depression Rating Scale (MADRS), Brief Psychiatric Rating Scale (BPRS), and Clinical Global Impression-Bipolar-Severity-Bipolar version (CGI-BP) at baseline and at week 1, 2, 3, and 6. To evaluate sleep quality, modified form of Leeds Sleep Evaluation Questionnaire (LSEQ) was used. The Simpson-Angus Scale (SAS), Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Rating Scale (BARS) were administered at each visit in order to assess tolerability. **Results:** Sixty-six of the 100 patients (66%) completed the study. Mean aripiprazole dose was 22.1 $\pm$ 4.8mg/day and mean divalproex dose was 1000.5 $\pm$ 290.6mg/day. The combination of aripiprazole with divalproex treatment was associated with clinically and statistically significant improvement in the mean scores of the YMRS from 29.7 $\pm$ 7.7 at baseline to 9.7 $\pm$ 4.4 at 6 weeks ( $p < 0.0001$ ). The mean scores of MADRS, BPRS, and CGI-BP were also significantly decreased at six weeks ( $p < 0.001$ ). All the efficacy variables showed significant improvement by week 1. The response rate, on the YMRS, was 73% and remission rate was 70% at week 6. Night time sleep quality measured by modified LSEQ was significantly improved. The combination of aripiprazole and divalproex was well tolerated and adverse events were mostly mild. Twenty four patients (24%) reported adverse events. No statistically significant changes were seen on the SAS, AIMS, BARS at the study endpoint compared to the baseline. Five adverse events led to withdrawal from the study. The reasons for withdrawal were skin eruption in two patients, akathisia, agitation and insomnia in one patient each. Mean body weight was significantly increased from 65.6 $\pm$ 12.3Kg at baseline to 66.7 $\pm$ 12.0Kg at week 6. **Conclusion:** The results of this open-label study suggest that aripiprazole combination with divalproex is an effective and safe treatment of the acute manic and mixed phase of bipolar disorder. When compared with the baseline, aripiprazole at mean doses of 22.1 $\pm$ 4.8 mg/day when combined with divalproex at mean doses of 1000.5 $\pm$ 290.6mg/day showed significant antimanic effects, as measured by the YMRS. Aripiprazole combination with divalproex also significantly decreased depressive symptoms as measured by changes in the MADRS as well as psychotic symptoms as measured by the BPRS. In conclusion, despite the many methodological limitations of this open label study, the results of this multi-centre, 6-week investigation showed that aripiprazole plus divalproex combination treatment for bipolar disorder with acute manic symptoms was safe and effective.

## Mirtazapine Augmentation Enhances Cognitive and Negative Symptoms in Schizophrenic Patients Treated with Risperidone: A Randomized Controlled Trial

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**Background:** Many researchers have suggested that the outcome of schizophrenia relies on the cognitive and negative symptoms of schizophrenic patients. To improve these symptoms, mirtazapine augmentation to the schizophrenic patients treated with antipsychotic drugs has been recommended. Previous studies investigating mirtazapine augmentation have been limited, as they lacked neuropsychological tests and prescribed heterogeneous antipsychotic drugs. **Methods:** This study was an 8-week double-blind, randomized controlled trial (RCT) of mirtazapine augmentation to risperidone. 21 stabilized participants diagnosed with schizophrenia, undergoing treatment with the homogenous, atypical antipsychotic drug, risperidone were randomized to adjunctive treatment with mirtazapine (15mg/day for the first 2 weeks, 30mg/day for the next 6 weeks) or placebo. Twelve patients were prescribed mirtazapine. One female patient withdrew her consent 1 day after taking mirtazapine and 11 patients remained at the end of the study. Nine patients were given placebo. Repeated measure analyses were used to find out the effectiveness of mirtazapine. **Results:** There was no significant difference between mirtazapine- and placebo-treated participants with respect to improvement in Positive and Negative Syndrome Scale total scores. However, the mirtazapine-treated group exhibited a statistically significant improvement in cognitive function, including vocabulary ( $p < 0.05$ ), immediate memory ( $p < 0.05$ ) and Scale for the Assessment of Negative Symptoms total scores ( $p < 0.01$ ), and showed 5.8kg of weight gain. This study suggests that the augmentation of risperidone with mirtazapine can effectively improve both the negative and some cognitive symptoms of schizophrenia. **Conclusions:** This is the first randomized controlled trial reporting the effects of mirtazapine augmentation of homogeneous atypical antipsychotic drug on cognitive and negative symptoms except clozapine. Future work should explore the possibility that our results can be replicated in a large-scale lengthy trial using various atypical antipsychotics.

## Effect of Quetiapine on the Subjective Estimates of Sleep in the 8 Weeks Treatment of Acute Bipolar Depression

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**Objective:** Sleep disturbance is a characteristic feature of bipolar depression, and both the quality and quantity of sleep are typically adversely affected during depressive episodes. The purpose of this study was to evaluate the subjective estimate of sleep after quetiapine treatment in bipolar I and II patients. **Methods:** Patients with bipolar I or II depression were included. They were treated with quetiapine and other mood stabilizers. The doses of quetiapine and mood stabilizers were flexible according to the clinical judgment. Clinical improvements were rated by severity of illness of Clinical Global Impression-Bipolar version (CGI-BP-S) and Montgomery-Asberg Depression Rating Scale (MADRS). Modified version of Leeds Sleep Evaluation Questionnaire (LSEQ) was used to assess the subjective measures of nighttime sleep and hangover, which included the factors covering four areas: i) getting to sleep (GTS), ii) quality of sleep (QOS), iii) awakening from sleep (AFS), and iv) behavior following wakefulness (BFW) or hangover during the next day. All assessments were done at baseline and week 4 and 8 after treatment. **Results:** A total of 877 patients [bipolar I depression; N=577 (65.7%), bipolar II depression; N=301 (34.3%)] were recruited and 44 (5%) patients were dropped out during the study. CGI-BP-S and MADRS were significantly improved at week 4 and 8 compared with baseline. Clinical improvements were not differed between bipolar I and II patients. The nighttime sleep parameters (GTS and QOS) were more impaired in bipolar II patients at baseline. But, all sleep parameters of modified LSEQ were improved at week 4 and 8 without impairment of daytime hangover in both bipolar I and II patients and significant differences were not found at week 4 and 8 between two groups. **Conclusion:** This result based on LSEQ suggests that quetiapine improved multiple dimensions of subjective estimate of sleep, including sleep quality and sleep duration, without daytime dysfunction.

## Effectiveness of Adjunctive Lamotrigine Treatment in Patients with Bipolar II Depression

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**Background:** This observational study examined the effectiveness of long-term adjunctive lamotrigine therapy for bipolar II depression.

**Methods:** A total of 109 outpatients with bipolar II depression were recruited from Seoul National University Bundang Hospital, and lamotrigine was added in a naturalistic fashion to prior treatment with mood stabilizers. Long-term changes in depression severity were prospectively monitored for up to 52 weeks using the prospective lifechart and the Clinical Global Impressions-Bipolar Version (CGI-BP). Kaplan-Meier curves were generated to evaluate time to relapse.

**Results:** An improvement of depression severity was achieved at week 4 sustained up to 52 weeks and the effect size based on t-statistic was large. The relapse rates were 44.0% (48/109) for the total sample with 14.3% (10/70) for responders at 24 weeks, and 50.5% (55/109) with 22.9% (16/70) at 52 weeks. Higher number of psychiatric hospitalization due to depressive symptoms and history of suicidal attempt were associated with insufficient response to lamotrigine treatment. Suicide attempters were 2.69 times more likely to be associated with insufficient response to lamotrigine.

**Conclusions:** Long-term benefits of lamotrigine add-on for depression were suggested in bipolar II disorder. Poor response to lamotrigine was more frequent in patients with prior psychiatric hospitalizations and history of suicide attempt. Long-term adjunctive use of lamotrigine was safe and generally well-tolerated in a clinical setting. Further replication studies with randomized and controlled designs are warranted.

## The Effectiveness and Tolerability of Lamotrigine in Adolescent Psychiatric Patients

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**Objective:** To determine the effectiveness and tolerability of lamotrigine in adolescent psychiatric patients. **Method:** Medical charts were reviewed retrospectively for 24 adolescents (age < 18) who had been treated with lamotrigine during the previous 2 years in the child and adolescent psychiatric clinic of the Ulsan university hospital in South Korea. The data were collected by chart review and included the following: age at onset, DSM-IV diagnosis, baseline Beck Depression Inventory (BDI) score, Beck Anxiety Inventory (BAI) score, duration of treatment with lamotrigine, prior and concurrent medication (i.e., antipsychotics, mood stabilizers, antidepressants, and stimulants). The Clinical Global Impression Severity and Improvement scores were obtained at baseline and at the 4th, 8th, and 12th weeks, and at the last visit. Adverse effects were also noted. **Result:** The average age of onset was 14.3 (8–17, SD = 2.2) years old. DSM-IV diagnoses included psychosis (N = 4, 16.7%), unipolar depressive episode (N = 3, 12.5%), bipolar depressive episode (N = 9, 37.5%), mixed episode (N = 11, 45.8%), externalizing disorder (N = 4, 16.7%), and anxiety disorder (N = 4, 16.7%). The mean daily lamotrigine dosage was 63.8 mg (range 12.5–143mg/day), the average full dosage was 101.6mg (12.5–200mg, SD = 62.2), and the average duration of lamotrigine treatment was 26.6 weeks. An improvement was seen in 18 (75%) patients. Sixteen (66.7%) patients were followed up until the end point. The mean CGI-S score decreased from 4.26 ± 0.42 at baseline to 3.526 ± 0.517 at the 4th week, to 3.368 ± 0.538 at the 8th week, and to 2.947 ± 0.467 at the 12th week of follow up (p < 0.001). Symptoms recurred in 6 (25%) subjects. After controlling for the effect of antipsychotics, mood stabilizers (i.e., lithium, valproate, and topiramate), antidepressants, and stimulants, the improvement remained consistent across the analysis. Mild extrapyramidal symptoms (EPS; N = 8, 33%) including sedation (N = 8, 33%), gastrointestinal discomfort (N = 6, 25%), and benign rashes (N = 6, 25%), were reported. Three (12.5%) patients dropped out because of side effects. **Conclusion:** Lamotrigine appears to be effective in treating depressive symptoms in adolescent psychiatric disorders and shows minimal adverse effects, although a double-blind controlled trial is needed to confirm this finding.

## Effectiveness of Quetiapine in Patients with Bipolar I and II Depression: A Multi-Center, Prospective, Open-label, Observational Study

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Bipolar depression has a disabling course, and its treatment represents a major challenge. Recent randomized, controlled trials have shown that quetiapine monotherapy significantly reduced the symptoms of depression in patients with bipolar depression. The purpose of this study was to evaluate and compare the therapeutic efficacy of quetiapine in bipolar I and II depression in the clinical setting. This study was a multi-center, prospective, open-label, observational, 8-week evaluation of the efficacy of quetiapine in patients with bipolar depression. Patients with a DSM-IV-TR diagnosis of bipolar depression (Bipolar I Disorder (BD-I), most recent episode depressed and Bipolar II Disorder (BD-II), most recent episode depressed) were included in the present study and treated with quetiapine. During the research period, the dose of quetiapine was flexible and concomitant medications were permitted based on the clinician's judgment. Clinical improvements were rated by the Clinical Global Impression-Bipolar version (CGI-BP) and the Montgomery-Asberg Depression Rating Scale (MADRS) at baseline, week 4 and week 8. A total of 1,097 patients were enrolled, and 39 patients (3.9%) were excluded from the study. The mean initial dose of quetiapine was 194.1±181.0 mg/d, and the mean doses at weeks 4 and 8 were 321.1±229.2 mg/d and 341.4±229.2 mg/d, respectively. Throughout the entire period of observation, the mean dose of quetiapine in BD-I patients was significantly higher than in BD-II patients. In a total of 808 patients (73.7%), psychotropic medications were concomitantly administered to BD patients. In addition, the combined administration of antidepressants, anxiolytics, or hypnotics and sedatives was more frequent in BD-II patients than in BD-I patients. CGI-BP and MADRS scores were significantly improved at weeks 4 and 8 in comparison with the baseline scores. In addition, the amount of improvement at week 8 was greater than that observed at week 4. The BD-I patients showed better clinical improvement than the BD-II patients. At the end of the 8-week study, the response rate (≥50% reduction in MADRS total score) was 59.3%, and the remission rate (≤12 in MADRS total score) was 50.6%. The rate of remission in the BD-I patients was 52.8%, and it was significantly higher than the 46.1% rate of remission in the BD-II patients. Subjectively, 76.0% and 75.4% of the patients reported therapeutic compliance above 75% at weeks 4 and 8. The rates of manic/hypomanic switch at weeks 4 and 8 were 0.6% (7 patients) and 0.3% (4 patients), respectively. The results of this study suggest that quetiapine improves depressive symptoms in patients with BD-I and II depression, with a minimal incidence of manic switching. The therapeutic efficacy increased with time. The therapeutic efficacy, including the remission rate, was better in the BD-I patients than in the BD-II patients. We suggest that quetiapine could be an effective and safe modality for the treatment of BD-I and II depression. **Keywords:** bipolar I depression; bipolar II depression; quetiapine; therapeutic efficacy

## Successful Treatment of Elderly Depression with Donepezil Augmentation

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**[Introduction]** Depression in the elderly has a less favorable prognosis than that in the non-elderly, because there might be a sub-group with depression in the transition to dementia. Here, we report a case of an elderly patient with depression, who was resistant to several antidepressants, that was treated with donepezil augmentation.

**[Patient's history]** A 69-year-old Japanese man was hospitalized twice for depression in X-16 year. In X-2 year, a stressful event led to recurrence of depression including depressive mood, lack of motivation, and insomnia. During the last two years, he has not shown any improvement despite treatment with more than four different antidepressants. In May X, the patient was admitted into our medical center. Scores of Hamilton's Rating Scale for Depression (HAM-D) and Hasegawa Dementia Scale-Revised (HDS-R) were 19/64 and 25/30, respectively. Treatment with an adequate dosage of milnacipran had no effect. Based on CT and SPECT brain image findings of mild atrophy and reduced cerebral blood flow in the temporal and parietal lobes, we hypothesized mild cognitive impairment may be intensifying his depressive symptoms and could be amenable to donepezil. After addition of donepezil (10mg/day) to milnacipran (100mg/day), his depressive symptoms gradually improved and he was discharged on the 70th day (HAM-D:5, HDS-R:24).

**[Conclusion]** Donepezil should be considered for augmentation therapy with an antidepressant in an elderly depressed patient, especially one with mild cognitive impairment.

## Switching to Sertraline in Patients with Depression Who are Intolerant to Paroxetine-induced Nausea

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Nausea and/or vomiting is reported to be one of the most frequent side effects induced by selective serotonin reuptake inhibitors (SSRIs). This undesirable side effect has been reported to be relieved in a few days after initiation of SSRIs' treatment. Patients, however, often decide to stop taking the drugs because of uncomfomrt of this incident. We described herein the effect of switching strategy to sertraline in patients with depression who are suffering from paroxetine-induced nausea. Twenty-two patients (DSM-IV, major depression) who stopped paroxetine due to nausea were switched to sertraline 25mg/day. The dose of sertlaline was determined by clinical judgment. Duration of this observational study was 12 weeks. Last observation carried forward (LOCF) was used in the analysis. Three patients (13.6%) were dropped out and 19 patients (86.4%) were completed. The mean MADRS score was significantly decreased from 27.9 at baseline to 14.3 at baseline. Five patients (22.7%) reached remission (MADRS score 9 or less) and 9 patients (40.9%) were considered as responders (Decrease of MADRS score 50% or more). These results suggest that switching to sertraline may be one of the treatment options in this population. All patients gave us oral approval in this study. On the other hand, .we did not ask for the approval of this study from ethical committee in our institution because this naturalistic-observational research was conducted in line with daily clinical practices.

## rTMS as an Add-on Treatment for Refractory Depression in Han Chinese

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Depression is a major psychiatric disorder. The standard treatment for depression is antidepressant. But the responses to antidepressant treatment are only partial, even poor, among 30-45% of the patients. Refractory depression is defined as depression which dose not response to antidepressant after 4 weeks of use.

There are evidences that repetitive Transcranial Magnetic Stimulation (rTMS) may exert effects in treating psychiatric disorder through moderating focal neuronal functions. Application of the rTMS in treating depression has been approved in Canada, the United States and other countries. High frequency rTMS on the left prefrontal area and low frequency rTMS on the right prefrontal area were shown to be effective in alleviating the depressive symptoms. Given the statistically significant antidepressant effect noted, the clinical application of rTMS for depression treatment warrant further studies. Application of rTMS as an add-on therapy would be a practical research model.

The present study will choose patient with refractory depression receiving antidepressant treatment as subjects, apply rTMS on the left or right prefrontal area as an add-on therapy, and assess the therapeutic effects with Hamilton Depression Rating Scale. We would report the data in the symposium.

## Lamotrigine Augmentation in the Treatment of Refractory Depression

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About 30% of depressed patients do not respond adequately to antidepressant treatment, and some of them become treatment-resistant. Lamotrigine (LMG) is the only mood stabilizer that is effective for preventing the depressive episode of bipolar disorder. This study aimed to evaluate the efficacy of LMG augmentation on refractory depression. The subjects were 23 refractory depressed patients who had not shown response to multiple pharmacotherapy. The diagnoses were major depressive episode in 10, bipolar disorder with depressive episode in 8, and dysthymic disorder in 5. The mean (range) of the number of mood episode was 4.4 (1-10) times, and that of the duration of the present episode was 13.7 (1-40) months. The patients gave written informed consent to use LMG outside its indication. The daily dose of LMG was titrated at the clinician's decision. The depressive symptoms were evaluated by using MADRS and GAF before treatment and after 8 week treatment. The mean MADRS and GAF scores (±SD) improved from 25.3±11.0 and 49.8±13.4 to 14.5±11.2 and 64.1±11.7 at 8 week treatment. 11 patients (47.8%) were responders (>50% reduction in MADRS score). The patients with higher number of mood episodes or shorter duration of the present episode showed higher improvement. The adverse skin reaction developed in 9 patients, including 6 responders. LMG augmentation is effective in the treatment of refractory depression, especially with recurrent episodes or shorter duration of the present episode. However, attention should be paid to the development of skin rash in LMG responders.

## The Effect of Psychotherapy Added to Pharmacotherapy on Cortisol Responses in Outpatients with Major Depressive Disorder

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The present study examined the changes of depressive symptoms and salivary cortisol responses in 36 outpatients with major depression. These patients were randomly assigned to receive combination therapy (CT), consisting of antidepressants and body-mind-spirit group psychotherapy, or monotherapy (MT), consisting of antidepressants only. The results indicated that CT and MT had similar effects on reducing depressive symptoms. Nevertheless, the results revealed that cortisol levels at night appeared to have a greater reduction in CT than in MT, indicating a downward trend in CT but an upward trend in MT. Moreover, a steeper diurnal pattern of cortisol-a larger deviation in cortisol levels between 30 and 45 minutes postwaking and evening-was more likely associated with CT than MT. The findings suggest that CT produced a protective effect on outpatients with major depression, preventing the increased night salivary cortisol levels and the flatter diurnal cortisol pattern that tended to occur in MT.

## Benefits of Switching Antidepressants Following Early Nonresponse

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**Background:** The guidelines for the treatment of major depression recommend the continuous use of antidepressants for 4 to 8 weeks. However, recent meta-analysis shows that antidepressants start to exert their antidepressant efficacy within 2 weeks (1). Early outcome at week 2 is proposed to be a predictor of subsequent outcome (2). In this 8-week study, we examine the benefits of switching antidepressants following early nonresponse in patients with major depression. **Methods:** Sertraline was initiated for patients with major depression, increased to 50mg on day 3, and maintained until day 14. In case of early nonresponse (i.e. less than 20% improvement in the MADRS total score from baseline), subjects were randomly divided into two groups. In one group, sertraline was continued and titrated at 50-100mg, whereas in the other group sertraline was switched to paroxetine 20-40mg. Assessments included the MADRS and the QIDS-SR. **Results:** 96 participants participated in this study; of these, 25 participants showed early nonresponse. Both Switching group (n=12, no dropout) and Continuing group (n=13, 4 dropouts) showed significant improvement at week 8 in the MADRS and the QIDS. However, in the Switching group, a greater number of remitters (7 vs. 2), and a greater improvement in the MADRS (-20.7 vs. -7.2) and the QIDS-SR (-21.3 vs. -9.6) were found at the endpoint. **Conclusion:** Our findings suggest that patients with depression who fail to show early response may deserve benefits from switching antidepressants at the early stage in terms of both subjective and objective outcomes.

## Efficacy and Acceptability of Milnacipran for Major Depression: A Cochrane Systematic Review and Meta-analysis

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**Objective:** To assess the evidence for the efficacy, acceptability and tolerability of milnacipran, a dual serotonin-norepinephrine reuptake inhibitor, in comparison with TCAs, SSRIs and other antidepressant agents in the acute-phase treatment of major depression, we conducted a systematic review and meta-analysis.

**Method:** We searched the Cochrane Collaboration Depression, Anxiety & Neurosis Controlled Trials Registers, journals, conference proceedings, databases of the drug-approving agencies and clinical trial registers (updated: August 2008) for all published and unpublished randomised controlled trials. All relevant authors were contacted for supplemental data. No language restriction was applied. Two reviewers independently checked eligibility, assessed methodological quality and extracted data from the eligible trials. Random-effects meta-analyses were conducted, combining data from the included trials.

**Results:** A total of 16 trials (n=2,277) were included in the review. There were no differences in efficacy, acceptability and tolerability when comparing milnacipran with other antidepressant agents. However, compared with TCAs, patients taking milnacipran were associated with fewer dropouts due to adverse events (OR 0.55; 95%CI 0.35-0.85). There was also some weak evidence to suggest that patients taking milnacipran experienced fewer adverse events of sleepiness/drowsiness, dry mouth or constipation compared with TCAs.

**Conclusions:** Currently, there is inadequate evidence to conclude whether milnacipran is superior, inferior or the same as other antidepressant agents in terms of efficacy, acceptability and tolerability in the acute phase treatment of major depression. However, there is some evidence in favour of milnacipran over TCAs in terms of dropouts due to adverse events and the rates of experiencing adverse events.

## Patients' Attitudes Toward Side Effects of Antidepressants; An Internet survey

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**[Objectives]** Few reports have investigated differences in patients' response to various antidepressant side effects between men and women. We conducted a large-scaled Internet survey to evaluate actions that patients had taken to counteract those side effects with a special focus on gender-difference.

**[Methods]** 1,305 participants who had been diagnosed with depression and received antidepressant medication within the past year were selected from 228,310 registrants with the Yahoo Japan research monitor through screening procedures. Participants were asked as to which side effects they had experienced, whether they had reported those side effects to their physicians, and whether they had taken any action to counteract them. This survey was conducted in February, 2008.

**[Results]** 1,187 participants completed the questionnaire. Side effects were reported in 73.4% of the participants; men had more frequently experienced them than women (80.4% vs. 68.3%, p<0.05). The ratio of participants who had taken any action to relieve side effect varies among side effects from 26.3% for sexual dysfunction to 89.5% for dry mouth. Compared to men, a lower percentage of women had reported sexual dysfunction to physicians (36.6% vs. 60.7%, p<0.05) and took any action to counteract it (19.8% vs. 36.9%, p<0.05).

**[Conclusion]** Given that patients are likely to be reluctant to report sexual side effects, physicians should be aware of the potential presence of sexual dysfunction in patients with depression, which seems especially true in women.

## Prescription Pattern and Side Effect Profiles of Bupropion

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**Objective:** Due to its unique mechanism of action and favorable side effect profiles, the use of bupropion has been increasing in Korea recently. In this cross-sectional survey, we examined the prescription pattern and side effect profiles of bupropion in psychiatric practice. **Methods:** A total of 107 psychiatrists participated this survey from April 2007 to September 2007. The survey questionnaire included the types of combined drugs, clinical diagnosis, clinical global impression, side effects, and age and sex of patients. Data of 1085 cases were **Results:** Mean age of cases was 43.4 ± 17.1 (range 6-80) years, 629 cases (58.0%) were female and 441 cases (40.6%) were male. The most common psychiatric diagnosis was depressive disorder (86.8%). Bupropion was also prescribed in anxiety disorder (7.2%), somatoform disorder (1.9%), attention deficit hyperactivity disorder (1.6%), psychotic disorder (1.3%) and adjustment disorder (1.1%). Fifty-one percents were used as bupropion monotherapy and 49% were used in combination with other antidepressants. Among combination therapy, most of them (96.6%) were used in combination with one other antidepressant. Commonly combined drugs were sedating antidepressants. The overall frequency of side effects was 11.9% in bupropion monotherapy. Common side effects were insomnia, nausea/vomiting, anxiety, loss of appetite. No sexual side effects were reported in bupropion monotherapy. **Conclusion:** Bupropion has been prescribed mostly in patients with depressive disorders. However, the data suggested that the prescription has expanded to other psychiatric disorders. Bupropion showed favorable side effect profiles with no sexual side effects. **KEY WORDS:** Bupropion; Prescription pattern; Side effect profiles.

## The Effects of St. John's Wort for Premenstrual Syndrome in Single Women: Randomized Double Blind, Placebo-Controlled Study

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**Objective:** St. John's wort (SJW) is known to be effective in treating depression and mood disorders. This study was designed to verify the effect of SJW for premenstrual syndrome in single women. **Methods:** From August 1st 2008 to October 31st 2008, 30 single women who suffer from premenstrual symptoms were recruited for this study. This study was carried out in a double blind randomized controlled clinical trial. Inclusion criterias were healthy single women, under no specific medication. We included those that had Beck depression inventory (BDI) scale scores over 10 or Premenstrual assessment form (PAF) scores over 217. Exclusion criterias were those that had endocrine disease, genitourinary, obstetric and gynecologic disease, and any psychiatric diseases, and those under medication. 30 women were divided randomly into two groups. The experimental group of 16 women were given 600mg/day of hypericin, extract of SJW. The control group of 14 women were given a placebo that looked similar to SJW extract. During 3 cycles of menstruation, all women wrote a daily diary for premenstrual syndrome. When the second menstruation cycle started, all women began to take two pills daily. We investigated BDI, PAF and VAS before starting the experiment and again at the end. Each variant was further analyzed via nonparametric test, the change in values before and after the study were studied using an Mann-Whitney U test. **Results:** Compared to the placebo group, the SJW group had no significant differences on VAS, total PAF, BDI. However, 3 subscales of PAF, lability, hostility/anger and impulsivity showed statistically significant difference ( $p < 0.05$ ). **Conclusion:** This study suggested that SJW shows the effectiveness on lability, hostility, anger, and impulsivity related to premenstrual syndromes in single women.

## Prevalence and Correlates of Hypnotic Use in Chinese Elderly Veteran Assisted-living Residents

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**Background:** Sleep disturbance in the elderly are common and are often treated with hypnotics. The aim of this study was to determine the prevalence and correlates of hypnotic use in Chinese aged veteran assisted-living residents. **Methods:** Residents aged 75 and over were enrolled for the study and interviewed by trained nurses. Insomnia diagnosed by DSM-IV criteria. Factors related to hypnotic use were evaluated by Mini-Mental Status Examination (MMSE), Geriatric Depression Scale-Short Form (GDS-SF), and Minimal Data Set (MDS) - a process for general assessment included of self-report physical illness, daily habits, and function of activity of daily living. The influence of age, cognitive impairment, mental health and physical illness were analyzed using multivariate logistic regression analysis to investigate significant independent risk factors for hypnotic use, which was identified by weekly frequency of hypnotic use recorded by trained staff.

**Results:** In total, 562 people (mean age 81.4±4.5 years, all males) participated in study. The mean MMSE and GDS-SF scores were 26.6±3.8 and 2.1±2.3. The rate of regularly hypnotic use was 20% (N=112). In logistic regression analysis, depression (OR = 2.2,  $p = 0.02$ ), and Parkinson's disease (OR = 3.7,  $p = 0.02$ ) showed association with hypnotic use.

**Conclusion:** Hypnotic using is common among our participants and was associated significantly to depression and Parkinson's disease but not insomnia. Screening and treating depression are important for elderly residents.

**Key Words:** hypnotic use, prevalence, elderly, risk factor

## Effects of Discontinuing Benzodiazepine-derivative Hypnotics on Cognitive and Motor Functions in the Elderly

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Benefits of discontinuing benzodiazepines (BZDs) have not systematically been investigated in the elderly. We therefore examined changes in motor and cognitive functions following discontinuation of BZD hypnotics in elderly persons. In this 8-week open-label study, subjects aged 65 or older who received BZD as a hypnotic and did not have any unstable physical or neurological illness were recruited. The BZD dose was tapered off in 4 weeks. The following assessments were performed 12 hours postdose at baseline and at endpoint: the Clinical Stabilometric Platform (CSP), the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), the Critical Flicker Fusion Test (CFF), and the Leeds Sleep Evaluation Questionnaire (LSEQ). This study was approved by the institutional review board, and subjects provided written informed consent. 30 subjects were enrolled (mean age=76.9 years; mean flunitrazepam equivalent BZD dose=1.6 mg/day; DSM-IV diagnosis: sleep disorder (n=13), schizophrenia (n=12), and dementia (n=5)). Four subjects dropped out due to a worsening of insomnia. Among the completers, the total length of the trunk motion was significantly decreased (73.2 cm to 65.2 cm with eyes closed). Significant improvements were also observed in the CFF and RBANS total score (27.2 Hz to 28.5 Hz and 97.1 to 119.4, respectively). No worsening in the LSEQ was found in those completers. These findings suggest that discontinuation of BZD hypnotics may be feasible in many elderly persons and will provide a recovery in cognitive function and body stability.

## The Effect of Herbal Prescription Yokukansan on Periodic Limb Movement in Elderly Patients

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**Introduction:** In the elderly population, alterations in sleep architecture and circadian sleep-wake rhythm disturbances are usually observed. Periodic limb movement during sleep (PLMs) has been suggested to induce frequent arousals at night. **Objective:** This study aims to investigate whether herbal prescription Yokukansan (YKS) improves PLMs and subjective sleep quality in the elderly. **Methods:** Eight patients who had been complained of subjective sleep disturbances were enrolled in this study. The subjects treated with YYS, neuroleptics or cholinesterase inhibitors were excluded. Polysomnography (PSG) at baseline was carried out following adaptation night, and PSG was also carried out 4 weeks after YYS treatment. Subjective sleep quality was evaluated with Pittsburgh Sleep Quality Index (PSQI). The local IRB approved this study. All patients gave informed consent according to institutional guidelines. This study was carried out at Shimane University. **Results:** Mean total sleep times were 245.0 min and 341.0 min at baseline and after YYS treatment, respectively. Treatment with YYS for 4 weeks resulted in the improvement of total sleep time and sleep efficiency. The significant decreases in PLM index, sleep latency and the number of arousals at night were observed. There was a significant difference in mean PSQI scores between baseline and YYS-treatment. **Conclusion:** Treatment with YYS for 4 weeks improved PSG variables including PLMs as well as subjective sleep quality. YYS was effective for sleep disturbances and well tolerated in the elderly subjects.

## Verbal Working Memory and Functional Outcome in Patients with Unipolar Major Depressive Disorder

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**Background:** Patients with major depressive disorder (MDD) have been reported to perform less well in neurocognitive tests than normal controls.

**Objective:** This naturalistic longitudinal study tested the hypothesis that verbal working memory (WM) in patients with MDD would predict functional outcome.

**Methods:** The subjects consisted of 20 clinic adult outpatients. The assessments were performed using the 7-item Hamilton Rating Scale for Depression (HAM-D7) for severity of depression, and Digit Sequencing Task (DST) for verbal WM. Functional outcome was rated from 0 (non-impaired) to 3 (severely impaired).

**Results:** First, six out of 20 patients with current episode of MDD did not take the second assessment. Second, after 3 months, six out of 14 patients with current episode of MDD became full remitted. Third, HAM-D7 scores decreased significantly (from  $12.9 \pm 3.2$  to  $5.9 \pm 4.4$ ). However, DST scores did not show significant increase. Fourth, at baseline, functional outcome was significantly correlated with HAM-D7 scores ( $r=0.49$ ), but, after 3 months, it was significantly correlated with DST scores ( $r=-0.61$ ). Fifth, in a multiple regression analysis with a forward stepwise procedure, DST scores at baseline significantly contributed to the prediction of functional outcome after 3 months, and HAM-D7 scores at baseline significantly contributed to the prediction of HAM-D7 scores after 3 months.

**Conclusion:** The findings in this study suggested relations between an MDD-associated deficit in verbal WM and functional outcome after treatment.

## Liaison Psychiatrists' Prescription of Antidepressants for Depressed Medical Inpatients in Thailand

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**Objectives:** The authors investigated the consultation-liaison psychiatrists' prescribing patterns of antidepressants in the hospitalized physically ill and associated factors with the choice of antidepressant types, comparing to the treatment recommendations. **Methods:** All inpatients referred for psychiatric consultation at Siriraj Hospital, a teaching general hospital, during a one-year period were studied. The data were collected from consultation request forms and medical records, and were analyzed by descriptive statistics and Chi-square tests. **Results:** Among all 840 referred patients, 656 had complete medical records available for studying. 159 (25.0%) of them had depression, ie. MDD, dysthymia, and adjustment disorder with depressed mood for 51.6%, 17.6% and 34.0%, respectively. 97 of them (61.0%) were prescribed antidepressants: 69.1% SSRIs, 28.5% tetracyclids and 12.4% tricyclids. There was a significant difference ( $p<0.001$ ) between diagnostic groups in the tendency of being prescribed an antidepressant; MDD 79.3%, dysthymia 67.9%, and adjustment disorder with depressed mood 33.3%. The most commonly used antidepressants were SSRIs, irrespective of diagnoses. Patients' factors associated with psychiatrists' choice of antidepressant types were old age, electrolyte imbalance, recent suicidal attempt, and post-operative status ( $p<0.05$ ). **Conclusion:** This is the first study on current antidepressants prescribing practice in the medically-ill inpatients with depression by liaison-psychiatrists in Thailand. The most commonly used antidepressants were SSRIs. Regarding the patients' factors contributed to psychiatrists' choice of antidepressant types, most psychiatrists seemed to follow the practice recommendations. Future researches on effectiveness of antidepressants in the medically ill are needed.

## The Inter-rater Reliability of Inventory of Depressive Symptomatology - Clinicians of the Japanese Version

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**Objective:** The Inventory of Depressive Symptomatology, Clinician Rated (IDSC), is a rating scale used to assess the severity of a major depressive episode. The inter-rater reliability of the Japanese version of the IDSC (IDSC-J) was examined using the Japanese version of the Structured Interview Guide for Combined Rating of the HAM-D (Hamilton Depression Rating Scale) and IDS-C [SIG (HAMD&IDSC)-J]. **Methods:** The IDSC and SIG (HAMD&IDSC) were translated into Japanese by our group. The subjects comprised 14 patients with major depressive episode. Two psychiatrists attended together, conducted a systematic interview to evaluate each item of the IDSC-J using SIG (HAMD&IDSC)-J, and independently rated the 30 items. **Results:** The severity of the scale assessed by the two raters ranged from 0 to 3 for 27 items and from 0 to 2 for 3 items. The Analysis of Variance Intraclass Correlation Coefficient inter-rater reliability values for the individual scale items ranged from 0.85 to 1.00. A number of representative reasons for scattering included: 1) for some items, persistence of a symptom was not always applicable to a proper anchor point; 2) the severity of a symptom was evaluable for multiple items in some cases; and 3) in some cases it was difficult to differentiate the symptoms of depression itself from those considered to be induced by antidepressants. **Discussion:** The present results suggest that the IDSC-J, when used in conjunction with the SIG (HAMD&IDSC)-J, is a potentially useful rating instrument with high inter-rater reliability for assessing the severity of depressive episode.

## Bipolar Diathesis of Unipolar Treatment Resistant Depression

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A medical record review of patients who were admitted at a university hospital with the diagnosis of major depressive disorder was conducted. We selected patients with "treatment resistant depression", which was defined as failure to respond to two adequate trials of antidepressants. Detailed clinical information including demographic data, age of illness onset, nature of symptoms, medical and psychiatric comorbidity, and psychiatric family history in first degree relatives was obtained. Patients were re-evaluated using the recently proposed criteria for bipolar spectrum disorder by Ghaemi et al. At discharge, 281 patients were diagnosed as major depressive disorder. Patients with treatment resistant depression (TRD) ( $n=68$ ) were compared on demographic data and clinical characteristics with patients who were diagnosed with a major depressive disorder except treatment resistant depression (MDD) ( $n=213$ ). Of the TRD group, 32 patients (47.1%) were bipolar spectrum disorder and 8 (3.8%) of the MDD group were bipolar spectrum disorder. ( $p<0.001$ ) At two year follow up, diagnosis of 38 patients was changed. There was a 8.9% prevalence of bipolar disorder in our sample. Of the TRD group, 18 (26.5%) were subsequently classified as having bipolar disorder, and 7 (3.3%) of the MDD group. ( $p<0.001$ ) There was no difference between these two groups in other clinical and demographic variables. The findings suggest that a large part of cases of unipolar treatment resistant depression has a bipolar diathesis. **Key words:** Treatment resistant, major depressive disorder, bipolar disorder.

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## Comparison of the Subjective Symptoms in Perimenopausal Women Between Japan and China: A Canonical Correlation Analysis Between Severity of Subjective Symptoms and Self-efficacy Scores

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Independently of geographical areas or races, each community has at least one of traditional rules for alleviating menopausal syndrome from ancient times down to present day, but there is little information concerning the characteristics of menopausal syndrome itself. We conducted a medicinal-anthropological study for exploring the characteristics in subjective symptoms between in Japanese and Chinese aged-women. In the present study, we examined 329 Chinese and 310 Japanese women (40-59 years old) and determined the dimensional structure statistically using confirmatory factor analysis. Subjects were subdivided into pre-menopause (Pre), menopausal transition (MT), and post-menopause (PM) stages. Our multidimensional inventory had good internal consistency, with a Cronbach's alpha coefficient of 0.96 and the five-factor model of subjective symptoms appeared to fit the data for all samples tested (N=639, root mean square error of approximation = 0.06). The most salient symptom was getting tired easily in Japanese and poor memory in Chinese. In all factors of Pre group, Japanese women showed significantly higher score than Chinese. Also, a significant difference was found in mental condition, interpersonal anxiety and autonomic balance factors of PM group. Canonical correlation analysis revealed that among factors on the two scales (5 x 3 factors) there was a significant canonical variable (Japanese:  $\lambda=0.701$ ,  $p<0.01$ ; Chinese:  $\lambda=0.458$ ,  $p<0.01$ ), confirming a negative correlation between the severity of menopausal syndrome and degree of self-efficacy score.

## Does Lithium Carbonate Promote Cancer Metastases? A Case Report

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I reported a bipolar patient with extremely rapid cancer metastases, to whom lithium had been administered for many years<sup>1</sup>. I think that this case suggests a possibility of enhancing effects of lithium on a cancer metastasis.

Since Dr. John Cade discovered lithium carbonate as an effective medication of bipolar disorder in 1949, 60 years of clinical use of this alkali metal do not implicate an increased risk for any type of cancer. Rather, intake of lithium may cause reduced tumor incidence compared to that of the general population<sup>2</sup>. However, whether it adversely affects metastasis of an existing cancer still remains as a cardinal problem. Lithium is a potent inhibitor of glycogen synthase kinase 3 $\beta$  (GSK-3 $\beta$ ). A recent investigation<sup>3</sup> showed that the inhibition of this enzyme allowed a cancer cell to become mobile and move away from a tumor by down-regulation of E-cadherin and by upregulation of Snail, a zinc-finger transcription factor, *in vivo*. Considering that metastasis is ultimately responsible for most cancer deaths, I think that blocking cancer cells from metastasizing could be superior to prevention of cancer development.

There have been no clinical trials to prove that dosages of lithium or GSK-3 $\beta$  inhibitors practically facilitate the cancer metastasis, but a prospective study will be needed to address this question.

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## The Characteristics of Suicide Attempts and Psychosocial Risk Factors in Correctional Institutions

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Objects: Suicide is one of the most common cause of deaths in correctional institutions. This study aimed to examine the characteristics of suicide attempts and related psycho-social factors in correctional institutions.

Methods: This study examined the characteristics of 101 suicide attempts from 2006 to 2007 in the two regional correction headquarters. And 37 male inmates (43 suicide attempts) and 40 matched controls were included in interview and review of personal records. Psychiatric illness was examined with Structured Clinical Interview for DSM-IV and medical outcome of suicide attempt with lethality scale of Diagnostic Interview for Genetic Studies.

Results: Over a half of suicide attempts occurred in solitary cell and the most common method was hanging. The level of medical outcome of 70% suicide attempts was more than severe. Poor social support, lifetime history of suicide attempt and incarceration were associated with suicide attempt. And psychiatric illnesses were more likely to increase the suicidal risk.

Conclusions: This study implicates that mental health issues and monitoring system are important to reduce suicide in correctional system. Regular check and management of suicide risk and mental illness are crucial to prevent suicide in correctional institutions.

## Hypomania-Like Syndrome Induced by Deep Brain Stimulation of Bilateral Anterior Limbs of the Internal Capsules

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**1. Introduction** Deep brain stimulation (DBS) is an experimental treatment for medication-refractory obsessive-compulsive disorder (OCD). The data from four centers support its therapeutic promise (Greenberg et al., 2008), but adverse effects such as panic induced by stimulation were reported (Shapira et al., 2006). In this case, we discuss hypomania-like syndrome induced by bilateral stimulation of the anterior limbs of the internal capsules.

**2. Case report** Mr. S was a 28-year-old ethnic Chinese male with a 10-year history of refractory OCD. After the patient signed informed consent, we implanted Model 3387 IES leads (Medtronic, Minneapolis, Minnesota) bilaterally. Two weeks after DBS implantation, brief stimulation paradigms were performed to evaluate acute effects. He said there were many ideas in his mind. With 8 volts, talkativeness, euphoria, grandiosity, and the flight of ideas were aggravated. (euphoria 10 points, obsession 0 points)

**3. Discussion** This case suggests that bilateral anterior limb stimulation of the internal capsules may induce hypomania-like syndrome, characterized by talkativeness, grandiosity, euphoria and the flight of ideas. The finding was noted at the ventral contacts (0 and 1) and aggravated with higher voltage ( $\geq 4$  volts). To our knowledge, this is the first description of an ethnic Chinese male with OCD who developed hypomania-like syndrome induced by DBS.

**4. Conclusion** In this case, we discussed hypomania-like syndrome induced by bilateral stimulation of the anterior limbs of the internal capsules. Our patient demonstrated an improved mood with this stimulation. This may suggest the use of DBS at the nucleus accumbens or anterior internal capsule as a treatment for depression.

## The Effectiveness of Low Dose of Fluvoxamine on Trichotillomania

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Trichotillomania is considered part of a spectrum of OCD, serotonergic medication was found to be effective for treating this condition. In the present study, we reported a case of trichotillomania who was successfully treated with a low dose of fluvoxamine. An 18-year-old female complains continued hair-pulling at her scalp. Severe hair loss was found in the temporoparietal and occipital areas on her head. She was evaluated using The Massachusetts General Hospital Hairpulling Scale (MGHHS) and an actual-pulling subscale of the MGHHS (MGHHS-AP), and her MGHHS and MGHHS-AP scores were 21 and 9, respectively. Fluvoxamine was started at 25 mg/day, and her MGHHS and MGHHS-AP scores were still 19 and 8, respectively after 2 weeks of the treatment. The fluvoxamine dosage was increased to 50 mg/day, and her MGHHS and MGHHS-AP scores dropped to 14 and 6, respectively, at 2 weeks after the increase in fluvoxamine dosage. The fluvoxamine dosage was subsequently increased to 75 mg/day. Two weeks after this increase, her MGHHS and MGHHS-AP scores had decreased to 9 and 4, respectively. Her hair-pulling behavior dramatically improved, resulting in the re-growth of hair on her scalp. We monitored her plasma levels of fluvoxamine, and observed a plasma fluvoxamine level of 55.0 ng/ml at a dose of 75 mg/day. The most important finding in the present study was that our case responded to a low dose with a low plasma concentration of fluvoxamine. Therefore, slow titration of fluvoxamine might be ideal, because some trichotillomanic patients might be relieved with a low dose of fluvoxamine.

## Region-specific Increase in the Hippocampal Synaptic Vesicle Protein 2A (SV2A) Following Pentylentetrazole Kindling

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Abnormal seizure susceptibility in kindled animals is thought to be caused by various mechanisms including altered neurotransmitter release. Recent studies showed that amygdala kindling changes the hippocampal levels of vesicle-secretory machinery proteins such as soluble N-ethylmaleimide sensitive factor attachment protein receptor (SNARE) complexes. Here we evaluated the effects of pentylentetrazole (PTZ) kindling on the levels of SNARE complexes and SNARE effectors, synaptic vesicle protein 2A (SV2A), Munc18-1, N-ethylmaleimide sensitive factor (NSF) and soluble NSF attachment protein ( $\alpha$ -SNAP), in mice. Male ddY mice were treated with PTZ (40 mg/kg) or vehicle (control) every week for 15 days to induce kindling. The brains were removed from the PTZ-kindled mice, homogenized and subjected to Western blot analysis for SNARE complexes and SNARE effectors. In PTZ-kindled mice, SV2A level in the hippocampus was significantly elevated as compared to the control while the SNARE complexes level remained unaltered. None of the levels of other SNARE effectors that regulate assembling (i.e., Munc18-1) or disassembling (i.e., NSF and  $\alpha$ -SNAP) of SNAREs, was affected by PTZ kindling. We also examined the SV2A levels in the cerebral cortices, striatum and cerebellum, but no significant changes were observed in any of above structures. The present study demonstrated that PTZ kindling region-specifically elevates the hippocampal SV2A level, which may contribute to altered neurotransmission release and/or increased seizure susceptibility in kindled animals.

## A Case of Persistent Disturbance of Consciousness Due to Lithium Intoxication

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Lithium induces various toxic symptoms, which are usually improved by elimination of the serum level of lithium. Herein, we describe a valuable case of lithium intoxication, showing a persistent disturbance of consciousness after removal of lithium from serum. The patient was a 71-year-old woman diagnosed with a bipolar II disorder. In September, X-1, she developed hypomania. By pharmacotherapy with risperidone, hypomania was improved, but a depressive state appeared. Next, pharmacotherapy was switched to lithium, and the dose of lithium was gradually increased to 800 mg/day. In June, X, she showed delirium with disorientation and dressing apraxia and was subsequently admitted to our medical center. On admission, because serum concentration of lithium was elevated to 1.30 mEq/L, and EEG recording demonstrated diffuse  $\delta$  waves without abnormality on brain CT and MRI imaging except lacunar infarctions, chronic lithium intoxication was diagnosed. By a fluid therapy, serum concentration of lithium was decreased to 0.06 mEq/L by the seventh day of admission, however, both consciousness disturbance and diffuse  $\theta$  waves on EEG remained. On the 21st day, the disturbance of consciousness and the EEG findings were finally normalized. Because lithium has low permeability through the brain blood barrier, serum level of lithium dissociates from the brain level. Therefore, chronic lithium intoxication could induce protracted symptoms. Particularly in the presence of advanced age and organic factor in the brain, lithium administration requires caution and the monitoring of symptoms.

## 5-HT<sub>1A</sub> and 5-HT<sub>2</sub> Receptor-mediated Inhibition of Absence-like Seizures in Groggy Rat, the Novel Rat Model of Epilepsy

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The groggy (GRY) rat has a missense mutation in the P/Q-type voltage-gated Ca<sup>2+</sup> channel  $\alpha_{1A}$  subunit gene and exhibits spontaneous absence-like seizures associated with spike-and-wave discharges (SWDs) at the age of 8 weeks or older. To explore the role of serotonergic system in modulating absence seizures, we examined the effects of 5-HT<sub>1A</sub> and 5-HT<sub>2</sub> agonists on the incidence of SWDs in GRY rats chronically implanted with EEG electrodes. Behavioral observation and EEG recording were made for 15 min before, 15-30 and 45-60 min after the administration of 8-OH-DPAT (5-HT<sub>1A</sub> agonist), DOI (5-HT<sub>2</sub> agonist) or vehicle. In the experiments using antagonists, WAY-100135 (5-HT<sub>1A</sub> antagonist), ritanserin (5-HT<sub>2</sub> antagonist) or methiothepin (subtype non-selective 5-HT antagonist) was given to GRY rat 30min before the 8-OH-DPAT or DOI administration. GRY rats exhibited absence-like seizures with a total SDW duration of about 300-400 sec/15 min. Either treatment of GRY rats with 8-OH-DPAT or DOI (0.3-1mg/kg, i.p.) significantly inhibited the incidence of SWDs in a dose-dependent manner. These inhibitory effects of 8-OH-DPAT and DOI were antagonized by WAY-100135 and ritanserin, respectively. In addition, methiothepin antagonized the actions of both 8-OH-DPAT and DOI while it slightly augmented SWD induction by itself, possibly reflecting its inverse agonistic action. The present study shows that stimulation of 5-HT<sub>1A</sub> or 5-HT<sub>2</sub> receptors can attenuate the incidence of SWDs in GRY rat, implying a potential role of serotonergic system in alleviating absence seizures.



## The Effects of Exercise or Sound on Dopaminergic Brain Functions

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On the basis of calcium-dependent dopamine synthesis, the effect of exercise or sound on brain functions was investigated through animal experiments. *Effect of exercise:* Exercise increases serum calcium levels, and the calcium is transported to the brain. This in turn enhances brain dopamine synthesis through a calmodulin-dependent system, and increased dopamine levels regulate various brain functions. There are abnormally low levels of dopamine in the neostriatum and nucleus accumbens of epileptic EL mice and spontaneously hypertensive rats (SHR). The low dopamine levels were improved following central administration of calcium chloride. Dopamine levels and blood pressure in SHR were also normalized by exercise. In EL mice, convulsions normalized dopamine levels and physiologic functions. These findings suggest that exercise or convulsions affect brain functions through calcium-dependent dopamine synthesis. *Effect of sound:* Blood pressure in SHR was reduced by exposure to Mozart's music (K.205), and the effect vanished when the dopamine-synthesizing pathway was inhibited. Exposure to sound also increased serum calcium levels and neostriatal dopamine levels. These results suggest that sound leads to increased dopamine synthesis in the brain, thus causing a reduction in blood pressure.

**Conclusions:** Exercise and sound might regulate and/or affect various brain functions through dopaminergic neurotransmission, and might therefore be effective for rectification of symptoms in diseases that involve dopamine dysfunction, such as Parkinson's disease or dementia with Lewy bodies.

## Motive Behind Moving and Staying in Conditioned Place Preference: An Examination by Recording Hippocampal Theta Rhythm in Rats

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Conditioned place preference (CPP) is widely used to detect the rewarding effect of drugs, as well as natural rewards such as food and sexual experience. CPP is thought to be based on the Pavlovian conditioning between the environment and the reward, but the neural mechanisms underlying CPP are still not well understood. Especially, one of the critical questions, why the body moves toward the drug-paired side, is unsolved. The purpose of present study is to reveal the questions to analyze animal behavior and hippocampal local field potential (LFP), especially theta rhythm. In results, we recorded hippocampal LFP and animal behaviors through procedure of CPP by cocaine from 8 rats. We observed that the appearance of phase locked theta activity before entering into cocaine paired side after conditioning was at earliest timing and the offset of theta occurred after entering there. This tendency of phase locked theta was particularly stronger at long staying in drug paired side than that of short staying. Phase locked theta in approaching to the reward has been thought to represent reward expectation, and its offset has been thought to get the reward in previous studies. Then, the motive behind moving and staying in CPP apparatus until drug-free after conditioning is thought that drug paired environment induced reward expectation and staying there is reward for animals that experienced addictive drug in itself.

## Comparative Study of the Effects of GR103691 and Edaravone on Ischemia-reperfusion Injury

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Previous results from our laboratory have demonstrated that GR103691 (GR) has protective effects against hypoxia-reoxygenation (H/R)-induced cell death, a model of ischemia-reperfusion (I/R) injury, in HT22 cells, originated from mouse hippocampal neurons. In order to characterize further the protective profiles of GR in the hippocampus, we compared the effects of GR on I/R-induced cell death in both *in vivo* and *in vitro* models to those of Edaravone (EDA), a free radical scavenger for cerebral protection. In HT22 cells, GR and EDA suppressed H/R-induced cell death, determined by lactate dehydrogenase release, in a concentration-dependent manner in the same concentration range. A marked elevation of intracellular reactive oxygen species (ROS) was observed 3 h after reoxygenation, and this elevation of ROS was also suppressed by GR (3 μM) and EDA (10 μM). Histochemical analysis of the degenerated cells stained by Fluoro-Jade B (FJB)- and single-stranded DNA (ssDNA)-positive cells showed that forebrain ischemia by bilateral carotid artery occlusion for 17 min induced selective neuronal death in the CA1 area 72 h after the reperfusion in C57BL/6J mice. Intravenous injections of EDA (10 mg/kg, 3 times; 0, 24 and 48 h after the reperfusion) and GR (10 mg/kg, the same schedule as EDA) decreased both FJB- and ssDNA-positive cells in this area. These results suggest that the protective effects of GR against I/R-induced cell injury *in vivo* and *in vitro* are comparable to those of EDA, and that GR is useful as a lead compound of new anti-ischemic drugs.

## Molecular Basis of Sustained MDMA Induced Augmentation of 5-HT Release in Raphe Serotonergic Slice Culture

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3,4-Methylenedioxymethamphetamine (MDMA) is a widely abused, psychoactive drug, which induces short- and long-term neuropsychiatric behaviors. MDMA is known to be a substrate for 5-HT transporter (SERT), and induces 5-HT release via reverse transport (efflux). Recently, we reported that sustained exposure of raphe slice cultures to MDMA caused the augmentation of 5-HT release, but little is known about the molecular mechanisms behind this augmentation. First, we investigated whether the augmented 5-HT release was caused by facilitation of efflux via SERT or exocytotic 5-HT release in the synaptosomes prepared from cultures exposed to MDMA for 4 days, [<sup>3</sup>H]5-HT efflux was not changed, compared to control. Next, we examined the effect of tetrodotoxin (TTX) on 5-HT release, in comparison to that of SSRI (*i.e.* 5-HT efflux), and found that 5-HT release without sustained MDMA was SSRI-sensitive and TTX-insensitive, while 5-HT release after MDMA was TTX-sensitive and SSRI-insensitive. These results suggest that the rise of Ca<sup>2+</sup>-dependent exocytotic release of 5-HT, but not efflux via SERT, is responsible for the augmentation by sustained MDMA. To elucidate the mechanisms of the development of this augmentation, we investigated the contribution of 5-HT<sub>1A</sub> and 5-HT<sub>1B</sub> receptors. But 4 days co-treatment of neither 5-HT<sub>1A</sub> antagonist nor 5-HT<sub>1B</sub> antagonist suppressed the augmentation. On the other hand, 4 days co-treatment of AMPA/kainate-type glutamate receptor antagonist blocked the development. Therefore, glutamatergic system may play a key role in the development of the augmentation.

### Glia-derived Neurotrophic Factor Expression Promotion in Cultured Rat Cortical Astrocytes Exposed to Nicotine

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Nicotine has been shown to protect neurons from cell death. This study was aimed at the investigation of the mechanisms underlying signaling mediated by nAChRs in cultured rat cortical astrocytes. RT-PCR analysis revealed constitutive expression of ten different nAChR subunits in cultured rat cortical astrocytes. Exposure to nicotine selectively induced mRNA expression of glia-derived neurotrophic factor (GDNF) amongst different neurotrophic factors in cultured cortical astrocytes. Exposure to nicotine significantly increased the luciferase activity in cortical astrocytes transfected with the luciferase reporter plasmid linked to the GDNF promoter. These results suggest that nAChRs may be functionally expressed by rat cortical astrocytes to induce mRNA expression of GDNF through gene transactivation toward neuroprotection.

### Involvement of the Inducible cAMP Early Repressor (ICER) Gene in Behavioral Sensitization to Methamphetamine

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The inducible cyclic adenosine monophosphate (cAMP) early repressor (ICER) is highly expressed in the central nervous system and functions as a repressor of transcription of several cAMP-response element binding proteins (CREB). We have tested METH-induced conditioned place preference (CPP) and locomotor sensitization in wildtype mice, ICER knockout mice, and ICER I overexpressing mice and found that ICER acts a negative regulator for METH-induced locomotor sensitization, although ICER had minimal effects on METH-induced CPP. In an experiment assessing METH-induced locomotor sensitization, both ICER wildtype mice and knockout mice displayed increased locomotor activity after continuous injections of METH. However, ICER knockout mice displayed a tendency toward higher locomotor activity compared with wildtype mice. Moreover, compared with wildtype mice, ICER I overexpressing mice displayed a significant decrease in locomotor activity after repeated METH administration. To elucidate the molecular components underlying the decreased locomotor sensitization in ICER I overexpressing mice, Western blotting was conducted to evaluate the METH-induced alterations of CREB expression in ICER I overexpressing mice and their littermates. Our results revealed that the increased expression of CREB in the striatum accompanying behavioral sensitization to METH in wildtype mice was blocked in ICER I overexpressing mice. These findings raise the possibility that ICER exerts negative effects on behavioral sensitization to METH by blocking the METH-induced up-regulation of CREB.

### Galantamine, But Not Donepezil, Improves Isolation Rearing-induced Deficits in Prepulse Inhibition: Implication of M<sub>1</sub> Muscarinic Acetylcholine Receptors

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Clinical studies show that galantamine, a weak acetylcholinesterase (AChE) inhibitor and allosteric potentiator of nicotinic acetylcholine (ACh) receptors (nAChRs), improves negative and cognitive symptoms in schizophrenia, while donepezil, a potent AChE inhibitor, does not. We have recently found that galantamine, but not donepezil, reversed isolation rearing-induced deficits of prepulse inhibition (PPI) in mice (*Psychopharmacology* **196**: 293-301, 2008). In addition, we unexpectedly found that the galantamine-induced improvements in PPI deficits were not prevented by the nAChR receptor antagonists. This paper reports possible mechanisms of the beneficial effect of galantamine in a model of isolation rearing-induced PPI deficits. Galantamine-induced improvements of PPI deficits were blocked by the muscarinic ACh receptor (mAChR) antagonists scopolamine and telenzepine (preferential for M<sub>1</sub> subtype). Like galantamine, the mAChR agonists oxotremorine and *N*-desmethylclozapine (selective for M<sub>1</sub> subtype) improved isolation rearing-induced PPI deficits. Galantamine, like donepezil, increased extracellular ACh levels in the prefrontal cortex. However, donepezil inhibited carbachol-induced Ca<sup>2+</sup> signal in SH-SY5Y cells, while galantamine did not. These findings suggest that galantamine improves isolation rearing-induced PPI deficits via mAChRs and the regulation of M<sub>1</sub> mAChRs may play key roles in the different effects of galantamine and donepezil.

### Early Environmental Enrichment Improves Some Behavioral Abnormalities in PACAP-KO Mice

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Clinical studies show that environmental factors as well as genetic factors play a key role in pathogenesis of many psychiatric disorders. Recent genetic analysis shows that genetic variants of the genes encoding pituitary adenylate cyclase-activating polypeptide (PACAP) are associated with schizophrenia. We have previously found that mice lacking the neuropeptide PACAP (PACAP-KO mice) display remarkable behavioral changes, including hyperactivity, abnormal jumping behavior and depression-like behavior, and prepulse inhibition (PPI) deficits. In the present study, we examined the effects of environmental factors on behaviors of wild-type and PACAP-KO mice. Locomotor activity was quantified using the Acti-Track system. Depression-like behavior was evaluated by the forced swim test. PPI responses were measured in a startle chamber (SR-LAB). Exposure to environmental enrichment for 4 weeks from 4-week-old attenuated the hyperactivity and jumping behavior, and shortened the immobility time in PACAP-KO mice, but did not improve PPI deficits. In contrast, exposure to environmental enrichment for 4 weeks from 8-week-old did not ameliorate the abnormal behaviors in PACAP-KO mice. There was no significant difference in the hippocampal protein levels of brain-derived neurotrophic factor (BDNF) between wild-type and PACAP-KO mice, and exposure to environmental enrichment increased BDNF expression in both groups. These findings indicate that exposure to environmental enrichment improves some, but not all, abnormal phenotypes in PACAP-KO mice and the effect is dependent on development.

## Effects of Neonatal NMDA Receptor Antagonism on Cognition in Adolescent Rats

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**Background:** The malfunction of glutamatergic neurotransmission in the neonatal or postnatal periods may be a risk factor for the appearance of neuroanatomical, neurochemical or functional changes that are characteristic of schizophrenia. Thus, the present study was undertaken to investigate whether blockade of N-methyl-D-aspartate (NMDA) receptors in the postnatal period can induce lasting cognitive dysfunctions that are relevant to schizophrenia.

**Methods:** Timed-pregnant Sprague-Dawley rats were purchased from the Department of Laboratory Animal Science, Peking University Health Science Center. The pups were combined and then cross-fostered to one of the lactating dams within 12 h of parturition, which was designated as Postnatal day 0 (PND 0). As often as possible, all litters were sex balanced. Pups were randomly assigned to one of two treatment groups: vehicle (saline) or MK-801 (0.25 mg/kg per injection). Beginning on PND5, pups received subcutaneous injections twice daily (09:00 and 16:00) for 5 days. Pups were weaned at PND21 and housed with their litter mates, three or four per cage. Beginning on PND42 (adolescence), they were tested for prepulse inhibition (PPI), locomotor activity, object recognition and working memory performed in Morris water maze task. All rats were tested in the same sequence.

**Summary of results:** Treatment with MK-801 impaired working memory in adolescent male rats, but not in female rats. Treatment did not affect PPI, locomotor activity or object recognition in males and females.

**Conclusion:** These results suggest that a brief disruption of NMDA receptors during a sensitive period of cortical development can produce selective cognitive deficits that are relevant to schizophrenia in male rats, but not in female rats.

## Pharmacological Treatment with Nicotine on Methamphetamine-induced Impairment of Sensorimotor Gating

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We have previously found that a disruption to prepulse inhibition (PPI) induced by methamphetamine (METH) is associated with impaired functioning of pallidotegmental neurons, which play a crucial role in PPI of the startle reflex, through the activation of GABA<sub>B</sub> receptors in pedunclopontine tegmental neurons (PPTg) in mice. Here, we examined the effect of nicotine on METH-induced impairment of PPI. Nicotine ameliorated the deficit in PPI induced by acute METH, and the ameliorating effect of nicotine was antagonized by nicotinic receptor antagonists such as methyllycaconitine and dihydro- $\beta$ -erythroidine. The acute METH-induced disruption of PPI was accompanied by suppression of c-Fos expression in the lateral globus pallidus (LGP) as well as its induction in the caudal pontine reticular nucleus (PnC) in mice subjected to the PPT test. Nicotine-induced amelioration of PPI deficits in METH-treated mice was accompanied by a reversal of the changes in c-Fos expression in both the LGP and PnC to the basal level. Finally, acetylcholinesterase inhibitors, donepezil and galantamine, dose-dependently reversed the disruption of PPI induced by METH. Nicotine receptors may therefore constitute a putative target in the treatment of neuropsychiatric disorders with sensorimotor gating deficits, such as schizophrenia and METH psychosis, and this therapeutic effect is associated with normalization of the pallidotegmental GABAergic neurons.

## Effect of Olanzapine on Glucose Transport System in 3T3-L1 Adipocytes

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Olanzapine, one of the second-generation atypical antipsychotics (SGAs), has shown relative advantages in patient adherence and outcomes. However, olanzapine has been associated with higher incidence of weight gain, hyperglycemia and hyperlipidemia than most of the other SGAs. We investigated effects of olanzapine and haloperidol on glucose transport system and cellular energy homeostasis in 3T3-L1 adipocytes. When adipocytes were treated with olanzapine (10 $\mu$ M) for 24 h, the basal glucose uptake was significantly reduced but not the insulin-stimulated glucose uptake. Haloperidol (10 $\mu$ M) showed no effect on glucose transport. These results suggested that olanzapine inhibits GLUT1 but not GLUT4 function. The expression of GLUT1 mRNA and protein was not changed by olanzapine (10 $\mu$ M). Treatment with olanzapine (10 $\mu$ M) for 24 h significantly increased the intracellular ATP levels in 3T3-L1. Blodgett et al. have reported that an elevation in the intracellular ATP levels inactivates GLUT1 function. We tentatively conclude that olanzapine inhibits glucose transport by inactivating GLUT1 through the increased intracellular ATP levels.

## Modulation of D-Amino Acid Oxidase Activity as a Novel Strategy for the Treatment of Schizophrenia

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D-Amino acid oxidase (DAO) has been proposed to be involved in the decreased glutamatergic neurotransmission in schizophrenia. Here we show the inhibitory effect of a classical antipsychotic drug, chlorpromazine, and an atypical antischizophrenic drug, risperidone, on human DAO catalytic activity. As for chlorpromazine, human DAO was inhibited to a lesser degree ( $K_i = 0.7\text{mM}$ ) than porcine DAO. Since chlorpromazine is known to induce phototoxic or photoallergic reactions and also to be transformed into various metabolites, we examined the effects of white light-irradiation on chlorpromazine. We found that irradiation triggered the oligomerization of chlorpromazine molecules and the oligomerized chlorpromazine showed a mixed type inhibition with inhibition constants of low  $\mu$ M range, indicative of enhanced inhibition. The effect of risperidone was then tested using rat C6 cells and stable C6 transformant over-expressing mouse DAO (designated as C6/DAO) as well as pig kidney epithelial cell line (LLC-PK<sub>1</sub>). Risperidone has a partial uncompetitive inhibition effect with  $K_i$  value of 41  $\mu$ M, on purified human DAO. Furthermore, risperidone exhibited a protective effect from D-amino acid- and oxidative stress-induced cell death in both C6/DAO and LLC-PK<sub>1</sub> cells. Taken together, these results indicate the involvement of intracellular DAO activity in extracellular D-serine metabolism and also suggest that modulation of DAO activity by chlorpromazine and risperidone might contribute to the therapeutic antischizophrenic effects of these drugs.

## Norzotepine, a Major Active Metabolite of Zotepine, Exerts Atypical Antipsychotic and Anti-depressive Actions through its Potent Noradrenaline Reuptake Inhibitory Actions

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Zotepine (ZTP) is an antipsychotic drug, with low extrapyramidal symptoms (EPS) liability. Norzotepine (norZTP) has been postulated to be a major metabolite of ZTP in human. In the present study, we evaluated norZTP in various *in vitro* studies and animal models of psychosis, depression and EPS, and compared the profiles with those of ZTP. While both compounds showed similar binding profiles, norZTP showed fourteen times more potent noradrenaline reuptake inhibition than zotepine (IC<sub>50</sub>: 17nM vs. 250nM). In the pharmacokinetic study, the concentration of norZTP was under detection limit both in plasma and brain after 3.2mg/kg (i.p.) injection of ZTP in mice. Both ZTP and norZTP showed good brain permeability (K<sub>p</sub>, brain: 22, 24) when each administered alone in mice. In the methamphetamine-induced hyperlocomotion model, norZTP and ZTP showed similar antipsychotic effects. On the other hand, norZTP did not induce catalepsy unlike ZTP. In the reserpine-induced hypothermia model and forced swim test in mice, norZTP showed significant effect at the effective doses for its antipsychotic action, while ZTP neither antagonized reserpine-induced hypothermia nor showed the antidepressant effect. Present results demonstrate that norZTP has potent noradrenaline reuptake inhibition, that presumably attributes to its antidepressant effect and low EPS propensity. Considering that plasma concentration of norZTP is comparable with that of ZTP in humans, norZTP might contribute to the unique clinical profiles of the mother compound, ZTP.

## The Effects of Antipsychotic Drugs on BDNF Promoter Activity in SH-SY5Y Human Neuroblastoma Cells - An Involvement of PI3K-AKT Signaling Pathway

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**Purpose:** Recent clinical studies have suggested that treatment with atypical antipsychotic drugs such as olanzapine may prevent progressive alterations of brain structure in patients with schizophrenia. However, the molecular mechanisms underlying these effects remain to be determined. We investigated the neuroprotective effects of antipsychotic drugs and the mechanisms of action of olanzapine in human neuroblastoma SH-SY5Y cells. **Methods:** Luciferase assays was adapted for the evaluation of the effect of antipsychotic drug on the BDNF (Brain-derived neurotrophic factor) promoter activity. To explore the drugs action, western blot was performed to examine the expression of p-GSK3 $\beta$  (glycogen synthase kinase-3 $\beta$ ), downstream of PI3K (phosphatidylinositol 3-kinase) -AKT pathway, and a possible involvement of protein kinases also investigated on BDNF activity. **Results:** The typical antipsychotic drug haloperidol did not show the significant difference of BDNF promoter activity. Amisulpiride and ziprasidone failed to show significant differences of BDNF promoter activity. Olanzapine (p<0.05), quetiapine (p<0.05), risperidone (p<0.05) showed increased BDNF promoter activity according to the increase of dose. Aripiprazole showed increased BDNF promoter activity only with higher dose (P<0.001). Particularly, western blot was showed that olanzapine increased the levels of p-GSK3 $\beta$  at a 100 $\mu$ M dose which BDNF promoter activity was robustly elevated. It was also found that wortmannin (0.01 $\mu$ M), an inhibitor of PI3K, significantly attenuated the stimulatory effect of olanzapine on BDNF promoter activity (p<0.0001), whereas H-89, an inhibitor of PKA (protein kinase A), did not affect. **Conclusions:** These results suggest that some atypical antipsychotic drugs have neuroprotective effect and this neuroprotective effect might be related to antipsychotic action through PI3K-AKT pathway **Key words:** BDNF, PI3K, PKA, antipsychotic drugs

## Involvement of Dopamine-D<sub>2</sub> and Serotonin<sub>1A</sub> Receptors in the Ability of Atypical Antipsychotic Drugs to Induce Prefrontal Dopamine Release

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This study investigated the mechanisms underlying the ability of atypical antipsychotic drugs to increase DA release in the mPFC, using microdialysis with dual probe implantation of awake, freely moving rats. When applied locally into the VTA, the DA partial agonist aripiprazole, like the full D<sub>2</sub> agonist quinpirole, decreased extracellular DA levels in the mPFC. By contrast, local application into the VTA with perospirone, an atypical antipsychotic with high affinity for both D<sub>2</sub> and serotonin (5-HT)<sub>1A</sub> receptors, as well as raclopride, a selective D<sub>2</sub> antagonist, increased extracellular mPFC DA levels. Interestingly, clozapine, a prototype agent of atypical antipsychotics, had no effect on extracellular mPFC DA levels. Thus, depending on the manner of binding to presynaptic D<sub>2</sub> autoreceptors, different types of atypical antipsychotic drugs may have distinct effects on the activity of VTA DA neurons. When applied directly into the mPFC, aripiprazole and clozapine, but not perospirone or risperidone, increased extracellular DA levels. These effects were attenuated by pretreatment with a 5-HT<sub>1A</sub> antagonist. The ability of clozapine to induce mPFC DA release was also attenuated by co-perfusion with the selective D<sub>2</sub> antagonist. Taken together with distinct receptor binding profiles of each drug, the interaction between weak D<sub>2</sub> antagonism and potent 5-HT<sub>1A</sub> agonism in the local circuitry of the mPFC may contribute to the ability of clozapine and aripiprazole to enhance prefrontal DA release. KAKENHI17591219

## Protective Effects of Antipsychotics Against MPP<sup>+</sup>-induced Apoptosis in PC12 Cells

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**Objectives:** Recent clinical studies have suggested that treatment with second generation antipsychotics (SGAs) may prevent progressive alterations of brain structure in patients with schizophrenia. To confirm these findings, we investigated the protective effects of the SGAs, such as olanzapine, aripiprazole, clozapine and ziprasidone on the N-methyl-D-phenylpyridinium ion (MPP<sup>+</sup>)-induced apoptosis in PC12 cells. **Methods:** PC12 cells were cultured with SGAs in medium with or without MPP<sup>+</sup> for 48-72 hr. Haloperidol, first generation antipsychotics (FGA), was used for comparison. We determined the effects of the drugs on cell viability, superoxide dismutase (SOD) activity, reactive oxygen species (ROS) levels and Bax levels against the cytotoxicity of MPP<sup>+</sup> inducing oxidative stress. **Results:** (1) MPP<sup>+</sup> (250  $\mu$ M) reduced cell viability to about 66% (p<0.01). Olanzapine (10-100  $\mu$ M) and aripiprazole (10-50  $\mu$ M) significantly inhibited cell death by MPP<sup>+</sup> (25-35% and 15-20%, respectively, p<0.05, p<0.01), whereas ziprasidone (10-50  $\mu$ M) did not affect this protective effect. Clozapine (10-50  $\mu$ M) strongly increased cell death due to MPP<sup>+</sup> in PC12 cells (20-40%, p<0.01), but did not show the toxic effect under MPP<sup>+</sup>-free conditions. The FGA haloperidol (10-50  $\mu$ M) did not show the significant difference of cell viability. (2) MPP<sup>+</sup> (1 mM) reduced SOD activity to about 63% (p<0.01). Olanzapine and aripiprazole significantly prevented the MPP<sup>+</sup>-induced decrease in SOD activity in a dose-dependent manner (20-60% and 20-40%, respectively, p<0.05, p<0.01), whereas ziprasidone and haloperidol did not affect this protective effect. Clozapine induced a strong reduction of SOD activity in MPP<sup>+</sup>-treated cells (20-25%, p<0.01), but had no effect on SOD levels under MPP<sup>+</sup>-free conditions. (3) One mM of MPP<sup>+</sup> reduced ROS levels to about 110% (p<0.01). Olanzapine (10-100  $\mu$ M), aripiprazole (10-100  $\mu$ M) and ziprasidone (10-100  $\mu$ M) significantly attenuated the MPP<sup>+</sup>-induced increase in ROS formation in a dose-dependent manner (70-80%, 40-50% and 50-60%, respectively, p<0.05, p<0.01). However, the MPP<sup>+</sup>-induced increase in ROS levels was not blocked by treatment with clozapine (10-100  $\mu$ M) and haloperidol (10-100  $\mu$ M). (4) MPP<sup>+</sup> (1 mM) significantly increased the levels of Bax expression to about 80% (p<0.01). Olanzapine (1-10 $\mu$ M), aripiprazole and ziprasidone significantly attenuated the MPP<sup>+</sup>-induced increase in Bax protein levels (60-70%, 70-80% and 50-60%, respectively, p<0.05, p<0.01). However, the MPP<sup>+</sup>-induced increase in Bax levels was not blocked by treatment with clozapine and haloperidol. Moreover, clozapine and haloperidol strongly increased the expression of Bax under MPP<sup>+</sup>-free conditions (40-50% and 35-45%, respectively, p<0.05). **Conclusions:** Olanzapine, aripiprazole and ziprasidone, but not clozapine and haloperidol showed protective effects against MPP<sup>+</sup>-induced apoptosis in PC12 cells. These results might suggest that some second generation antipsychotics have protective effects and these effects might be helpful to understand their novel effects in not only improving the profiles of positive, negative and cognitive symptom but also a low incidence of extrapyramidal side-effects in patients with schizophrenia. **Key words:** First generation antipsychotics, Second generation antipsychotics, PC12 cells, Apoptosis, MPP<sup>+</sup>, SOD, ROS, protective effect

### Effects of Quetiapine on Frontal Transmission in Rat Brain

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Quetiapine (QTP), is effective in schizophrenia and mood disorders, but induces seizures compared to other antipsychotics. To explore mechanisms of action of QTP, we determined its effects on extracellular levels of monoamine, GABA and glutamate in medial prefrontal cortex (mPFC) using microdialysis, and neuronal firing (NF) in ventral tegmental area (VTA), locus coeruleus (LC), dorsal raphe nucleus (DRN), and mediodorsal thalamic nucleus (MTN) by telemetry in free-moving rats. QTP activated NF in VTA, LC, and MTN without affecting that in DRN. QTP increased extracellular levels of norepinephrine, dopamine, and glutamate without affecting serotonin or GABA levels in mPFC. Stimulatory effects of QTP on norepinephrine and dopamine were mediated by positive AMPA/glutamatergic- and negative GABA-mediated NMDA/glutamatergic regulation. Dopaminergic terminal projecting from VTA received inhibitory GABA/NMDA regulation, but not stimulatory AMPA regulation. However, both dopaminergic and noradrenergic terminals from LC received stimulatory AMPA regulation from MTN, but not inhibitory GABA/NMDA regulation. These findings correlating NF in nuclei with neurotransmitter release suggested that effects of QTP on transmission in mPFC depend on activated neuronal projections located outside mPFC. Furthermore, positive interaction between LC and MTN afferents are potentially important in pharmacological mechanisms of transmitter regulation by QTP and hint at mechanisms underlying atypical profile of QTP for treatment of schizophrenia, as mood stabilizer and proconvulsant.

### Effects of Blonanserin, a Novel Antipsychotic Agent, on the Forebrain Fos Expression in Mice

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Blonanserin (BNS) is a novel antipsychotic agent that preferentially interacts with dopamine D<sub>2</sub> and 5-HT<sub>2A</sub> receptors. To assess the atypical antipsychotic property of BNS, we studied its effects on catalepsy induction and forebrain Fos expression in mice and compared them to those of haloperidol (HAL). Catalepsy test was carried out 30 min after administration of BNS (0.3-10 mg/kg, p.o.) or HAL (0.3-3 mg/kg, p.o.) and, 90 min later, the brain were removed for Fos expression analysis. Immunohistochemical staining of Fos protein was performed by the ABC methods and the number of Fos-immunoreactivity (Fos-IR) positive cells was counted. HAL significantly prolonged catalepsy time at doses of 1 mg/kg or more whereas BNS did not at any dose tested. BNS and HAL markedly enhanced Fos expression in the shell (AcS) and core (AcC) region of the nucleus accumbens, and the dorsolateral striatum (dlST), but barely in the cerebral cortex or lateral septum. Extents of striatal Fos expression by BNS was smaller than those in AcS, and BNS tended to show a ceiling in its striatal actions. In contrast, HAL dose-dependently increased the striatal Fos expression, the enhancement of which was as prominent as in AcS. BNS showed higher atypical indices (i.e., Fos expression in the AcS minus that in the dlST) than those of HAL. These results demonstrate that BNS behaves as an atypical antipsychotic agent both in inducing extrapyramidal symptoms and in modulating the forebrain Fos expression.

### Serotonergic Mechanism in Regulating Antipsychotic-induced Extrapyramidal Motor Disorders: Potential Role of 5-HT<sub>3</sub> and 5-HT<sub>6</sub> Receptors

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5-HT<sub>2</sub> and 5-HT<sub>1A</sub> receptors play an important role in modulating antipsychotic drug (APD)-induced extrapyramidal side effects (EPS). To further clarify the serotonergic mechanisms in regulating EPS, we studied the effects of 5-HT stimulants and various 5-HT antagonists on haloperidol (HAL)-induced bradykinesia and catalepsy in mice. EPS were evaluated by catalepsy and pole tests 30 min after the HAL (0.3 mg/kg, i.p.) injection. A 5-HT precursor, 5-hydroxytryptophan (5-HTP), or selective 5-HT reuptake inhibitors (SSRI), fluoxetine and paroxetine, were given 60 and 30 min before the HAL injection, respectively. For the 5-HT receptor antagonism, 5-HT<sub>2</sub> (ritanserin), 5-HT<sub>3</sub> (ondansetron), 5-HT<sub>6</sub> (SB-258585) or 5-HT<sub>7</sub> (SB-269970) antagonist was administered simultaneously with 5-HTP or SSRI. Treatment with 5-HTP (25-100 mg/kg, i.p.) dose-dependently augmented HAL-induced bradykinesia in the pole-test and catalepsy. Fluoxetine (5-20 mg/kg, i.p.) and paroxetine (5-20 mg/kg, i.p.) also enhanced the induction of EPS symptoms by HAL. The potentiation of HAL-induced EPS by 5-HTP was significantly reduced by ritanserin, ondansetron and SB-258585, but was unaffected by the SB-269970. Furthermore, an enhancement of EPS by fluoxetine was also antagonized ondansetron or SB-258585. These results suggest that stimulation of serotonergic system enhances the APD-induced EPS, which seems to be mediated by not only 5-HT<sub>2</sub>, but also 5-HT<sub>3</sub> and 5-HT<sub>6</sub> receptors. EPS should be carefully monitored especially in the combination therapy with APD and antidepressants for affective disorders.

### Receptor Reserve-dependent Properties of Antipsychotics at Human Dopamine D<sub>2</sub> Receptors

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Aripiprazole is the first dopamine D<sub>2</sub> receptor partial agonist approved in the world for the treatment of schizophrenia. Aripiprazole has demonstrated a relatively favorable side effect profile compared to other commonly prescribed antipsychotics, including a low propensity for parkinsonism, hyperprolactinemia, and body weight gain. In an effort to elucidate aripiprazole's pharmacological activity in relation to clinically relevant fluctuation of dopamine D<sub>2</sub> receptor reserves, we compared the properties of aripiprazole to other antipsychotics, quetiapine, clozapine, olanzapine, ziprasidone, risperidone and haloperidol using forskolin-stimulated cAMP accumulation in clonal CHO cell lines expressing low and high densities of human dopamine D<sub>2S</sub> receptors (hD<sub>2S</sub>-Low and hD<sub>2S</sub>-High, respectively). In hD<sub>2S</sub>-Low cells lacking receptor reserves for dopamine, all drugs antagonized dopamine responses, and their potencies correlated well with respective affinities. In hD<sub>2S</sub>-High cells possessing receptor reserves, all antipsychotics except aripiprazole antagonized dopamine responses, and their antagonist potencies were less than those in hD<sub>2S</sub>-Low cells treated with the equal dopamine concentration. In contrast, aripiprazole acted as a full agonist. These data suggest that the level of receptor reserves influence antagonist potencies and side effects associated with antipsychotics. Aripiprazole's unique receptor reserve dependent properties may account for its favorable tolerability in the clinical setting.

### Identification of Antidepressant Ingredients in Korean Ginseng Root Using the Animal Model of Menopausal Depressive-like State in Ovariectomized Mice: A Possible Interaction with Sigma-1-receptor

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The development of new remedies for alleviating menopausal depression in women receives greater attention. Although gender differences exist in both the features of depressive state and the effectiveness of antidepressants, virtually all the antidepressants has been preclinically evaluated in male animals. We noticed it and have recently developed a procedure for predicting drug effects on menopausal depressive-like state in female mice (Psychopharmacology, 2005;2006). Using this animal model, we evaluated the effect of ginseng root, which is one of the earliest known materials for keeping an aged-women healthy. As compared with red ginseng, white ginseng showed a weak effect on menopausal depressive-like state in mice. Consequently, we employed the constituents of red ginseng root in this study. We found that only saponin fraction prevented the development of menopausal depressive-like state in ovariectomized mice, and that ginsenoside Rb<sub>1</sub> is one of the psychoactive components of ginseng root. Because either saponin fraction or ginsenoside Rb<sub>1</sub> did not affect the general motor activity of ovariectomized mice, the preventive effect of these materials is not due to an augmentation of motor behavior. Furthermore, we found that (+)-pentazocine, sigma-1-receptor agonist, prevented the suppressive effect of ginsenoside Rb<sub>1</sub> on our model. On the other hand, NE-100 could not antagonized the effect of ginsenoside Rb<sub>1</sub>. We anticipate that our findings provide a clue for developing a new therapy in the prevention or treatment of mood disorder in menopausal women.

### The Effect of Fluoxetine on Behaviors in Transient Forebrain Ischemic Gerbil

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**Objective:** This study aims to explore the effect of fluoxetine on memory, locomotor and depressive behavior in transient forebrain ischemic model of gerbil.

**Methods:** The two doses of fluoxetine (10, 40 mg/kg) or vehicle were intraperitoneally administered once 30 min before ischemic surgery in gerbil. Novel object recognition test, spontaneous motor activity, learned helplessness test were performed 4 days, 8 days, or 9 days, respectively, after sham or ischemic surgery.

**Results:** Fluoxetine treatment (40 mg/kg) significantly reduced recognition memory in sham operated gerbil. However, fluoxetine (10, 40 mg/kg) did not affect ischemia-induced impairment in recognition memory. The treatment of fluoxetine (10, 40 mg/kg) significantly inhibited locomotor hyperactivity induced by transient ischemia even though fluoxetine (40 mg/kg) did not affect spontaneous motor activity in the sham operated gerbils. Fluoxetine did not affect depressive behavior in sham and ischemic gerbils.

**Conclusion:** The treatment of fluoxetine inhibited ischemia - induced hyperactivity, but did not affect memory and depressive behavior in transient forebrain ischemic gerbils.

### A Possible Role of Sigma-1-receptors in Mediating the Effect of Progesterone on Menopausal Depressive-like State in Ovariectomized Mice

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Mood disorders in menopausal women are of increasing concern, and gender differences exist in both the features of depression and the effectiveness of antidepressants. Compared to the numerous studies of male rodents, information on females is limited. We recently developed a procedure for investigating menopausal depressive-like state in female mice: two weeks after bilateral ovariectomy, virtually all female mice remarkably prolonged the immobility time in the forced swimming test (Psychopharmacology, 2005; 2006). The prolongation of immobility time following ovariectomy was antagonized by either 17β-estradiol or clinically-used antidepressants. Recently, we also found that progesterone significantly prevented the prolongation of immobility time in a dose-dependent manner. Interestingly, the effective doses of estrogen remarkably increased in the uterine weight, whereas progesterone did not affected. Because it has been reported that sigma-1-receptors may participate in the mediation of depressive-like state in male rodents, we investigated the possible involvement of sigma-1-receptors in modulating the antidepressant-like effect of progesterone in ovariectomized mice. In contrast to previous report in male animals, (+)-pentazocine, agonist, antagonized the preventing effect of progesterone on ovariectomy-induced prolongation of immobility, and NE-100, sigma-1-receptors antagonist, did not alter the effect of progesterone. Our findings suggest that the role of sigma-1-receptors in mediating the immobility time might depends upon an endogenous estrogen levels.

### Enhanced Formation of 4-hydroxynonenal-adducted Proteins During Neuroregeneration after Neurodegeneration by TMT Treatment in the Hippocampal Dentate Gyrus

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Our previous study showed that trimethyltin chloride (TMT) causes neuronal loss in the hippocampal dentate gyrus selectively 2 days later, with recovery of the dentate gyrus 14 days afterward. Our previous reports have demonstrated that TMT-induced neuronal damage is caused by activation of cell death signals induced at least in part by oxidative stress. In this study, we evaluated if in vivo acute treatment with TMT produces formation of 4-hydroxynonenal (4-HNE), which is a major lipid peroxidation product, in the hippocampus of mice. A systemic injection of TMT (2.8 mg/kg, i.p.) produced a marked lipid peroxidation in the hippocampus on day 1 and afterward. Immunohistochemical studies revealed that formation of 4-HNE was seen selectively in the dentate gyrus on day 1 after TMT treatment. Immunoblot analysis revealed that TMT treatment produced a new 4-HNE-adducted protein, whose molecular weight is 48 kDa, in the dentate gyrus, but not in the CA subfield. Additionally, 4-HNE-adducted protein at 48 kDa was not shown in the cerebral cortex, striatum, hypothalamus, midbrain, cerebellum, and olfactory bulb. The 4-HNE-adducted protein was found from days 2 to 21, with a peak on day 10 after TMT injection. The 4-HNE-adducted protein was found in nucleus, cytosol, and microsomes fractions, but not in mitochondria fraction. Taken together, our results suggest that 4-HNE may be involved in both neurodegeneration at the early time window and neuroregeneration at the late time window after TMT treatment.

## Effects of Acute and Chronic Treatment with ADHD Drugs on the Extracellular Levels of Monoamine in Mouse Brain

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Atomoxetine and methylphenidate are widely used in the treatment of attention-deficit/hyperactivity disorder (ADHD). However, it is not known about the long-term effects of exposure to the drug on extracellular concentrations of monoamine neurotransmitters. In addition, neurochemical effects of atomoxetine and methylphenidate have not been studied in mice. Thus, the present study investigated, using *in vivo* microdialysis technique, the effects of acute and chronic treatment with these ADHD drugs on the extracellular levels of noradrenaline (NA), dopamine (DA) and serotonin (5-HT) in the prefrontal cortex (PFC) and striatum (STR) of adolescent mice. Acute treatment with atomoxetine (1 and 3 mg/kg) caused robust increases in extracellular NA and DA, but not 5-HT, levels in the PFC. Unlike the PFC, these monoamine levels in the STR were not changed. Acute treatment with 3 mg/kg methylphenidate also increased NA and DA levels in the PFC, but not in the STR, and it did not affect 5-HT levels in both brain regions. Atomoxetine-induced increases in NA, but not DA, levels in the PFC were markedly reduced in mice pretreated chronically with atomoxetine. On the other hand, pretreatment with methylphenidate did not affect the acute effect of methylphenidate on extracellular monoamine levels in the PFC. These observations suggest that ADHD drugs selectively affect catecholaminergic systems in the PFC of mice, and atomoxetine, but not methylphenidate, induces neurochemical desensitization of noradrenalinergic neurons in the PFC.

## Effects of Imipramine and Lithium on the Suppression of Cell Proliferation and Neurogenesis of Dentate Gyrus of Hippocampus in ACTH-treated Rats

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Abnormalities in the hypothalamic-pituitary-adrenal axis represent a risk factor for the occurrence or recurrence of a depressive episode. We previously reported that the decreasing effect of immobility time of tricyclic antidepressants, selective serotonin reuptake inhibitor and serotonin noradrenaline reuptake inhibitor are blocked by repeated adrenocorticotrophic hormone (ACTH) treatments in the rat forced swim test. The inhibition of the immobility decreasing effect of imipramine is reversed by coadministration of lithium and imipramine. Thus, we proposed that repeatedly ACTH-treated rats might serve as a valuable animal model for tricyclic antidepressant-resistant depressive conditions. The possibility that chronic antidepressant treatment increases cell proliferation and granule cell survival and is able to reverse the stress-induced decrease of hippocampal cell proliferation and neurogenesis. The effect of ACTH on neurogenesis in the brain is obscure. The present study was undertaken to investigate changes in cell proliferation and neurogenesis in the hippocampus of ACTH-treated rats. Interestingly, ACTH decreases the number of Ki-67-labeled cells in the dentate gyrus. The suppression of the number of Ki-67-labeled cells is reversed by the coadministration of lithium and imipramine, but not imipramine treatment only. These results suggest that chronic ACTH treatment causes hippocampal morphological changes, including atrophy and suppression of cell proliferation and neurogenesis.

## Aberrant Fear-related Behaviors in BSRP-TKO Mice

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Brain-specific receptor-like proteins (BSRPs) were predominantly expressed in the soma and dendrites of neurons and localized in the endoplasmic reticulum (ER). BSRPs form three isoforms including BSRP-A, BSRP-B and BSRP-C. *In situ* hybridization analyses, BSRP mRNA expressed in brain region including cerebellar cortex, hippocampus, olfactory bulb and cerebellum, especially (Miyazaki et al., FEBS Lett, 2006). In the present study, we performed fear-related behavioral analyses including fear conditioning task, elevated-plus maze task, marble burying task and light-dark task using BSRP-TKO mice. BSRP-TKO mice showed increased immobility time of tone-dependent memory, but not contextual-dependent memory in fear-conditioning task. In the elevated-plus maze task, BSRP-TKO mice increased the number of closed arm entry and decreased the number of open arm entry. In addition, BSRP-TKO mice showed increased of the number of marble buried in marble burying task and increased of entry time of open compartment in light-dark task. These data suggested that BSRP-TKO mice showed the increased of fear-related behaviors. In immunoblot analyses, the autophosphorylation of calcium-calmodulin-dependent protein kinase II (CaMKII) significantly increased in the lateral amygdala of BSRP-TKO mice. In conclusion, BSRP-TKO mice shows the increased of fear-related behaviors and augments of CaMKII activity in the lateral amygdala in immunoblot analyses. CaMKII activity in the lateral amygdala may relate to the aberrant fear-related behaviors.

## Antidepressant Like Effect of Sodium Butyrate and Its Biological Actions in the Rat Hippocampus

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Recent epigenetic studies using an animal model of depression, have proposed that the epigenetic regulation of gene expression, such as histone acetylation and DNA methylation, plays an important role in the pathophysiology of major depression. In line with this proposal, we first examined whether sodium butyrate (SB), histone deacetylase inhibitor, had an antidepressant effect using forced swim test (FST). Second, we investigated the mechanism of the antidepressant-like effect of SB using DNA microarray and real-time PCR. Third, we examined whether tricyclic antidepressant, imipramine, exhibited the same action found in SB. Chronic (once daily for 1w), but not single, administration of SB (1.2 g/kg) shortened the duration of immobility in Sprague-Dawley rats (8w, male) in FST 24 h after final administration. We found no behavioral change in the open field locomotor test and elevated plus maze test in response to chronic SB administration.

The analysis of the hippocampal gene expression profiles using DNA microarray followed by real-time PCR revealed the increased levels of transthyretin (Ttr) mRNA in rats chronically treated with SB. In addition, chronic administration of imipramine (15 mg/kg, 1w and 2w) didn't affect the levels of hippocampal Ttr mRNA. Ttr is reported to be involved in stress vulnerability and pathophysiology of major depressive disorder. The results of the present study suggest that chronic SB treatment exerts a potential effect of antidepressant through the increased levels of Ttr mRNA in the hippocampus that is a different mechanism from imipramine.

## An Antidepressant Related Transcription Factor Math2 Regulates Prg1 Expression and Induces Neurite Differentiation

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We have previously identified a basic helix-loop-helix (bHLH) transcription factor Math2 which is involved in neuronal differentiation and maturation, as an antidepressant related gene. In the present study, we identified the genes targeted by Math2 using DNA microarrays and cultured rat cortical cells transfected with Math2. Of the genes regulated by Math2, we focused on plasticity-related gene 1 (Prg1). Prg1 expression induced by Math2 was confirmed in cultured rat cortical cells and PC12 cells analyzed by real-time quantitative PCR. Using chromatin immunoprecipitation assays, we found that Math2 directly bound to the E-box in the Prg1 promoter. Investigation of the functional roles of Math2 and Prg1 in PC12 cells revealed that 72 hours after transfection with either Math2 or Prg1, neurite length and number were significantly induced. Co-transfection with Prg1-siRNA completely inhibited Math2-mediated morphological changes. On the other hand, 3-week treatment with fluoxetine and sertraline significantly increased Math2 and Prg1 mRNA expression in rat frontal cortex. However, 1-day or 1-week treatment did not affect Math2 and Prg1 expression. The mechanism underlying antidepressant actions is thought to occur by means of plastic changes in the nervous system, because clinical effects are generally observed after repeated administration over several weeks. Our results may support the hypothesis that Math2-Prg1 mediated plastic changes of nervous system in frontal cortex are involved with therapeutic action of antidepressants.

## Differential Effects of Amisulpride and Haloperidol on BDNF-Mediated Signal Changes in SH-SY5Y Cells

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**Background:** Recent studies have suggested that first and second generation antipsychotics (FGAs and SGAs) have different effects on neuroprotection. However, the molecular mechanisms of SGAs are not fully understood, and investigations into changes in intracellular signaling related to their neuroprotective effects remain scarce. In the present study, we compared the SGA amisulpride with the FGA haloperidol in SH-SY5Y human neuroblastoma cells via brain-derived neurotrophic factor (BDNF)-mediated signaling, notably BDNF, glycogen synthase kinase-3 $\beta$  (GSK-3 $\beta$ ), cAMP response element-binding (CREB) and B cell lymphoma protein-2 (Bcl-2). **Methods:** We examined the effects of amisulpride (1, 10, and 100  $\mu$ M) and haloperidol (1 and 10  $\mu$ M) on the changes in BDNF, p-GSK-3 $\beta$ , p-CREB, and Bcl-2 levels were measured by Western blot analysis. **Results:** Western blot analysis showed that amisulpride (1, 10, and 100  $\mu$ M) significantly increased the levels of neuroprotective proteins such as BDNF, p-GSK-3 $\beta$ , p-CREB and Bcl-2 whereas haloperidol (1 and 10  $\mu$ M) did not affect these effects. Cells treated with amisulpride effectively increased the levels of BDNF (20%, 45% and 119%), p-GSK-3 $\beta$  (25%, 36% and 74%), p-CREB (25%, 45% and 91%) and Bcl-2 (19%, 33% and 65%) at doses of 1, 10 and 100  $\mu$ M ( $p < 0.05$  or  $p < 0.01$ ). **Conclusions:** This study showed that amisulpride, but not haloperidol, appeared to offer neuroprotective effects on human neuronal cells. The actions of signaling systems associated with BDNF may represent key targets for both amisulpride and haloperidol, but the latter may be associated with distinct effects. These differences might be related to the different therapeutic effects of FGAs and SGAs in patients with schizophrenia. **Keywords:** Aripiprazole, Amisulpride, Haloperidol, SH-SY5Y, BDNF, GSK-3 $\beta$ , Bcl-2, Neuroprotective effect

## Antidepressants Activate FGF Receptor Signaling in Glia: Involvement in GDNF Production

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**Back ground:** Recently, clinical and animal studies have shown that neuronal and glial plasticity are important for the therapeutic action of antidepressants. We previously reported that total GDNF levels in whole blood in patients with mood disorders were significantly lower than those in healthy control subjects, and antidepressants increased GDNF production through monoamine-independent protein tyrosine kinase and ERK activation in glia. In this study, we attempt to clarify which types of tyrosine kinase are involved in the effects of antidepressants in normal human astrocytes and rat C6 cells.

**Results:** (1) The amitriptyline (a tricyclic antidepressant)-induced ERK activation was specifically inhibited by FGFR inhibitors and siRNA for FGFR1 and 2. (2) Treatment with several different classes of antidepressants acutely increased phosphorylation of FGFRs and FRS2 $\alpha$ , which is a substrate for FGFR kinase. (3) The amitriptyline-induced ERK activation was inhibited by heparin, bFGF neutralize antibody, and MMP inhibitors. (4) The amitriptyline-induced CREB phosphorylation and GDNF production were blocked by FGFR inhibitors.

**Conclusion:** Taken together with our results, antidepressants activate the FGFRs/FRS2 $\alpha$ /ERK/CREB signaling cascade through monoamine-independent mechanism, finally resulting in GDNF production. The antidepressant-induced FGFR activation might occur a shedding of bFGF. Our data suggest a possible existence of monoamine-independent novel target of antidepressant in glia, which activates FGFR and GDNF production.

## Effect of Mood Stabilizers on Marble-burying Behavior in Mice

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In the present study, we examined the effects of mood stabilizers on marble-burying behavior, which is an animal model of obsessive-compulsive disorder (OCD). Valproate (100 mg/kg, i.p.) significantly inhibited marble-burying behavior without affecting locomotor activity in mice. On the other hand, carbamazepine, lithium carbonate and lamotrigine had no effect on marble-burying behavior. We also found that a selective GABA<sub>A</sub> receptor agonist muscimol (1 mg/kg, i.p.) significantly inhibited marble-burying behavior, whereas a selective GABA<sub>B</sub> receptor agonist baclofen did not inhibit marble-burying behavior. Moreover, a selective GABA<sub>A</sub> receptor antagonist bicuculline (3 mg/kg, i.p.) antagonized the inhibition of marble-burying behavior by muscimol. Similarly, bicuculline (3 mg/kg, i.p.) antagonized the inhibition of marble-burying behavior by valproate. These findings suggest that valproate may be a useful drug for the treatment of OCD, and that valproate inhibits the marble-burying behavior via GABA<sub>A</sub> receptor-dependent mechanisms.



### Risperidone Attenuates Methamphetamine (METH)-Induced NO Increase in Rats

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The abuse of methamphetamine (METH) has been popular in many parts of the world, and its use has become a major health issue. One of the most acute and life-threatening adverse effects of METH is hyperthermia. It is reported that METH induces the release of dopamine (DA) as well as other neurotransmitters, including serotonin (5-HT) in the brain. Risperidone is an atypical antipsychotic drug that potently blocks D<sub>2</sub> receptors and 5-HT<sub>2A</sub> receptors. We reported that risperidone attenuates METH-induced hyperthermia and DA, 5-HT release in rats. Furthermore, several studies have suggested that nitric oxide (NO) plays a role in neurotoxicity and hyperthermia due to METH. Therefore, we hypothesized that risperidone could prevent METH-induced NO increase. We measured changes in the NO in the anterior hypothalamus by using microdialysis in METH-injected rats. It is difficult to measure NO changes directly. Therefore, we measured NO metabolites, NO<sub>2</sub> and NO<sub>3</sub>. Male Wistar rats were used in the experiments. Risperidone (0.5 mg/kg) or saline was intraperitoneally injected 15 min prior to the subcutaneous administration of METH (10 mg/kg), and NO was measured every 15 min. When rats were subcutaneously injected with 10 mg/kg METH, the NO<sub>2</sub>, NO<sub>3</sub>, and NOx (NO<sub>2</sub> + NO<sub>3</sub>) levels in the hypothalamus increased by 20%, 100% and 80% from baseline, respectively. Risperidone pretreatment significantly suppressed the increase in NO<sub>2</sub> and NOx levels. It is reported that NO is implicated in METH-induced hyperthermia. The present study shows that risperidone attenuates METH-induced NO increase.

### Is There Any Effect on Schizophrenia Model Rats (Gunn rats) with the Treatment of Antipsychotic Medicine?

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There are some reports which find a positive relationship between schizophrenia and hyperbilirubinemia. Patients with schizophrenia show a significantly higher frequency of hyperbilirubinemia than patients suffering from other psychiatric disorders as well as the general healthy population. Recently, it was reported that unconjugated bilirubin exhibited neurotoxicity in the developing nervous system. We have observed that patients suffering from schizophrenia frequently present an increased unconjugated bilirubin plasma concentration when admitted to the hospital. Therefore, we noticed a relationship between unconjugated bilirubin and the etiology of a vulnerability to schizophrenia. We also reported that Gunn rats, which are hyperbilirubinemia rats, may possibly be used as a schizophrenia animal model. We would like to report that we are continuing to study Gunn rats while trying to determine if there is any effect on the schizophrenia model rats (Gunn rats) with the treatment of antipsychotic medicine. We examined their behavior after treatment with Risperidone (0.1 mg/kg), Haloperidol (0.2 mg/kg) and Aripiprazole (0.4 mg/kg) with an open-field test, social interaction test and a prepulse inhibition test. Their hyperlocomotion was inhibited after treatment with the aforementioned medications. The results obtained to date have been encouraging and we feel warrant further research.

### Parkin Knockout Mice Show Enhanced MDMA-Induced Hyperthermia

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MDMA (3,4-methylenedioxyamphetamine) is reportedly severely toxic to both dopamine (DA) and serotonin neurons. MDMA significantly reduces the number of DA neurons in the substantia nigra, but not in the nucleus accumbens, indicating that MDMA causes selective destruction of DA neurons in the nigrostriatal pathway, sparing the mesolimbic pathway. Parkinson's disease (PD) is a neurodegenerative disorder of multifactorial origin. The pathological hallmark of PD is the degeneration of DA neurons in the nigrostriatal pathway. Mutations in the parkin gene are frequently observed in autosomal recessive parkinsonism in humans. Because parkin is hypothesized to protect against neurotoxic insult, we attempted to clarify the role of parkin in MDMA-induced hyperthermia, one of the causal factors of neuronal damage, using parkin knockout mice. Body temperature was measured rectally before and 15, 30, 45, and 60 min after intraperitoneal injection of MDMA (30 mg/kg) at an ambient temperature of 22–24°C. Significantly enhanced hyperthermia was observed in parkin knockout mice treated with MDMA compared with wildtype mice, suggesting that parkin plays a protective role in MDMA neurotoxicity.

### Long-term Effects of Neonatal MK-801 Treatment on Prepulse Inhibition in Young Adult Rats

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**Rationale:** Blockade of N-methyl-D-aspartate (NMDA) receptors has been shown to produce some of the abnormal behaviors related to schizophrenia in rodents and human. Neonatal treatment of rats with non-competitive NMDA antagonists has been shown to induce behavioral abnormality in a later period.

**Objectives:** The aim of this study was to determine whether brief disruption of NMDA receptor function during a critical stage of development is sufficient to produce sensorimotor gating deficits in the late adolescence or early adulthood in the rat.

**Methods:** All experiments were reviewed and approved by the Committee of Animal Research, University of Toyama. Male pups received the NMDA receptor blocker MK-801 (0.13 or 0.20 mg/kg), or an equal volume of saline on postnatal day (PD) 7 through 10. The animals were tested twice for prepulse inhibition (PPI) and locomotor activity in pre- (PD 35–38) and post- (PD 56–59) puberty.

**Results:** Neonatal exposure to both doses of MK-801 disrupted PPI in the adolescence and early adulthood. Low-dose MK-801 elicited long-term effects on startle amplitudes, whereas high-dose MK-801 did not. Neither dose of MK-801 showed a significant effect on spontaneous locomotor activity, whereas the high dose attenuated rearing.

**Conclusions:** The results of this study suggest neonatal exposure to MK-801 on PD 7 through PD10 disrupted sensorimotor gating in the adolescence and early adulthood stages. These findings indicate that rats transiently exposed to NMDA blockers in neonatal periods are useful for the study of the pathophysiology and treatment of schizophrenia.

## Acetylcholinesterase Inhibitor Reduces the Tyrosine Nitration Induced by Amyloid Beta Peptide

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In the Alzheimer's disease (AD), decrease of acetylcholine is suggested as one of the factors of cognitive dysfunction. A selective acetylcholinesterase inhibitor, donepezil, is used as a medicine to treat cognitive dysfunction in AD. Furthermore, donepezil protects the neuronal cells from damage induced by amyloid beta. We have recently reported the contribution of tyrosine nitration to amyloid beta-induced cognitive dysfunction in mice. However, it remains to be determined if donepezil affects the tyrosine nitration induced by amyloid beta. In this study, we evaluated the effect of donepezil on tyrosine nitration levels of hippocampal proteins in amyloid beta-treated mice. Five weeks old male ICR mice were treated with amyloid beta 1-40 by i.c.v. injection, and cognitive ability of the mice was examined by a novel object recognition test 3 days after the injection. Donepezil (1mg/kg) were administrated i.p. for 3 days before the test. Injection of amyloid beta 1-40 remarkably reduced cognitive ability of mice, but donepezil inhibited this reduction. After the novel object recognition test, tyrosine nitration of hippocampal proteins was investigated by western blotting. Amyloid beta 1-40 injection remarkably increased the tyrosine nitration compared with the saline-treated control group. However, donepezil treatment reduced this induction of tyrosine nitration. These results suggest that donepezil reduces tyrosine nitration induced by amyloid beta 1-40, which may be associated with the ameliorating effect on memory impairment in amyloid beta-treated mice.

## LPS-Induced Transglutaminase 2 Expression and the Involvement of NO Production in Cultured Astrocytes

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**[Introduction]** Activation of glia has been observed in neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD) and multiple sclerosis. Excessive production of nitric oxide (NO), as a consequence of increased inducible nitric oxide synthase (iNOS) in glia, contributes to neurodegeneration. Transglutaminase 2 (TG2) is a cross-linking enzyme, which is activated in neurodegenerative diseases such as AD, PD and Huntington's diseases. However, mechanisms contributing to the increased TG activity in neurodegenerative diseases remain to be clarified. In the present study, we examined the expression of TG2 in cultured astrocytes activated with lipopolysaccharide (LPS). **[Methods]** Cultured astrocytes were prepared from brain hippocampus dissected from Wistar rat embryo 19-20. The concentration of nitrite in the medium was measured by fluorescent assay with DAN reagent. iNOS and TG2 expression were detected by western blotting with each specific antibodies. **[Results]** We found that expression of TG2 mRNA and protein were increased by LPS-stimulation, in a dose-dependent manner. On the other hand, LPS-induced NO production was inhibited by cystamine (inhibitor of TGs) in a dose-dependent manner. Furthermore, LPS-induced TG2 expression, as well as NO production and expression of iNOS were diminished by ammonium pyrrolidine-1-carbodithioate (NF-κB inhibitor). **[Conclusion]** These results suggest that NF-κB is involved in LPS-induced TG2 expression in cultured astrocytes and that TG2 induction in the activated astrocytes may associate with NO production.

## Comparison of Antiepileptogenic Actions of Levetiracetam and Valproate in a Pentylenetetrazole Kindling Model

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Levetiracetam (LEV) is a novel antiepileptic drug that preferentially interacts with synaptic vesicle protein 2A. In this study, we examined the effects of LEV on the development of pentylenetetrazole (PTZ) kindling in mice and compared them to those of sodium valproate (VAL) to assess the antiepileptogenic potential of LEV. Male ddY mice were treated with sub-convulsive PTZ (40mg/kg, i.p.) every weekday for 2 weeks. LEV, VAL or vehicle (Control) was given to the animals 30min before each PTZ injections, and the incidence and severity of seizures were evaluated over 15 min immediately after the PTZ injections. Repeated administration of sub-convulsive PTZ progressively increased seizure susceptibility in mice and consistently induced clonic seizures in about 80-90% of animals at 10-12 days after the treatment. LEV did not affect PTZ seizures in naïve animals even at high doses (~300 mg/kg, i.p.). However, combined treatment of LEV (30 and 100 mg/kg, i.p.) with PTZ significantly suppressed the development and acquisition of PTZ kindling in a dose-related manner. In contrast, VAL at sub-anticonvulsive doses (30 and 100 mg/kg, i.p.) failed to prevent the development of PTZ-kindling although a slight inhibition of the seizure induction was observed in early stage (~Day 5) of the treatment with 100 mg/kg of VAL. These results show that LEV contrasts the typical antiepileptic VAL by preventing the development of PTZ kindling, supporting the notion that LEV possesses antiepileptogenic activity.

## Lamotrigine Prevented Apoptosis Induced by Repeated Administration of a High-dose of Methamphetamine

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**Rationale:** In schizophrenia, there is atrophy of brain from early or prodromal stage of disease. This atrophy may be relevant with apoptosis of neurons. Methamphetamine (METH) induces apoptosis in cortical neurons in the medial prefrontal cortex (mPFC). Our recent studies have shown that second-generation antipsychotics blocked apoptosis induced by repeated administration of METH. Moreover, lamotrigine (LTG) has been shown to have beneficial effect for the treatment of schizophrenic patients. We confirmed that LTG prevented the repeated-administration of METH-induced neuroplastic prepulse inhibition deficit.

**Objectives:** In this study, we examined the effects of LTG on the development of apoptosis induced by repeated of METH using Sprague-Dawley rats.

**Materials and methods:** We examined the effects of repeated administration of METH (2.5 mg/kg) on the expression of TUNEL-positive cells in the mPFC, 7 days after the METH treatment, and examined the effects of posttreatment with LTG (30 mg/kg) after METH (2.5 mg/kg) injection on the expression of TUNEL-positive cells, 7 days after the co-administration.

**Results:** Repeated administration of METH induced expression of TUNEL-positive cells in the mPFC but not saline. Posttreatment with LTG attenuated the repeated administered METH-induced expression of TUNEL-positive cells.

**Conclusions:** LTG may influence glutamatergic system, and prevented expression of TUNEL-positive cells in the mPFC induced by repeated administration of METH. This result suggests that LTG prevents progressive brain atrophy by suppression of apoptosis.

## Functional Analysis of Glutamatergic System in Dominant-negative DISC1 Transgenic Mice with Neonatal polyI:C Treatment

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Interactions between environmental and genetic factors play a role in the pathogenesis of schizophrenia. Recently, we have reported a novel animal model of schizophrenia by inducing abnormal immune response during perinatal period in transgenic (tg) mice with dominant-negative form of disrupted-in-schizophrenia 1 (DN-DISC1). The mouse displays schizophrenia-like behaviors and a marked reduction of parvalbumin-positive interneurons in the prefrontal cortex in adulthood. In the present study, we investigated glutamatergic neuronal function in this animal model of schizophrenia. From postnatal day 2 to 6, neonatal wild-type (wt) and DN-DISC1 tg mice were repeatedly injected vehicle or polyribonucleic-polyribocytidilic acid (polyI:C) that induces strong innate immune responses. Neurochemical analyses were performed in adult mice. The high potassium-evoked glutamate release in the hippocampus did not differ between saline-treated wt mice and polyI:C-treated DN-DISC1 tg mice. In contrast, the expression level of phosphorylated-NR1 was significantly decreased in the hippocampus of DN-DISC1 tg mice compared with wt mice while neonatal polyI:C treatment had no effect in wt and DN-DISC1 tg mice. There were no significant changes in the expression levels of total-NR1, phosphorylated-NR2B, total-NR2B, GLT-1 and GLAST among 4 groups of mice. These results suggest that overexpression of DN-DISC1 leads to dysfunction of NMDA receptors in the hippocampus.

## PCP Treatment in Mice During Neurodevelopmental Period Induces Behavioral, Histological and Neurochemical Abnormalities in Adulthood

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In this study, we investigated the brain-functional abnormalities induced by injection of phencyclidine (PCP) to ICR mice during the neurodevelopmental period. Neonatal mice were injected with PCP at 10 mg/kg or saline on postnatal days 7, 9 and 11, and their behavioral, anatomical and neurochemical changes were analyzed in adulthood. PCP-treated mice exhibited an increase in PCP-induced hyperactivity and impairments of spatial working memory and social interaction behavior. The impairment of social interaction behavior was significantly reversed by administration of clozapine, D-cycloserine, flumazenil, or SHC50911, a GABA<sub>B</sub> receptor antagonist. A decrease in the number of parvalbumin-positive cells and spine density in the frontal cortex, nucleus accumbens and hippocampus were evident in the brains of PCP-treated mice. Measurement of brain monoamine and their metabolite contents in adulthood indicated brain area-dependent and neurotransmitter-specific changes in monoamine metabolism. These findings suggest that neonatal treatment with PCP in mice leads to enhanced sensitivity to PCP and impairment of spatial working memory and social interaction behaviors in adulthood, which may be associated with reduced spine density and GABAergic interneurons and changes in monoamine metabolism. Furthermore, pharmacologic experiments suggest the potential applicability of neonatally PCP-treated mice as a useful animal model for new antipsychotic drug screening.

## Amygdala CRH Activity After Chronic Stress

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**[INTRODUCTION]** The acoustic startle response (ASR) is a model in the behavioral neurosciences for the study of anxiety and fear in rats. The ASR can be augmented by stress such as footshock. This enhancement of ASR is regulated by the corticotropin releasing hormone (CRH) neurons in the central nucleus of amygdala (CeA). We have previously reported that the basal level of CRH immunoreactivity in the CeA and the paraventricular nucleus are decreased after chronic variable stress (CVS) whereas CRH immunoreactive response is augmented by footshock, corresponding to the sensitization of the ASR to footshock after CVS. In the present study, we investigate the sensitization of the ASR to footshock on day-1 and day-8 after CVS. **[METHODS]** Rats were treated with CVS for 13 days. The ASR was measured on day-1 or day-8 after the last stress of CVS. All rats were presented with 120 startle stimuli. We performed all experiments based on guideline of St. Marianna University School of Medicine Center Experimental Animal Management Commission. **[RESULTS & CONCLUSION]** The ASR sensitization to footshock was found in both day-1 and day-8 groups after CVS, suggesting that CVS could produce a long-term excess CRH response. The peak time of day-1 (10 min) or day-8 (25 min) sensitization was brought forward or delayed and prolonged compared with handling groups, respectively. It is possible that the delayed CRH sensitization in the CeA might be elicited on day-8 after CVS in the distinct mechanism from the early sensitization.

## Analysis of 5-HT<sub>2A</sub> Receptor and 5-HT Transporter Bindings of Brain in Various Strains of Mouse

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It is well known that serotonergic system is involved in depression and effects of antidepressants. We previously reported that mouse strain differences in immobility in the forced swimming test, which is the evaluation method of antidepressants. Furthermore, sensitivity to the selective serotonin reuptake inhibitor (SSRI), fluvoxamine is different in various strains of mouse. We proposed that these differences may be related to variation in brain 5-HT transporter bindings. It was reported that 5-HT<sub>2A</sub> receptors may be associated with effects of antidepressants, although its involvement is controversial. Administration of antidepressants elicits changes in population of brain 5-HT<sub>2A</sub> receptors. Therefore, strain differences in immobility in the forced swimming test may be also related to the 5-HT<sub>2A</sub> receptor. In the present study, we compared with bindings of 5-HT<sub>2A</sub> receptor and 5-HT transporter in brain of five strains of mouse. Male ICR, ddY, C57BL, DBA/2, BALB/c mice were used. Forced swimming test was performed following the method of Porsolt et al. The 5-HT<sub>2A</sub> receptor bindings of brain are significantly different among five strains of mice. However, there is no correlation between the B<sub>max</sub> of 5-HT<sub>2A</sub> receptor bindings and immobility time, while positive correlation was observed between immobility time and 5-HT transporter bindings. These results suggest that strain differences in immobility time are not related to the amount of 5-HT<sub>2A</sub> receptor bindings but to 5-HT transporter bindings.

## The Effects of Acetaminophen, Fentanyl, Fluvoxamine and Gabapentin on a Novel Conditioned Nociceptive Response in Mice

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Organisms repeatedly exposed to noxious stimuli learn the stimuli, resulting in the development of a conditioned nociceptive pain. However, there has been only limited experimental study on the conditioning of pain without neuronal disruption. [Objective] The first sought to confirm the prediction that nociceptive pain can be conditioned. The second was to investigate the neurobehavioral mechanisms and effect of analgesic drugs in animals. [Methods] Mice were used to assess hind paw-licking responses during 30 min of observation after an injection of formalin (F) in the left and right hind paws at intervals of 24 hrs in the training phase, with saline (S) given in the test phase. [Results] The conditioned response in the test phase was similar to that in the training phase, when the external context was the same, but decreased when the context was different. Naloxone (N) facilitated a conditioned nociceptive response, suggesting that conditioned nociceptive pain releases opioids. Hypoalgesic drugs such as fentanyl (s.c.) and acetaminophen (i.p.) were ineffective against a conditioned nociceptive response. However, fluvoxamine maleate was effective. These novel findings suggest that the Pavlovian conditioned nociceptive response developed by the association between external contexts and nociceptive stimuli, and the conditioned nociceptive response are refractory to narcotic drugs but are sensitive to a selective serotonin reuptake inhibitor. The mechanisms of the effects of these drugs are discussed in relationship with learning and neurophysiology.

## Antidepressive Properties of Dopamine Receptor Agonist Cabergoline

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Cabergoline (Cab) is a dopamine D2 receptor-like agonist with less affinity to D1-like, adrenergic and serotonergic receptors. In the present study, we used eight-week-old male Wistar or Wistar-Kyoto (animal model of depression) rats to elucidate the effect of Cab on depression- and anxiety-like behaviors. Male rats were injected with ascending doses of Cab (0, 0.25, 0.5, 1, 2 μmol/kg, i.p.) and their corresponding behavior was monitored four hours after the injection in a acute treatment paradigm. In a chronic treatment paradigm, male rats were treated with vehicle or 0.5 μmol/kg Cab for 14 days and their behavior was observed from day 10 to 14. The forced swim test (FST), the open field test (OFT) and the elevated-plus maze test (EPT) was used for analyzing the depression- and anxiety-like behaviors. In the acute treatment, Cab reduced the immobility of the Wistar rat in the FST in a dose dependent manner, and the same effect was observed in the Wistar-Kyoto rat at the most effective dose of 1 μmol/kg. Cab also demonstrated less distance traveled in both strains of rats, especially during the first 10 min in the OFT and the EPT. In contrast, Cab enhanced the distance traveled in the OFT and in the EPT after chronic administration regimen. Reduced immobility was still observed after the chronic Cab administration. In summary, Cab demonstrated its antidepressive effect by the acute/chronic treatment, and its activating effect emerged during the chronic treatment. These results suggest that Cab may be a promising drug candidate for depressive disorders.

## Blockade of Brain 5-HT<sub>7</sub> Receptors Under the Stressful Condition Induces the Emotional Abnormality in Mice

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The ability to adapt to stress is an important defensive function of a living body. We have previously obtained the evidence that this ability is mediated, at least in part, by brain 5-HT neuronal systems. The aim of the present study was to examine whether brain 5-HT<sub>7</sub> receptors are involved in the mechanisms of stress adaptation. A single exposure to restraint stress (60 min) induced the decrease in exploratory activity in the hole-board test, as well as the increase in anxiety-like behavior in the elevated plus-maze test and the light-dark test in mice. These emotional stress responses disappeared in mice exposed to repeated restraint stress (60 min) once day for 7 days, confirming the development of stress adaptation. On the contrary, daily i.c.v. injection of SB269970 (10 μg/mouse) immediately after the stress exposure induced the abnormal behaviors that reflect the low sensitivity to anxiety and/or the enhancement of impulsivity. Furthermore, western blot analysis revealed that expression of 5-HT<sub>7</sub> receptors increased in the frontal cortex and hippocampus of mice that have adapted to stress. However, these biochemical changes were not observed in mice that have not adapted to stress by daily i.c.v. injection of SB269970 (10 μg/mouse), or rather expression of cortical 5-HT<sub>7</sub> receptors was decreased. These findings suggest that brain 5-HT<sub>7</sub> receptor-mediated signaling may play an important role in the processes of stress adaptation, and impairment of this brain mechanism may be one of the risk factor for emotional abnormality.

## A Glutamate Release Inhibitor Rapidly Attenuates Hyperemotional Responses in OBX Rats

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Monoaminergic antidepressants immediately increase synaptic concentrations of norepinephrine and/or serotonin. However, a latency period of several weeks generally elapses before therapeutic effects of antidepressants are observed. This discrepancy implies that mechanisms beyond the monoaminergic systems are involved in the treatment of depression. Growing evidence indicates that the glutamatergic neurotransmitter system is central to the neurobiology and treatment of depression. Riluzole, a drug currently used to slow the progression of amyotrophic lateral sclerosis, directly affects the glutamatergic system. In this study, we investigated the effects of riluzole in olfactory bulbectomy (OBX) rats as an animal model of depression. OBX-induced hyperemotional responses may mimic symptoms, such as psychomotor agitation, anxiety, aggression, and irritability, in depressed patients. We provide the first experimental evidence that single and subchronic riluzole treatment significantly and dose-dependently reduced hyperemotional responses in OBX rats. Our results may suggest that riluzole could improve symptoms at an earlier stage in the treatment of depressed patients. In addition, we examined and confirmed that riluzole treatment decreased extracellular glutamate levels in mPFC of OBX rats by in vivo microdialysis. In the future, the association between the glutamate nervous system and each psychiatric symptom will be clarified concerning the antidepressant effects of riluzole in depressed patients.

## Treatment with Risperidone Did Not Increase Plasma Nitric Oxide Metabolites Levels in Schizophrenic Patients: A Pilot Study

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Objective Nitric oxide (NO) is synthesized from L-arginine by a family of isoformic enzymes known as nitric oxide synthase (NOS). From the review of Bernstein (2005), NO system is involved in the pathogenesis of schizophrenia. However, findings about NO metabolites (NOx) in schizophrenic patients have been inconsistent. Aim We hypothesized that plasma NOx levels in schizophrenic patients were lower than in healthy subjects, and treatment with risperidone increase plasma NOx levels. To investigate the hypothesis, we examined the effects of risperidone on plasma NOx levels in schizophrenic patients, and compared those in healthy subjects. Subjects and Methods This study included 30- or outpatients in our university hospital who met the DSM-IV criteria for schizophrenia (M/F: 18/12, age: 38±15 yr). All patients were treated with risperidone (3.8±1.5 mg/day) for 8 weeks. This study was approved by the ethics committee of the University of Occupational and Environmental Health, and written informed consent was obtained from all participants. Results A trend for decrease in plasma NOx levels was found in schizophrenic patients. A significantly negative correlation was observed between plasma NOx levels and PANSS-N scores. However, treatment with risperidone for 8 weeks did not raise plasma NOx levels. Conclusion Our hypothesis was not confirmed. However, these results suggest that plasma NOx levels might be partially involved in the pathogenesis of schizophrenia, especially associated with negative symptoms.

## What Do D-neurons Do in Relation Between Pathogenesis of Mental Disorders?

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D-neurons are defined as aromatic L-amino acid decarboxylase (AADC, = dopa decarboxylase; DDC)-positive neurons that do not contain dopamine (DA) and serotonin (5-HT). Since the discovery of D-neurons in the rat central nervous system, Jaeger et al. specified their localization from the spinal cord to the bed nucleus of stria terminalis, D1~D14 (Jaeger et al. 1983, 1984). Animal studies showed that the D-neurons convert monoamine precursors including 5-hydroxytryptophan, L-dopa, and exogenous droxidopa (L-threo-DOPS) to monoamines including 5-HT, DA, and noradrenaline, respectively. The D-neurons synthesize trace amines including tyramine and phenylethylamine, and AADC act as the rate-limiting enzyme for trace amine synthesis. The trace amine receptor gene might relate to pathogenesis of schizophrenia (Pae et al. 2008). In our immunohistochemical study, human striatal D-neurons (D15) showed the reduction in number in post-mortem brains of patients with schizophrenia, notably in the nucleus accumbens (Ikemoto et al. 1997, 2003). The D neurons, which are abundant in the rat and cat midbrain, pons, and medulla, were hardly detectable in homologous regions in the human brain, although they were clearly distinguishable in the forebrain (Kitahama et al. 2009). In parkinsonian model rats with midbrain 6-OHDA lesions, striatal AADC neurons increased, and they synthesized DA after L-dopa administration (Mura et al. 1995, 2000). The significance of D-neurons should further be elucidated in relation between the pathogenesis of mental disorders (Ikemoto 2004).

## Membrane Fatty Acid Levels as a Predictor of Treatment Response in Schizophrenia

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**[Objectives]** This study was conducted to test the hypothesis that the ability of antipsychotic drugs to ameliorate positive symptoms and social cognition would be predicted by baseline saturated fatty acids (SFAs) and essential polyunsaturated fatty acids (EPUFAs) concentrations in the erythrocyte membrane, a peripheral measure of phospholipid composition in neural membranes, in subjects with schizophrenia.

**[Methods]** Thirty-four chronically ill out-patients (male/female=22/12) meeting DSM-IV criteria for schizophrenia participated the study. After blood drawing, they were switched to monotherapy with olanzapine or perospirone. The Scale for the Assessment of Positive Symptoms (SAPS) and the Scale for Assessment of Negative symptoms (SANS), as well as the script tasks were administered at baseline and three months after the start of medication switch. Erythrocyte membrane levels fatty acids were analyzed using a gas chromatography system.

**[Results]** Scores of SAPS and SANS, as well as script task performance were improved during treatment with either antipsychotic drug. Baseline (n=3+n=6) EPUFAs concentrations were positively and negatively correlated with percent improvement of the SAPS Total score and script task performance, respectively, while there was a positive association between baseline SFAs levels and percent improvement of script task performance.

**[Conclusions]** The results of this study suggest composition and turnover of SFAs and EPUFAs in the erythrocyte membrane provide a feasible measure to predict treatment response in patients with schizophrenia.

## Association Between Autonomic Nervous System Activity in Schizophrenia and Antipsychotic Medication

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Objective: Schizophrenic patients have been reported to have an increased prevalence of cardiovascular diseases, and antipsychotic medication is one of the causes of these diseases. On the other hand, we reported reduced autonomic nervous system (ANS) activity in schizophrenia, which was considered a possible risk factor for cardiovascular diseases. In the present study, we investigated the influence of antipsychotic medication on the ANS activity in schizophrenic patients.

Methods: Subjects were 189 Japanese patients with schizophrenia. All subjects received an explanation of our study and written informed consent was obtained. ANS activity was assessed by means of heart-rate variability power spectral analysis, which enables us to identify separate frequency components, i.e., total power (TP: overall ANS), low-frequency (LF: sympatho-vagal) power, and high-frequency (HF: vagal) power, during a resting condition.

Results: We found significant associations between ANS activity and neuroleptics dose (TP,  $p=0.001$ ; LF,  $p=0.014$ ; HF,  $p=0.002$ ) using multiple regression analyses for ANS, sex, age, and neuroleptics dose calculated in terms of chlorpromazine equivalents as independent variables. We observed a trend toward associations of low ANS activities in patients treated with olanzapine, although no significant difference was found.

Conclusion: Our findings suggest that neuroleptics dose influence on reduced ANS activity in schizophrenic patients.

## Plasma Substance P Level in Patients with Schizophrenia: A Cross-sectional Survey

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Substance P is a neuropeptide and its plasma level has been reported to be associated with swallowing reflex activities, leading to a suggestion that substance P level may be a useful predictive marker of aspiration. This would be especially important in patients with schizophrenia, given they frequently suffer aspiration pneumonia. We therefore measured plasma substance P level and examined its relationship with demographic and clinical variables, using a univariate general linear model, in patients with schizophrenia (DSM-IV). This study was approved by the institutional review board of Sakuragaoka Memorial Hospital, and all participants provided informed consent. 34 patients participated in this study; mean  $\pm$ SD age, duration of illness, and daily antipsychotic dose were 70.9 $\pm$ 10.8 years, 45.5 $\pm$ 13.7 years, and 362 $\pm$ 337 mg chlorpromazine equivalent (CPZ eq.), respectively. Plasma substance P level was inversely associated with the number of cigarettes. Patients who received a high antipsychotic dose (>600 mg/d CPZ eq.) showed a lower mean plasma substance P level than those with a middle dose (300-599 mg/d CPZ eq.). Given the reported relationship between substance P level and reflex activity, our results suggest that reducing the number of cigarettes and antipsychotics dosage may enhance reflex activities. This in turn might prevent aspiration pneumonia in patients with schizophrenia. Further investigations are warranted to clarify the relationship of plasma substance P level with reflex activities and incidence of aspiration pneumonia.

## The Relation of Haloperidol and Risperidone Usage Duration to Blood Fasting Glucose Rate

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Background: Antipsychotic, haloperidol and risperidone, are used to treat the symptom of schizophrenia and other functional psychotic disorders. Previous researches showed there was an influence of those drugs to blood fasting glucose, although the result might vary. Objective: The aims of the research was to find out the relation of duration of haloperidol and risperidone usage to the blood fasting glucose rate. Method: The research used the cross sectional design with 77 samples, consist of 58 haloperidol samples and 19 risperidone. The correlation analysis was made by Pearson correlation analysis test. Result: As the result, we found that in the group of haloperidol, the blood fasting glucose rate was higher in those with duration of usage in 1.1 - 2.0 years (mean 99.60) compared to those in 0.1 - 1.0 year (mean 88.85). The same result was found in the group of risperidone, that showed the higher rate of blood fasting glucose in those with duration of usage in 1.1 - 2.0 years (mean 100.50) compared to those in 0.1 - 1.0 year (mean 93.12). Within the usage of 0.1 - 1.1 years, the impaired fasting glucose was already found in 40% of the group of risperidone whereas the result in haloperidol group still in normal rate. In the period of 1.1 - 2.0 years, we found the increased of impaired fasting glucose to 57.1% in the group of risperidone and 40% in the group of haloperidol. After the usage in 2 years, we found the all the samples in risperidone group got diabetes (100%) whereas there was only 7.5% samples got diabetes in haloperidol group. Conclusion: 1. There was a meaningful relation of antipsychotic usage duration to blood fasting glucose rate. The longer usage of haloperidol and risperidone effected to the the higher blood fasting glucose rate. 2. There was a meaningful difference in blood fasting glucose rate of the group of risperidone compared to the group of haloperidol. In both first and second year of usage, the blood fasting glucose showed a higher rate in the risperidone group compared to the haloperidol group.

## Treatment-unresponsive Schizophrenia with Diabetes in National Mental Hospitals

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Introduction: Clozapine (CLOZ) is effective for patients with treatment-unresponsive schizophrenia (TUR). In Japan, diabetes mellitus (DM) is regarded as contraindication for prescribing CLOZ except for cases the use of CLOZ is considered essential. However, there are no reliable data on prevalence of TUR patients with DM in Japan. Therefore, we estimated prevalence of TUR patients with DM, based on cross-sectional database constructed in Japan. Subjects: The sixth Japan Extensive Study of Schizophrenia (JESS2005) was a cross-sectional survey conducted for 3355 inpatients in 15 Japanese national mental hospitals on September 1, 2005. We extracted data on 1909 psychotic inpatients and analyzed for this study. 56.7% were male. The mean $\pm$ SD age was 55.2 $\pm$ 14.5 years. Methods: We conducted the study with following definitions. TUR patient is whom prescribed at least two SGAs concurrently, or one SGA plus first generation antipsychotics concurrently; each of whose dose is at least 600mg/day chlorpromazine equivalent and; the Global Assessment of Functioning score is less than 40 on the surveillance day. A patient prescribed oral hypoglycemic agents or insulin is assumed DM patients. Results: Among 1909 patients, 181 (9.5%) were TUR patients. Of 181, five patients (2.8%) were regarded as DM. Conclusion: Considering that not all diabetic patients take medication, our finding of 2.8% DM patients among TUR patient might be considered underestimation. However, our study suggested that in Japan at least about 3% of TUR patient are regarded as relatively contraindicated for CLOZ due to DM.

## Abnormal Glucose Metabolism in Schizophrenic Patients Treated with Antipsychotics: Evaluation with 75g Oral Glucose Tolerance Test

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**[Objective]** This study investigated abnormal glucose metabolism with 75-g oral glucose tolerance test (OGTT) in patients with schizophrenia who were taking antipsychotic medication.

**[Methods]** 177 hospitalized patients with schizophrenia (SZ) (male : female = 102: 75) and 99 healthy controls (CON; M:F = 60:39) were evaluated with 75-g OGTT. The main outcome measures were HbA1c, plasma glucose level (GL), plasma insulin level (INS) and area under the time curves (AUC) for GL and IRI. SZ was compared with CON in male and female respectively. The study was approved by the ethics committee, and all subjects gave written informed consent.

**[Results]** In female group, OGTT showed significantly higher GL in SZ compared to CON in 30, 60, 90, 120 minute time points (149.2 vs 130.9, 140.7 vs 120.0, 125.2 vs 107.1, 117.4 vs 101.1 mg/dl), and INS were also significantly higher in SZ than in CON in 30, 60, 90, 120 minute time points (85.7 vs 49.3, 75.7 vs 45.2, 59.9 vs 33.1, 48.5 vs 24.7 $\mu$ IU/ml). Both AUCs for GL and for IRI were greater in SZ than in CON. On the contrary male SZ patients showed significant difference only in 60 minute time point for GL (146.5 vs 131.7 mg/dl) and IRI (77.5 vs 54.1 $\mu$ IU/ml).

**[Conclusions]** The results indicate abnormal glucose metabolism in schizophrenic patients treated with antipsychotics and sex difference in this dysregulation.

## Antipsychotic Drug, Hyperlipidemia and 10-Year Coronary Heart Disease Risks: Results of a 6-year Naturalistic Study on Middle Aged Schizophrenic Patients

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Our previous study had showed short-term effect of antipsychotic drugs on lipid profiles and obesity. In this study, we tried to investigate the long-term impacts and estimate the risk of 10-year coronary heart disease (CHD). Therefore, we follow up 97 schizophrenic patients and 59 healthy control subjects in our previous study 6 years later. During a 1-year period, 25 schizophrenic patients and 25 healthy controls were enrolled in this study. The blood pressure, fasting plasma glucose (FPG) and body mass index (BMI), and lipid profiles including high-density lipoprotein-cholesterol (HDL-cholesterol), triglycerides (TG), and total cholesterol (TC) were assessed again. In addition, the Framingham Point Scores (FPS) were estimated to evaluate the risk of 10-year CHD. We use analysis of variance (ANOVA) with repeat measure to compare the differences between two time points and then covariance (ANCOVA) with age, BMI and baseline adjustment to compare the two groups. TC in patients group showed significant increase between two time points. In addition, the data of both groups showed significant increase in FPS and HDL-cholesterol level between two time points. However, there were no significant differences in systolic blood pressure, diastolic blood pressure, HDL-cholesterol, TG, TC, FPG levels and FPS between two groups. In conclusion, both group showed increased HDL-cholesterol level and risk of 10-year CHD after 6 years. In addition, antipsychotic drugs do not present persisting impact on metabolic parameters on middle aged schizophrenic patients after comparing with healthy controls. Therefore, we need to clarify effects of other factors on the changes of metabolic parameters in addition to the antipsychotic drugs. It needs a larger sample size to prove these results.

## Add-On Effects of Aripiprazole in Improving Dyslipidemia in Patients Taking Antipsychotics

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**Background:** Dyslipidemia has been linked to antipsychotic treatment. The authors investigated the effect of 8-week adjunctive treatment with aripiprazole on lipid measures in patients who received antipsychotics and had dyslipidemia.

**Methods:** Aripiprazole was added to 41 (24 females and 17 males) patients who received antipsychotics and had dyslipidemia. The pre-existing antipsychotics were risperidone (N=15), olanzapine (N=10) amisulpiride (N=5) and quetiapine (N=5) and others (N=6). The doses of pre-existing antipsychotics were fixed, while aripiprazole was dosed from 5 to 20 mg/day during an 8-week study period. Serum lipid profiles were measured at baseline and week 8. Symptoms and side effects were assessed with the Positive and Negative Syndrome Scale (PANSS), Abnormal Involuntary Movement Scale, Simpson-Angus Scale, Barnes Akathisia Scale, and metabolic measures at baseline and weeks 2, 4 and 8.

**Results:** Of the subjects, 36 completed the trial. Mean (SD) age was 38.5 (9.7) years. The mean dosage of aripiprazole was 10.3 (3.0) mg/day. For these subjects, there were significant reduction in body mass index ( $p=0.024$ ), triglyceride ( $p=0.002$ ) and total cholesterol/ high-density lipoprotein-cholesterol ratio ( $p=0.028$ ) over 8 weeks.

There was also significant change in adiponectin ( $p=0.022$ ). The PANSS and scales of movement side effects improved significantly. The most commonly reported adverse events included dizziness (5.6%), akathisia and restlessness (5.6%).

**Conclusions:** The addition of aripiprazole improved lipid profiles and reduced weight and was well tolerated. A double-blind controlled design is suggested to replicate these findings.

## Effect of Second Generation Antipsychotics on Dyslipidemia and Metabolic Hormonal Markers in Japanese Psychiatric Patients

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### [Background]

Second generation antipsychotics (SGA) induce gluco-regulatory abnormalities. While antipsychotics may increase adiposity, which can decrease insulin sensitivity, disease- and medication-related differences in glucose and lipid regulation might also occur in adiposity.

### [Methods]

One hundred and seventeen schizophrenic patients and 161 untreated healthy controls participated in this study. The patients were treated with olanzapine (OLZ), risperidone (RIS) or quetiapine (QTP). The parameters of lipid and glucose regulation were analyzed among three SGAs and control groups. The present study was approved by Ethics Committee on Genetics of Niigata University School of Medicine, and written informed consent was obtained from all subjects.

### [Results]

ANOVA showed significant differences in levels of high density lipoprotein cholesterol (HDL:  $P<0.001$ ) and leptin ( $P=0.001$ ) between four groups. A post-hoc test revealed that the HDL levels were significantly lower in OLZ ( $P<0.001$ ), RIS ( $P<0.001$ ) and QTP ( $P=0.001$ ) groups than in control group, and that the leptin levels were significantly higher in OLZ group than in control group ( $P=0.02$ ). In addition, female patients treated with SGAs showed significantly higher levels of leptin ( $P<0.001$ ) and HOMA-IR ( $P=0.016$ ) compared to male patients.

### [Conclusion]

OLZ, RIS and QTP treatment decreased HDL level and OLZ treatment increased leptin level and HOMA-IR. These SGAs apparently produce glucolipid dysregulation and there seems to be sex difference in this effect.

## Frequency of Metabolic Screening in Outpatients Treated with Second-Generation Antipsychotics in Japan

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**Background:** Although it is recommended frequent screening of metabolic factors for patients treated with second generation antipsychotics (SGAs), there are few data on the frequency of screening in Japan. **Objective:** Estimating the frequency of metabolic screening in Japanese outpatients with mental disorders on SGAs medications. **Methods:** Health insurance claim database, constructed by Takeshima et al. (2006), was utilized in the current study. Originally, this database comprises 1595 outpatient-clinic-derived claims in February 2006, selected from all of 47 prefectures in Japan. Based on the laboratory and SGA items, metabolic monitoring rate in those under treatment with SGAs were estimated. **Results:** Of 1595 outpatients surveyed, 499 were prescribed at least one SGA. Of those on SGAs, 228 (45.7%) were male. The mean±SD age was 45.1±15.2 years. 433 (86.8%) were classified as psychotic disorders. 28 (5.6%), 5 (1.0%), 40 (8.0%), 35 (7.0%) and 8 (1.6%) were screened their levels of serum glucose, hemoglobin A<sub>1c</sub>, total cholesterol and triglyceride, and the existence of glucose in urine, respectively. **Conclusion:** In a US survey by Morrato et al. (2009), annual screening rates of serum glucose and lipid were 38% (around 4% per month) and 23% (around 2%), respectively. In Japan, psychiatric patients treated with SGAs might tend to be monitored metabolic factors more frequently than in the US.

## A Study of Metabolic Syndrome and Its Impact on Health Related Quality of Life and Body Image in Patients with Schizophrenia

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**Objectives:** 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 evaluate 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 measured by Body Image Index. Statistical analysis was done using SPSS 12.0 for Windows. Statistical significance was set at  $p < 0.01$ .

**Results:** The prevalence of metabolic syndrome in patients with schizophrenia was 37.5% in male patients and 27.3% in female patients. The patients with metabolic syndrome had negative body image, especially body feature, compared to the patients without metabolic syndrome. The patients with metabolic syndrome showed poorer health related quality of life, especially role physical and bodily pain in SF-36-K.

**Conclusion:** The prevalence of metabolic syndrome was 33.3% in patients with schizophrenia, which was higher prevalence compared to the healthy people. The patients with metabolic syndrome has poorer quality of life and body image. These results suggest that metabolic syndrome of schizophrenia could be considered selecting antipsychotics.

**Key words:** Schizophrenia, Metabolic syndrome, Health related Quality of life

## Prevalence and Its Correlates of Night Eating Syndrome in Schizophrenic Outpatients

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**Objective:** The aim of study was to examine the prevalence of night eating syndrome (NES) and its correlates in schizophrenic outpatients.

**Method:** The 14 items of self-reported night eating questionnaire (NEQ) was administered to 165 schizophrenic patients in psychiatric outpatient clinic. We examined demographic and clinical characteristics, body mass index (BMI), subjective measures of mood, sleep, binge eating, and weight-related quality of life using Beck's Depression Inventory, Pittsburgh Sleep Quality Index, Binge Eating Scale and Korean version of Obesity-Related Quality of Life Scale, respectively.

**Results:** The prevalence of night eaters in schizophrenic outpatients was 9.1% (15 of 165). Comparisons between NES group and non-NES group revealed no significant differences in sociodemographic characteristics, clinical status and BMI. Compared to non-NES, patients with NES reported significantly greater depressed mood and sleep disturbance, more binge eating pattern, and decreased weight-related quality of life. While 'morning anorexia' and 'delayed morning meal' (2 of 5 NES core components in NEQ) were not differed between groups, 'nocturnal ingestions', 'evening hyperphagia', and 'mood/sleep' were more impaired in NES group.

**Conclusion:** These findings are the first to describe the prevalence and its correlates of night eaters in schizophrenic outpatients. These results suggest that NES has negative mental health implications, although it was not associated with obesity. Further study to generalize these results is required.

## Prevalence and Characteristics of Metabolic Syndrome in Schizophrenic Inpatients

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**Objective:** This study was aimed to investigate the prevalence of metabolic syndrome (MS) and associated characteristics in schizophrenic inpatients.

**Method:** In this cross-sectional study, 214 inpatients with schizophrenia or schizoaffective disorder defined by DSM-IV criteria were included. Prevalence of MS was assessed based on the Asian-Pacific Criteria of National Cholesterol Education Program (NCEP, Adult Treatment Protocol, ATP-III).

**Results:** Prevalence of MS was 22.9% in our sample. MS was associated with male sex, but not with duration of illness, or current use of antipsychotic medications. Compared with patients without MS, patients with MS had higher risk for cardiometabolic morbidity. Of the individual cardiometabolic risk factors, waist circumference (65%) and HDL-cholesterol (54.7%) were more common than triglyceride (29.4%), blood pressure (8.9%) and blood glucose (5.1%).

**Conclusion:** Although prevalence of MS in schizophrenic inpatients was common in our sample, it was not quite high than general population in Korea. But, it should be critical part of clinical management of schizophrenic patients to assess of the presence and monitoring of the MS.

## The Psychometric Properties of Night Eating Questionnaire in Schizophrenic Outpatients

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**Purpose:** 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:** Among 165 schizophrenic outpatients who completed the NEQ, 14 (9.1%) patients screened as having NES (total NEQ >25). NEQ demonstrated high internal consistency (Cronbach's alpha=0.72) and item-total correlations ( $r=0.29-0.75$ ;  $p < .001$ , respectively) were acceptable except morning anorexia. Test-retest reliability was also good ( $r=0.74$ ,  $p < .001$ ). Principal components analysis revealed the presence of five factors (nocturnal ingestions, evening hyperphagia, mood/sleep, morning anorexia, and delayed morning meal), explaining 65.3% 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.

**Conclusion:** Our results showed that NEQ appears to be an efficient, valid measure of NES in schizophrenic outpatients.



## Concentration-dependent Effect of Risperidone on QT Interval

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### Introduction

QT prolongation on electrocardiogram (ECG) is a surrogate marker for torsades de pointes (TdP) and ventricular fibrillation. Most antipsychotic agents can cause QT prolongation. QT prolongation is considered to be introduced by increase in action potential duration. It was reported that risperidone (RIS) lengthened the action potential duration in concentration-dependent manner *in vitro*. We investigated the relationship between the plasma RIS concentration and QT interval.

### Methods

The study was carried out with the approval of the ethics committee of Niigata University School of Medicine, Japan. All participants gave their informed consent. Twenty-four-hour Holter ECGs were recorded in 12 inpatients receiving RIS once a day at 2000 hours. We corrected QT intervals with Fridericia's formula ( $QTcF = QT/RR^{1/3}$ ). Blood samples were taken 10 hr after the last dosage. Using the mean QTcF in the daytime (9 AM to 5 PM) or at night (10 PM to 6 AM) as dependent variables ( $y$ , msec) and the RIS plasma concentration as independent variables ( $x$ , ng/mL), we carried out linear regression analyses.

### Results and Discussion

The linear regression analysis showed that RIS prolonged QT interval in concentration-dependent manner only at night ( $y = 393.5 + 2.3x$ ,  $P = 0.095$ ). We suggested the concentration-dependent effect of RIS on QT interval in the clinical setting. A high concentration of RIS may be a risk factor of QT prolongation and TdP.

## Role of Aripiprazole in Treating Medication Induced Tardive Dyskinesia

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**Objectives:** To review the effects of aripiprazole in treatment of medication induced tardive dyskinesia

**Methods:** Medline search was performed using key words of 'aripiprazole' and 'tardive dyskinesia'. We searched overall articles published between 2000 and 2008.

**Result:** Aripiprazole inhibits central dopaminergic neuron activity by a partial agonistic effects on presynaptic D2 dopamine autoreceptors and also acts as an antagonist at postsynaptic D2 dopamine receptors. Through this mechanism, aripiprazole exerts activity as a dopaminergic agonist in hypodopaminergic states, while acting as a dopamine antagonist when dopaminergic activity is increased. There is also evidence from basic science studies that aripiprazole causes D2 receptor up-regulation

**Conclusions:** It is plausible that aripiprazole, by virtue of its dopamine agonistic activity, can potentially normalize D2 dopamine receptor up-regulation. this properties may play a role in both prevention of the emergence of tardive dyskinesia and the treatment of Tardive dyskinesia. Double blind placebo-controlled studies would be needed to enlighten this issues.

**Key words:** Tardive Dyskinesia, Aripiprazole, Action mechanism.

## Sulpiride Induced Insomnia: A Long-forgotten Side Effect

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### Background

Sulpiride is a benzamide neuroleptic and was developed as an antipsychotics by French drug maker, Delagrang, in 1967. In Japan, it was first applied for the treatment of peptic ulcers in 1973, then expanded its application to depression and schizophrenia. But nowadays, it is not used in North America (United States and Canada), and used only for schizophrenia in United Kingdom (UK).

### Method

Case series of sulpiride induced insomnia with non-systematic review of literature.

### Results

We have three cases of sulpiride induced insomnia with primary disease of major depressive disorder (MDD). All of them got complete remission of MDD with antidepressants including sulpiride, but distressed by intractable insomnia which could not resolved by strong hypnotics. They had no apparent manic or hypomanic symptoms. With discontinuation of sulpiride or quitting administration of it after evening time, the hypnotic-resistant insomnia was rapidly resolved and soon got no hypnotics been needed. With literature search, we found a very old literature of 1970s pointing out insomnia with sulpiride as common side effect and there is another literature which recommends not to put this drug after evening time.

### Conclusion

Sulpiride evokes refractory sleep disturbance in depressed patients which may be as a result of its dopaminergic effect. Clinicians should be cautious about this long-forgotten side effect and examine the possibility of this side effect in case of hypnotic-resistant insomnia of MDD in remission.

## Extract of Ginkgo Biloba Treatment for Tardive Dyskinesia in Schizophrenia: A Randomized, Double-Blind, Placebo-Controlled Trial

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**Objective:** Free radicals may be involved in the pathogenesis of tardive dyskinesia (TD). Extract of Ginkgo Biloba (EGb) is a potent antioxidant possessing free radical-scavenging activities. The aim of the study was to evaluate the efficacy of EGb-761 in treating TD in schizophrenia patients.

**Method:** Inpatients with schizophrenia and TD ( $n = 157$ ) were randomly assigned to 12 weeks of treatment with either EGb-761, 240 mg/d ( $n = 78$ ), or a placebo ( $n = 79$ ) in a double-blind manner. Primary outcome measures were: 1) change from baseline in the Abnormal Involuntary Movement Scale (AIMS) and 2) proportion of patients with a 30% reduction in their total AIMS score at week 12. Secondary outcome measures included the Positive and Negative Syndrome Scale (PANSS) and cognitive performance as measured by the CPT-37 Version and the three-card Stroop task.

**Results:** Of the 157 patients who were randomly assigned, 152 (96.8%) completed the study. EGb-761 treatment significantly decreased the total AIMS score in patients with TD compared to those who were given a placebo ( $2.16 \pm 1.75$  versus  $-0.11 \pm 1.74$ ;  $p < .0001$ ), with 40 (51.9%) and 4 (5.3%) patients achieving efficiency in the EGb-761 and placebo treatment groups, respectively. There were no between-group differences in the PANSS total score or cognitive measures from baseline to week 12.

**Conclusions:** EGb-761 appears to be an effective treatment for reducing the symptoms of TD in schizophrenia patients, and improvement may be mediated through the well-known antioxidant activity of this extract.

## Attitudes Toward Menstruation in Females with Schizophrenia or Schizoaffective Disorders in Taiwan

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Female patients with schizophrenia or schizoaffective disorder often suffer from menstrual irregularity caused by unwanted blockages of dopamine D2 receptors of the tubero-infundibular tract. The prevalence of oligomenorrhoea and amenorrhoea following treatment with conventional antipsychotic medications and second-generation antipsychotics is 45% and 48%, respectively. The aims of this cross-sectional, control study were: (i) to exam attitudes toward menstruation between female patients with schizophrenia or schizoaffective disorder and a control group; and (ii) to explore the associations between attitudes toward menstruation and psychopathology, menstrual regularity, and menstrual distress symptoms. Psychopathology was assessed by psychiatrists using the Positive and Negative Syndrome Scale (PANSS). Fifty-eight patients treated with anti-psychotic medications for at least the previous six months were placed in irregular (irregular menstrual cycle) (n=31) and regular (regular menstrual cycle)(n=27) groups. Sixty-two, age-matched, and healthy female participants with regular menstruation cycles were enrolled as a control group. The Menstrual Attitude Questionnaire (MAQ) was used to assess attitudes toward menstruation, and symptom checklists based on the Moos Menstruation Distress Questionnaire (MMDQ) were used to assess menstrual distress symptoms. Patients with psychotic disorders (both irregular and regular groups) had more negative attitudes toward menstruation than the control group. There was no association between the severity of psychotic symptoms and their influence on attitudes toward menstruation. Menstrual regularity and the number of menstrual distress symptoms were the best predictors of total score of attitudes toward menstruation in women with psychotic disorders. This is one of the first studies to explore the relationship between psychotic symptoms and attitudes toward menstruation. The findings provide more support for the assumption that attitudes toward menstruation are derived from a woman's perception of her bodily experience as opposed to psychiatric disorder. Key Words: Antipsychotics, menstrual attitude questionnaire, schizophrenia, menstrual irregularity, menstrual distress questionnaire

## A Two-year Prospective Follow-up Study of Lower Urinary Tract Symptoms in Patients Treated with Clozapine

○In Won Chung, Jin Young Kim, Seong Hoon Jeong

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**Objective:** Urinary incontinence and nocturnal enuresis are well-known side effects of clozapine medication. However, clinical experience has shown that patients also suffer from diverse lower urinary tract symptoms (LUTS). The natural course of clozapine-related LUTS is quite unclear. Thus, a longitudinal follow-up study of the wide range of LUTS is needed. **Methods:** A total of 101 subjects who was taking clozapine initially participated. Their LUTS were evaluated with the International Prostate Symptom Score (IPSS), other questionnaires and the medical records review. After two years, 87 of the original subjects could be contacted and the status of their LUTS was re-evaluated. **Results:** The average IPSS total was 7.4+5.9 at the initial evaluation. Though only 11 subjects (10.9%) reported actual incontinence of the urge type, 42 subjects (41.6%) were found to have clinically significant LUTS (IPSS total score  $\geq$  8). No influencing factors could be found among the demographic and clinical variables. At the follow-up, the average IPSS total (7.9+6.0) and the percentage of subjects with clinically significant LUTS (43.7%) had both increased, though not statistically significantly so. About two-thirds of the subjects with significant LUTS at the initial evaluation still had similar symptoms two years later. **Conclusion:** The prevalence of LUTS in clozapine-medicated patients was higher than in the general population of the same age. However, the prevalence of actual incontinence was only a quarter of that of LUTS. If the clinicians focus only on incontinence, distress from other LUTS will not receive appropriate attention. Furthermore, contrary to literature observations, clozapine-related LUTS did not remit easily but, rather, persisted even into the long-term maintenance phase. More concern and active research efforts should be directed at these troublesome and often neglected side effects.

## Antipsychotics and Bone Density in Patients with Schizophrenia

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**Objectives:** Patients with schizophrenia is associated with high rates of low bone density but the etiology of which remains obscure. Previous studies explained by the prolactin-raising properties of antipsychotic medication. This study investigate the association between prolactin level and low bone mineral density and to get comprehension into etiology of low bone density.

**Methods:** In a cross-sectional study, 45 schizophrenic patients were the participants in the study and 20 of them were treated with risperidone, 15 with olanzapine and 10 with clozapine. All patients had been monotherapy for at least 1 years. The authors used dual X-ray absorptiometry to determine bone mineral density. A blood sample was taken to measure prolactin and sex hormone axis measures.

**Results:** There was no significant statistical difference between patients treated with risperidone, olanzapine and clozapine in BMD z scores. Bone mineral density showed highly negative correlation with Positive and Negative Syndrome Scale's negative subscale. Correlations between the levels of prolactin were not significance.

**Conclusion:** These results suggest that the high rates of low bone density may not result from hyperprolactinemia as a consequence of prolactin raising antipsychotics. but these finding support to more attention about activities, calcium intake, sunlight exposure on patients with schizophrenia.

**KEY WORDS:** bone density, antipsychotics, prolactin, PANSS

## Fixed Drug Eruption Induced by Risperidone

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Risperidone is a novel antipsychotic agent with relatively few side effects. No case describing fixed drug eruption associated with risperidone have been reported. I experienced a case of risperidone induced fixed drug eruption in a patients with vascular dementia.

Case1: A 73-year old female vascular dementia patient lived in an asylum for the old. She has a medical history of hypertension, hemorrhage in right thalamus and left hemiparesis. She had erythematous indurated swelling on the tongue and could not eat and shut her mouth, following ingestion of 1mg tablet of risperidone. After discontinuation of risperidone erythematous indurated swelling on the tongue was subsided spontaneously and she could eat and shut her mouth. 1 week later, I retried risperidone 1mg at night, Next morning erythematous indurated swelling of the tongue was reappeared and she could not eat and shut her mouth. Risperidone therapy was replaced with 25mg tablet of trazodone, on the following day erythematous indurated swelling of the tongue was subsided without any specific treatment and she could eat again.

Discussion: A fixed drug eruption can be defined as a fixed exanthem which is induced by drug. Fixed refers to recurrence of lesions of same sites. Risperidone is a novel antipsychotic agent with relatively few side effects. In this case erythematous indurated swelling of the tongue was reappeared when I rechallenged risperidone. Although no other laboratory study was done because of her medical and environmental condition. her clinical manifestation was fixed drug eruption according to the definitions.

## Treatment of Catatonia with Olanzapine: A Case Report

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**1. Introduction** Catatonia is characterized usually by fixed posture, waxy flexibility, mutism, negativism and echolalia. It can be caused by various neurological, medical, or psychiatric disorders. Available data supports the efficacy of benzodiazepines and electroconvulsive therapy (ECT) in the treatment of this condition, but the treatment response is limited by the chronicity of symptoms (Weder et al., 2008). Here we report a case of an ethnic Chinese male with catatonia who responded to olanzapine. **2. Case report** Mr. W., a 22-year-old ethnic Chinese male, has been treated for schizophrenia (DSM-IV-TR criteria) for the past 6 years. On admission, he was experiencing about two weeks of catatonic symptoms including mutism, and catalepsy with extended posturing (>20min). Extensive laboratory evaluations were unremarkable. Scores of the Bush Francis Catatonia Rating Scales (BFCRS) was 23 on his first day in hospital. Lorazepam (2mg) was given twice within six hours, but his catatonic symptoms persisted. Because he could not take medication and catatonic schizophrenia was suspected, olanzapine (10mg) was started on day 1 via muscular injected per 12 hours. His catatonia improved dramatically within three days (BFCRS : 12 points on 2nd day, 4 points on 3rd day). He was discharged 5 weeks after his admission, and on olanzapine 20mg daily. There has been no recurrence of his catatonia after 6 months. **3. Discussion** Recently, increasing reports shows that typical antipsychotics may aggravate catatonia, but atypical antipsychotics may improve catatonic signs in patients without neuroleptic malignant syndrome (NMS). (Van Den Eede et al., 2005) Atypical antipsychotics such as olanzapine have decreased D2 receptor binding affinity compared with typical antipsychotics, and therefore may be less likely to precipitate NMS and/or worsen catatonia in catatonic schizophrenia. (Martenyi et al., 2001) A functional magnetic resonance imaging study during negative emotional stimulation shows orbitofrontal cortical dysfunction in akinetic catatonia (Northoff et al., 2004). Further image studies will be helpful in realizing the mechanism of olanzapine in catatonic patients.

## Risperidone Orodispersible Tablet and Intramuscular Haloperidol in Treatment of Psychotic Agitation

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**Objectives:** Psychotic agitation of psychiatric patients is a common manifestation that needs emergent management. Traditionally, parenteral or intramuscular injection of antipsychotics was conducted for treatment of psychotic agitation. Considering rapidly absorbed form of risperidone (risperidone orodispersible tablet) could be used for the agitated patient, comparison of oral risperidone and intramuscular haloperidol was performed in emergency treatment of psychotic agitation in this study.

**Methods:** One hundred and twenty four patients with psychotic agitation were recruited at emergency room or inpatient ward. They were randomly assigned to either group of oral risperidone or intramuscular haloperidol. Efficacy of both treatments were measured and compared by the scores of 5-item acute-agitation cluster from the Positive and Negative Syndrome Scale (PANSS-EC) and Clinical Global Impressions-Severity of Illness scale (CGI-S). Tolerability and safety were also compared between two groups.

**Results:** The PANSS-EC and CGI-S scores were significantly decreased over time in both treatment groups without any significant group difference and time by the group interaction effect ( $F=459.7$ ,  $P<0.0001$ ). There were no serious adverse events in both groups.

**Conclusion:** For the emergency treatment of psychotic agitation, risperidone orodispersible tablet was as effective and tolerable as intramuscular administration of haloperidol. Therefore, it is considerable to choose oral medication instead of intramuscular injection for treatment of patients with acute psychotic agitation.

## Prospective Observational Study in Acute Schizophrenic Patients Treated with Olanzapine in Japan

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**[Purpose]** Evaluating the safety and efficacy of olanzapine in acute schizophrenia for 6 weeks under clinical practice **[Methods]** CGI-S: Parkisonism (CGI-S:P), CGI-S: Akathisia (CGI-S:A), Agitation-Calmness Evaluation Scale (ACES), adverse events (AE), body weight (BW), blood glucose (BS) types, blood lipid level, BPRS positive sub-scale score (BPRS) and CGI-S: Schizophrenia (CGI-S:S) were collected. An analysis was made in three groups divided by the olanzapine starting dose ( $\leq 10$ mg/day,  $>10$ mg/day and  $\leq 20$ mg/day,  $>20$ mg/day). The label recommended starting dose of olanzapine is 5 to 10 mg/day, with dosing not to exceed 20mg/day. **[Results]** 1123 patients were enrolled and 965 remained at 6 week. At week 6, CGI-S:P and CGI-S:A were decreased and ACES score improved. Adverse events were observed in 19.06 %. Mean BW was increased for 0.83kg. According to the categorical BS analysis, the incidence of BS type worsening was 4.94%. BPRS and CGI-S:S improved. At baseline, the number of patients in the three starting dose groups were 807, 306 and 10, respectively. The BPRS were  $17.60\pm 4.80$ ,  $19.93\pm 4.5$  and  $24.30\pm 4.03$ , respectively. At 6 weeks, the differences were not statically significant. Changes in BW were  $0.88\pm 2.51$ kg,  $0.70\pm 2.75$ kg, and  $1.00\pm 1.81$ kg respectively, these were not statistically significant. **[Conclusion]** Administering the appropriate dose of olanzapine, within the approved dose range, based on the severity of symptoms provide safe and effective treatment for patients with acute schizophrenia.

## The Prescription of Zyprexa and Other SDAs at Twin Super Emergency Ward

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Tokyo has wards that admit patients who are forced to admit by legal control. These wards are called super emergency wards, and we have a couple of them. Our psychiatric department has 637 beds, and our 2 psychiatric super emergency wards have 87 beds. Inpatients averaged 50 days, staying in the hospital. The number of inpatients in 2007 were 1994, and within them 1681 were psychiatric patients. Approximately 1000 patients or 60% were new patients, and they are the key to Tokyo's psychiatric emergency department. There are two super emergency wards, which are nearly identical. We compared the dosage of 10 different major tranquilizers such as Zyprexa, given to patients at these wards from June 2008 to May 2009. We allocated serotonin dopamine antagonists (SDA), which include Zyprexa to ward A (44beds), and typical antipsychotic agents to ward B (43). The drugs that gained the highest sales for each ward were Zyprexa for ward A, and Risperidone for ward B. Ward A uses Zyprexa 3 times more, and Aripiprazole 2.5 times more than ward B. Ward B uses chlorpromazine twice, and Haloperidol 3 times more than Ward A. Super acute phase wards such as Ward A may use SDA drugs for main treatment. However, the drug cost was twice more expensive for ward A than for ward B. Drugs to reduce EPS were not used, but the drug costs were still more expensive. Expensive drugs reduce the profit for hospitals since the government determines the hospital admission rate per person. SDAs such as Zyprexa were proven to be a choice for drug treatment at super acute phase wards. However, there still lies financial problems.

## Comparison the Effect of Intramuscular Antipsychotics Injection in the Treatment of Acute Agitation in Psychosis

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**Purpose of this study:** This study aimed to compare effectiveness and safety of intramuscular Haloperidol and intramuscular Olanzapine, intramuscular Haloperidol plus Lorazepam for psychotic patients with acute agitation state.

**Methods:** 37 psychotic patients with acute agitation were randomly assigned to Haloperidol 5mg IM or Olanzapine 10mg IM or Haloperidol 5mg IM plus lorazepam 4mg IM groups. The Positive and Negative symptom Syndrome Scale excitement component (PANSS EC) and Clinical Global Impression-Severity (CGI-S), Clinical Global Impression-Improvement (CGI-I) were assessed at baseline, 30minute, 60minute and 120minute after injection respectively. Side effect Checklist and blood pressure were used for the assessment of side effect at baseline, 30minute, 60minute and 120minute after injection.

**Results:** There are no difference in sociodemographic datas. PANSS EC scores were significantly ( $p < 0.0001$ ) decreased over time, without any significant group differences. CGI-s were decreased over time in three groups. CGI-I were improved in all groups. Intramuscular Haloperidol and intramuscular Olanzapine, intramuscular Haloperidol plus Lorazepam for psychotic patients with acute agitation state are all effective approach. There were no serious adverse events in all groups.

**Conclusions:** This study showed that Haloperidol IM, Olanzapine IM and Haloperidol plus Lorazepam IM treatment would be effective and tolerable for treatment of psychotic patients with acute agitation state. Further study is needed for another rapid management approach of severe psychotic agitated state.

## Efficacy of Aripiprazole on Acute Schizophrenic Patients: Views From Plasma Levels of Catecholamine Metabolites and Brain-derived Neurotrophic Factor

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**Background:** We previously reported that plasma levels of 3-methoxy-4-hydroxyphenylglycol (MHPG) in first-episode schizophrenic patients were significantly decreased, and treatment of atypical antipsychotic drugs increased those levels (Yoshimura et al, 2000; Hori et al, 2007). **Object:** We investigated the effects of aripiprazole on plasma levels of MHPG, homovanillic acid (HVA), and brain-derived neurotrophic factor (BDNF) in acute schizophrenic patients. **Subjects and Methods:** Thirty-one patients (M/F: 16/15, age:  $31 \pm 5$  yr) who met DSM-IV criteria for schizophrenia and treated with aripiprazole ( $20 \pm 5$  mg/day) were enrolled in the study. Their psychotic symptoms were evaluated by using PANSS, and plasma levels of MHPG, HVA, and BDNF were measured. The protocol of this study was approved by the Ethics Committee of the University of Occupational and Environmental Health. **Results:** The total scores of PANSS were significantly decreased at 2 weeks after administration of aripiprazole. The plasma HVA levels were significantly decreased at 8 weeks, and the plasma MHPG levels were significantly increased at 8 weeks. A positive correlation was found between the changes in MHPG levels and the changes in PANSS-N scores. Plasma BDNF levels were not altered at 8 weeks. **Conclusion:** Aripiprazole improves psychotic symptoms via influencing catecholaminergic neurons in schizophrenic patients.

## Efficacy and Safety of Aripiprazole in First-episode Schizophrenia: An Open-label Study

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**Aims:** The aim of the present study was to investigate the efficacy, safety and tolerability of aripiprazole in patients with first-episode schizophrenia. **Methods:** This study was prospective, single-group, 28-week open study of patients with schizophrenia. A total of 32 Japanese patients participated in the study. The efficacy measure was the Positive and Negative Syndrome Scale (PANSS), Clinical Global Impression-Severity of Illness (CGI) and Global Assessment of Function (GAF). Tolerability and safety were assessed by monitoring the frequency and severity of treatment-emergent adverse events, extrapyramidal symptoms (EPS), weight and laboratory tests. **Results:** Aripiprazole produced rapid and significant improvements on all efficacy measures. As evidenced by PANSS, GAF and CGI-S scores, first episode patients demonstrated significant greater efficacy. **Conclusion:** Aripiprazole is an effective antipsychotic in the treatment of both positive and negative symptoms.

## The Prospective Comparison of Efficacy and Safety of Aripiprazole, Risperidone, Olanzapine, Quetiapine and Haloperidol in Patient with Schizophrenia or Schizoaffective Disorder

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In our two study we evaluate the efficacy of comparative effects on therapeutic efficacy and metabolic side effects among aripiprazole, risperidone, olanzapine, quetiapine and haloperidol in psychiatric patients. We have investigated the therapeutic efficacy, metabolism of glucose and lipid and change in prolactin in aripiprazole, risperidone, olanzapine, quetiapine and haloperidol in psychiatric patients in two different time period. In this study, we analyzed the two collective data collected from July in 2003 to February in 2004 and from December in 2004 to April in 2007. During the former period, we were working on three different drugs with risperidone, olanzapine and quetiapine. Whereas during the latter period, we were working on two other drugs. All subjects met the inclusion criteria of schizophrenia and schizoaffective disorder, as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR). A 12-week, non-randomized, open-label, parallel-group study were carried in both studies. In order to compare the efficacy of the drugs, we conducted the PANSS scores at baseline and endpoint. Similarly, we measured the fasting glucose level, cholesterol level and serum prolactin level at baseline, week 4, 8 and 12. The demographic characteristics of the participants indicate no significant differences. There was a decrease in PANSS score in every study drug. however, for risperidone, olanzapine and quetiapine, they showed better efficacy in positive symptoms than aripiprazole and haloperidol. For aripiprazole, it was better efficacy in negative symptoms although they were not statistically significant. All drugs but aripiprazole have increased the serum glucose level and among those, risperidone has increased the most at  $19.0 \pm 28.3$  ( $p < 0.05$ ). The serum cholesterol level of olanzapine and aripiprazole was mildly increased and decreased respectively at  $5.3 \pm 32.8$  and  $-5.8 \pm 29.82$  although they were not statistically significant. At the same time, regarding the serum prolactin level, risperidone, olanzapine, and haloperidol was increased to  $23.5 \pm 25.0$ ,  $14.0 \pm 16.7$  and  $14.79 \pm 36.45$  respectively. On the contrary, regarding aripiprazole, the serum prolactin was decreased to  $-12.94 \pm 25.99$ . All treatment group showed improved in PANSS score, while there was no significant difference among treatment groups. risperidone and quetiapine have increased the serum glucose level. In serum cholesterol level, there was mildly increased or decreased respectively, but they were not statistically significant. Regarding aripiprazole, there was significant decreased in the serum prolactin, although risperidone, olanzapine, and haloperidol were increased it.

## Low Dose vs. Standard Dose of Antipsychotics for Relapse Prevention in Schizophrenia: Meta-analysis

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**Objective:** It remains unclear as to whether the antipsychotic dose needed for the acute phase is also necessary for relapse prevention. The objective of this meta-analysis was to compare the efficacy between standard dose (i.e., equal to or more than the defined daily dose by the World Health Organization) vs. low dose (less than the defined dose, but equal to or greater than half the dose) or very low dose (less than half the defined dose) for the maintenance treatment of schizophrenia. **Method:** Double-blind randomized controlled trials, including at least two dosage groups of the same antipsychotic drug for the maintenance treatment of schizophrenia, were identified. Data on overall treatment failure, hospitalization for psychopathology, and dropouts due to side effects were extracted on an intention-to-treat basis and combined in a meta-analysis. **Results:** A total of 13 studies with 1,395 subjects were included. The low dose therapy showed non-inferiority to standard dose treatment in terms of overall treatment failure and hospitalization. The very low dose group was found to be inferior to the standard dose group in those two efficacy parameters. No significant difference was found in the rate of dropouts due to side effects between either standard dose vs. low dose or very low dose. **Conclusions:** Currently available data suggest that not very low, but modestly low dose antipsychotic therapy is equivalent to standard dose therapy in terms of efficacy. These findings have important implications for dosing of antipsychotics for relapse prevention in schizophrenia.

## The Importance of Consistently Taking Medication to Obtain and Keep Good Adherence - Medication Event Monitoring System (MEMS) Trial to Evaluate the Compliance of Patients with Schizophrenia in Japan -

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**Background:** Good adherence in patients using medicine is important for a good prognosis. Early intervention and relapse prevention is essential when treating patients with schizophrenia. This is the first multicenter study (one university hospital and six psychiatric hospitals) in Japan using MEMS to research relationships between relapse possibilities and medication taking consistency. **Methods:** Compliance was evaluated with MEMS for 6 months in 50 outpatients with schizophrenia and schizoaffective disorders using DSM-IV criteria. The patients had just been discharged. Pill counts, physicians' reports and self-ratings by patients were also used for estimation purposes. **Results:** 64% of patients showed compliant behaviors, 12% were non-compliant, and 24% failed to finish the study. Only patients with compliant behaviors continued to take medicine regularly as instructed, however a 20% drop in compliance was observed within one week after discharge. They also took their medicine within a 103 minute range from the instructed time. Non-compliant patients needed 192 minutes, and other patients 172 minutes. **Conclusion:** It is difficult to correctly estimate good adherence. The first week after discharge is a turning point in the level of compliance. Medicine needs to be taken regularly at this early stage to prevent relapses. If the patient feels that taking medicine every day is difficult, they should have the choice to use long acting injection therapy. It is also possible to support patients by teaching them about their illness, treatment and skills to solve problems by themselves.

## Cross-Section Study about Schizophrenic Drug Use of Ten Provinces and Cities in China in 2006

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**Object:** to learn the current situation of schizophrenic drug use of ten provinces and cities in China. **Method:** Chinese provinces are divided into five levels by gross national product per capita. In 2006, 5898 in-patient or out-patient psychopath in 41 mental hospitals or mental departments of general hospitals of ten provinces and cities are sampled. Self-made Questionnaire was used to make a cross-section study about schizophrenic drug use. **Result:** in 5898 patients, the number of outpatients is 2719, the number of inpatients is 3182; there are 3041 male patients, and 2803 female patients. 5848 patients are treated by schizophrenic drug. Top seven kinds of drugs used most frequently are 1888 cases of clozapine (31.7%), 1803 cases of risperidone (30.5%), 860 cases of sulpiride (14.5%), 638 cases of chlorpromazine (10.8%), 545 cases of perphenazine (9.2%), 424 cases of quetiapine (7.2%), 342 cases of haloperidol (5.8%). Among 5898 patients, 2261 patients are received typical schizophrenic drug treatment, 4290 patients are received atypical schizophrenic drug treatment. 4461 patients are received a single non-lente schizophrenic drug treatment. 1312 patients are received two or more schizophrenic drug treatment. 74 patients are received a single lente schizophrenic drug treatment. Converting to chlorpromazine equivalent dose, the treatment dosage is 12.5-4125mg/d, the average dosage is (365±253) mg/d the dosage of inpatients is (409±274) mg/d, which is higher than outpatients (300±201) mg/d (t=8.97, p=0.00). The most common mental symptoms are "affect abilities of social communication and work", "language and behavior disorder", "delusion and hallucinosis", "negative symptom", "depression", "attack", "overly low self-assessment or self-accusation" **Conclusion:** comparing to outpatients, inpatients are older, and the male ratio is higher, clozapine is used most frequently; inpatients are mainly treated by a single drug; the use rate of atypical schizophrenic drug is higher than typical schizophrenic drug.

## Dose Pattern and Effectiveness of Paliperidone in Patients with Schizophrenia: Results of 24-Week Study

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This 24-week multicenter, open label, non-comparative study was performed to determine the efficacy and dose pattern of paliperidone ER. All patients received 6mg of paliperidone ER during first 2 weeks of the study and after this 2 weeks the dose could be adjusted at each visit (2, 4, 8, 12, 16, 20, and 24 weeks) based on the patient's response to paliperidone ER. When the score of CGI-I was  $\geq 3$  (minimally improved) at each visit, the dose was either increased or maintained at the investigator's discretion until next scheduled visit. When the score of CGI-I was  $\leq 2$ , the dose increase was not allowed. We investigated treatment response rates based on CGI-S response criteria defined as a reduction of  $\geq 2$  from baseline (when baseline CGI-S  $\geq 5$ ) or reduction of  $\geq 1$  from baseline (when baseline CGI-S=4) for consecutive 2 visits. The response rate at 12 weeks and 24 weeks were 67.3%, 75.6%, respectively, when estimated using Kaplan-Meier method. To investigate the effect of early dose pattern (dosages at 2 and 4 weeks) of paliperidone on the treatment response, we compared the changes in CGI-S scores from baseline to endpoint between three subgroups of dose patterns (early increase, late increase, and maintenance group) for patients with inadequate response (CGI-I  $\geq 4$ ) at 2 weeks. We found that CGI-S scores significantly improved from baseline to 12 weeks to a greater extent in 'early increase group' than in 'late increase' (p<0.001) or 'maintenance group' (p=0.042). When we looked at the relapse rate among the responder at 12 weeks, we found only 9% of responder at 12 weeks failed to maintain the response until 24 weeks when estimated using Kaplan-Meier method. In conclusion, this study have shown the short (12 weeks) and long-term (24 weeks) effectiveness of paliperidone ER in treating schizophrenia. When early treatment response on the initial dose of 6mg is not adequate, dose increase is recommended as early as possible. Acknowledgement: This study was supported by Jassen Korea Ltd. and performed cooperatively in the PANDORA study group.

## A Double-Blind, Randomized, Risperidone-Comparative Study to Evaluate the Efficacy and Safety of Blonanserin in Patients with Schizophrenia

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**Objectives:** The objective of this study was to evaluate the efficacy and tolerability of Blonanserin, a combined 5-HT<sub>2A</sub> and D<sub>2</sub> receptor antagonist, for the treatment of adult patients with schizophrenia. **Methods:** This was a multi-center, randomized, double-blind, risperidone-comparative trial from January 2006 to December 2008. Patients aged 18 through 65 years with schizophrenia (DSM-IV criteria) and a baseline PANSS score of  $\geq 60$  were randomly assigned to blonanserin or risperidone for 8 weeks. The efficacy was assessed by mean change from baseline to week 8 on the PANSS total score as the primary variable. Mean change from baseline to week 8 was also assessed for the BPRS and CGI-I scores. Safety assessments included vital sign, physical routine clinical laboratory tests, and adverse events including extrapyramidal adverse drug reactions assessed according to the Drug-induced extrapyramidal symptom scale. The full analysis set was used in the primary efficacy analysis and the per-protocol set was used in an additional analysis to verify the accuracy of results of the primary analysis. **Results:** Of 212 randomly screened patients, 103 receiving blonanserin and 103 receiving risperidone were included in the analysis. The change in PANSS total score at the final evaluation time point was  $-10.80 \pm 9.57$  for the blonanserin group and  $-11.87 \pm 9.52$  for the risperidone group. The BPRS total score was decreased from baseline in both treatment groups ( $-14.58 \pm 11.60$  vs.  $-15.84 \pm 11.79$ ). Adverse drug reactions (ADR) occurred in 72 of 96 subjects (75.0%) in the blonanserin group and 73 of 93 subjects (78.5%) in the risperidone group. ADRs of which incidences were lower in the blonanserin than in the risperidone group ( $p < 0.05$ ) included dizziness ( $p = 0.0139$ ), dysarthria (0.0288), blurred vision (0.0288) and increased ALT and AST ( $p = 0.0183$ , 0.0067, respectively). Blonanserin may have advantage in weight gain and hyperprolactinemia ( $p < 0.0504$ ) although there was no statistical significance ( $p = 0.0504$ ). On the other hand, ADRs of which incidences were higher in the blonanserin than in the risperidone group ( $p < 0.05$ ) included tremor ( $p = 0.0010$ ). **Conclusions:** This study indicated that the therapeutic effect of blonanserin was comparable to that of risperidone while having a better safety profile, suggesting that blonanserin is useful for the treatment of schizophrenia.

## Effectiveness of Switching to Aripiprazole from Atypical Antipsychotics in Patients with Schizophrenia

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**Objectives:** To examine changes in cognitive function and clinical features following a switch from atypical antipsychotics to aripiprazole in patients with schizophrenia. **Method:** Sixty-one patients with schizophrenia treated with atypical antipsychotics participated in this open-label, 26-week study. Antipsychotics were switched to aripiprazole and neurocognitive functions were measured at 12 and 26 weeks using the computerized battery. The secondary outcome measures were the Positive and Negative Syndrome Scale (PANSS), Social and Occupational Functioning Assessment Scale (SOFAS), Calgary Depression Scale for Schizophrenia, Subjective Wellbeing under Neuroleptics Scale, and Drug Attitude Inventory (DAI). Safety measures included metabolic parameters, the Simpson-Angus Scale (SAS), Barnes Akathisia Scale, and Abnormal Involuntary Movement Scale (AIMS). **Results:** Significant improvements in cognitive function were observed in Verbal Learning Test (VLT), Wisconsin Card Sorting Test, and Trail Making Test type-A following a switch to aripiprazole. Scores on the PANSS, SOFAS, DAI, SANS and AIMS were significantly improved. Metabolic parameters, including serum cholesterol levels, were also improved. The changes in cognitive measures were not correlated with the changes in positive symptoms or movements scales. The improvement of the scores on the DAI and delayed recall of VLT were significantly greater in the patients treated with antipsychotics for less than 1 year than in those treated for more than 1 year, in whom the improvement in metabolic parameters was significantly greater. **Conclusion:** Patients with schizophrenia who were switched from their prior antipsychotic to aripiprazole demonstrated improvements in cognitive function, psychotic symptoms, social function, attitude toward medication, and metabolic abnormalities.

## Blonanserin: Clinical Efficacy and Safety in Schizophrenia, a Multicenter Naturalistic Study

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### [Objective]

Blonanserin (BNS) inhibits D<sub>2</sub> and 5-HT<sub>2A</sub> receptor with the profile of a Dopamine-Serotonin Antagonist (DSA). We conducted a research with prescribing BNS to patients with schizophrenia in several facilities to study the effectiveness and safety of BNS.

### [Methodology]

BNS was prescribed to 39 schizophrenic patients. Evaluations by BPRS, DIEPSS, CGI-I, and CGI-S were made after 4 and 8 weeks. By blood tests metabolic influences such as weight gain were considered. Tests included multiple Friedman tests. The Wilcoxon test was a significant one used for post hoc analysis. 19 cases of BPRS, DIEPSS, CGI-I, and CGI-S analysis results shall be reported.

### [Results and Summary]

Patient age:  $44.9 \pm 13.6$  years, sex (M/F): 10/9, time passed since onset:  $215.8 \pm 167.2$  months, initial occurrence/reoccurrence: 3/13, out-patient/in-patient: 6/11, previous medical history/none: 6/13, complications/none: 2/17, BNS initial dosage was  $7.58 \pm 1.26$ /day, maintenance dosage was  $18.74 \pm 6.26$ mg/day.

The BRPS scores showed significant improvement:  $52.9 \pm 11.0 \rightarrow 44.7 \pm 11.2 \rightarrow 39.5 \pm 11.3$ . Improvements were significant for all items other than disorientation. No significant differences were seen in DIEPSS, but there were improvements in bradykinesia after 8 weeks. Significant improvements were seen in CGI-S:  $4.05 \rightarrow 3.68 \rightarrow 3.50$ , and in CGI-I:  $3.05 \rightarrow 2.67$ . 10 reports showed no increase in the average weight.

16 out of 19 cases with effectiveness being recognized were switched from another medication. We will present the results of the analysis of 39 cases.

## Perospirone and Aripiprazole Showed Equal Efficacy for Japanese Schizophrenia - A Randomized Clinical Trial -

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**OBJECTIVE:** To compare the therapeutic efficacy of Perospirone and aripiprazole in patients with schizophrenia. **SUBJECTS AND METHOD:** All patients were diagnosed as schizophrenia according to DSM-IV-TR. The patients who gave the informed consent to this 8-week, single-blind and flexible-dose trial were randomly assigned to PER ( $n = 24$ ) or APZ ( $n = 26$ ). The clinical symptoms were evaluated using PANSS before and every 4 weeks. The efficacy was assessed by changes from baseline for PANSS score. For 40 patients who completed 8 weeks study, all PANSS and DIEPSS evaluations were available. An intention-to-treat analysis was instead carried out for the 10 patients who underwent a baseline and at least 1 other assessments; the last observation was carried forward on the PANSS score. The study was approved by the Ethical Review Board of Kansai Medical University. **RESULT:** No significant difference of sex, age, but total PANSS score at the baseline was observed between the two groups. Therefore baseline score was included as covariate in all analyses. Both groups showed significant improvement during the study with reduction of total PANSS scores. There were no significant differences in PANSS total, positive and negative subscale score change overtime between PER and APZ treatment group between two treatment groups. **Conclusion:** PER and APZ showed equal efficacy on schizophrenia patients. Both drugs showed good efficacy for the treatment of schizophrenia. To our best knowledge, this is the first study about clinical comparison of PER and APZ.

## Immediate Versus Gradual Suspension of Previous Treatments During Switch to Aripiprazole: Results of a Randomized, Open Label Study

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The aim of the present work was to investigate possible differences in terms of efficacy and tolerability between different switching options to aripiprazole. 77 subjects were randomly assigned to: (Group 1) administration of aripiprazole (10 mg/day) with simultaneous discontinuation of current antipsychotic; (Group 2) administration of aripiprazole (10 mg/day) while tapering off current antipsychotic over 4 weeks with half dose after the first 2 weeks AND (Group 3) administration of aripiprazole (10 mg/day) and tapering off current antipsychotic over 4 weeks after maintenance of current dose for 2 weeks. Efficacy assessments included CGI-S, CGI-I, BPRS and SANS. Safety assessments included SAS, BAS and AIMS. Severity of symptoms significantly decreased from baseline over the 12 weeks of treatment. Patients switched to aripiprazole with immediate discontinuation of the previous antipsychotic showed an increase of symptoms' severity at week 1. However, severity of side effects did not overall change significantly during the 12-weeks follow-up. Previous treatment's tapering off strategy for switching patients to aripiprazole could be preferable as compared to abrupt discontinuation, in order to prevent early worsening of symptoms and premature discontinuation of treatment, though this results has to be considered with caution given the limitations of the study.

## Attitudes of Korean Psychiatrists Toward Long - acting Injectable Antipsychotic Treatment

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**Objectives:** Long acting injectable antipsychotic medication with the ability to sustain drug effect for long duration enables advances in management of psychiatric patients who have poor compliance or difficulty to get oral forms of antipsychotics. However, the earlier studies reported that depot antipsychotics are not prescribed enough much in the treatment of schizophrenia or schizoaffective disorder. Psychiatrist's attitude toward depot antipsychotics has influence on decision-making about selection of medications. There was not data about psychiatrist's attitude about long-acting injectable antipsychotics in Korea until now. This study examined psychiatrists' attitudes toward antipsychotic depot medications and factors which would contribute to the choice of depots.

**Methods:** We questioned 347 psychiatrists attending a conference about their attitudes toward depot antipsychotic treatment.

**Results:** The most important factor reluctant to prescribe depot treatment pertaining both classes is a presumed sufficient compliance with oral antipsychotic treatments. In addition, typical depots are not considered to be appropriate treatment options for the first-episode patient, whereas atypical long-acting injectable drugs are avoided due to strict criteria of insurance and high treatment costs.

**Conclusion:** Aversions to prescribe depot treatment are frequent among psychiatrists and appear to be unrelated to the antipsychotic class. The stated reasons for not choosing depots are generally not supported by the current studies and evidence, and further researches are required to clarify the advantages of depot treatments.

**KEY WORDS:** Attitude of Health Personnel, Depot, Antipsychotic Agents, Delayed-Action Preparations, Schizophrenia

## Aripiprazole in Schizophrenic Patients with Predominantly Negative Symptoms: A 52-week Prospective Study

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**OBJECTIVE:** The present study aimed to investigate the long-term efficacy of aripiprazole in Korean patients with schizophrenia, schizophreniform disorder, or schizoaffective disorder with predominantly negative symptoms.

**METHOD:** A prospective, multicenter, open, single group study with 52 week aripiprazole administration in a total of 300 patients was performed from July 2004 to August 2006 in South Korea, among which 39 were selected based on a definition of negative symptom predominance-the negative subscale score was 6 points higher than the positive subscale score at the baseline on The Positive and Negative Syndrome Scale (PANSS). PANSS and the Clinical Global Impression (CGI) score were serially measured 12 times during the 52-week treatment with aripiprazole. We analyzed the data with intention-to-treat (ITT) and last-observation-carried-forward (LOCF) method.

**RESULTS:** Aripiprazole demonstrated significant long-term improvements across total scores and all subscales of PANSS (all scales,  $p < 0.001$ ) and CGI-Severity of Illness score ( $p < 0.001$ ). The difference between PANSS negative and positive subscale scores at the baseline ( $9.85 \pm 3.63$ ) was decreased significantly than at the 52-week ( $5.69 \pm 5.76$ ;  $p < 0.001$ ). The effectiveness was apparent as early as the first week of treatment and continued significantly throughout 52 weeks.

**CONCLUSIONS:** The present study has demonstrated that aripiprazole was effective for the treatment of both positive and negative symptoms of schizophrenia spectrum patients with predominantly negative symptoms.

## Attitudes of Patients with Schizophrenia Toward Treatment with Long-acting Injectable Antipsychotic Medication

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**Objectives:** The poor compliance of patients with schizophrenia is the major cause of recurrence and lead to the poor prognosis. Long-acting injectable antipsychotics has a benefit to resolve the poor compliance. The attitude of patients with schizophrenia toward these treatment have never been investigated. This study examined the perspective on depot antipsychotics of patients with schizophrenia and their care-givers.

**Methods:** We surveyed 800 schizophrenic outpatients and 200 care-givers who visited the National Seoul Hospital for attitude toward long-acting injectable antipsychotic treatment. The study was conducted from November 2008 to May 2009.

**Results:** 245 (28.6%) of patients preferred long-acting injectable antipsychotic treatment, and 149 (17.4%) didn't have no fear about it. 59 (27.3%) of care-givers preferred depot antipsychotics, 49 (22.7%) didn't reject it. Comparing according to demographic variables, there was the difference in preference about injection between group of age under 40 and group of age over 40. ( $p = 0.05$ ). Moreover there was the meaningful difference in preference about depot antipsychotics between group of which interval of visiting out-patient clinic is under 8 weeks and group of over 9 weeks. ( $p = 0.005$ ).

**Conclusion:** In both schizophrenia patient and care-giver group, they preferred long-acting injectable antipsychotic treatment. Preference toward depot antipsychotics was higher in younger group and same result was showed in group under 8 weeks of outpatient clinic visiting interval.

**KEY WORDS:** long-acting injectable antipsychotic medication, schizophrenia, preference

## Psychopharmacology and Psychopathology of Dopaminergic System

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It is well known that psychotropic agents, which block the dopaminergic system, show remarkable effects in schizophrenia especially in those cases with positive symptoms. Moreover, in my personal opinion, the equivalent amount of psychotropic agents actually works extremely well in dissociative identity disorder (multiple personality disorder) as well. There is also a certain amount of medical literature stating that anti-dopaminergic psychotropic agents are effective in the treatment of pathological gambling (compulsive gambling). In other words, it can be said that the development of schizophrenia, dissociative identity disorder (multiple personality disorder), and pathological gambling (compulsive gambling) somehow involves the dopaminergic system. If so, what is the psychopathological feature common to these pathologies which involve the dopaminergic system in their development? The objective of this article is to start discussion of the psychopharmacology (psychobiology) of the dopaminergic system from this point.

## A Single Ascending Dose of Desvenlafaxine Administered to Healthy, Female Japanese Subjects

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**Objectives:** To assess the pharmacokinetics and tolerability of single desvenlafaxine doses in healthy, female, Japanese subjects. **Methods:** This randomized, double-blind, placebo-controlled, inpatient study was conducted using single ascending doses of desvenlafaxine. Eight subjects (desvenlafaxine: 6; placebo: 2) were assigned to receive single doses of desvenlafaxine 50, 100, 200 mg or placebo. The primary outcomes, measured using validated liquid chromatography/tandem mass spectrometry, were area under the plasma concentration-versus-time curve (AUC) and peak plasma concentration (C<sub>max</sub>). Treatment-emergent adverse events (TEAEs) were also assessed. **Results:** Twenty-three healthy, female, Japanese subjects aged 22 to 41 years were enrolled. Six subjects received desvenlafaxine 50 and 200 mg, 5 received 100 mg, and the remaining 6 received placebo. The AUC of desvenlafaxine 50, 100, and 200 mg were 3290, 5646, and 12178 ng·h/mL. The C<sub>max</sub> of desvenlafaxine 50, 100, and 200 mg were 158, 238, and 547 ng/mL. Thirteen subjects receiving desvenlafaxine and 2 receiving placebo experienced TEAEs. The most common were nausea, somnolence, asthenia, and diarrhea. Nausea was more frequently reported in the desvenlafaxine 200-mg group (67%) than in the 100 (40%) and 50-mg group (17%), whereas no subjects in the placebo group reported nausea. No subjects withdrew from the study because of TEAEs. **Conclusions:** The AUC and C<sub>max</sub> of desvenlafaxine were proportional to the dose of desvenlafaxine administered. Desvenlafaxine was generally well tolerated at doses of 50, 100, and 200 mg.

## Effects of Paroxetine on Plasma Concentrations of Aripiprazole and its Active Metabolite, Dehydroaripiprazole in Schizophrenic Patients

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The effects of paroxetine (PAX) on plasma concentrations of aripiprazole (ARI) and its active metabolite, dehydroaripiprazole (DARI) were studied in 8 schizophrenic patients being treated with ARI (6 mg/day in 4, 12 mg/day in 3 and 24 mg/day in 1). PAX 10 mg/day was co-administered for 1 week, and the dose was increased to 20 mg/day for the next 1 week. Blood samples were taken three times prior to the start of PAX and then at 1 and 2 weeks after PAX coadministration. On the same days, the severity of illness and side-effects were evaluated using the Clinical Global Impression (CGI) and the Drug Induced Extra-Pyramidal Symptoms Scale (DIEPSS), respectively. Plasma concentrations of ARI and DARI were measured by using LC-MS/MS. This study was approved by the Ethics Committee, Faculty of Medicine, University of the Ryukyus, and the patients gave written informed consent to participate in this study. Plasma concentrations of ARI during coadministration of PAX 10 and 20 mg/day were 1.4 and 1.7-fold higher than that before PAX coadministration, respectively. Those of the active moiety (ARI plus DARI) were 1.3 and 1.5-fold higher than that before PAX coadministration, respectively. Plasma concentrations of DARI remained unchanged. CGI score was improved during coadministration of PAX 10 mg/day, compared to that before PAX coadministration. DIEPSS scores remained constant. This study suggests that PAX coadministration is safe for the treatment of schizophrenia treated with ARI, in spite of the increased plasma concentrations of ARI and the active moiety in a dose-dependent manner.

## Altered Blood Levels of Neuronal Cell Adhesion Molecule (NCAM) in Patients with Mood Disorders: An Involvement of Glial Cell Line-derived Neurotrophic Factor (GDNF) Signaling

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**[Background]** We have previously reported that blood levels of glial cell line-derived neurotrophic factor (GDNF) were decreased in remitted patients with mood disorders (Takebayashi et al., 2006). During adult stage, GDNF promotes cellular plasticity via an isoform (140kDa) of neuronal cell adhesion molecule (NCAM) as a GDNF receptor in brain. This study was aimed to test whether the blood levels of NCAM were altered or not, and whether the blood levels of NCAM were associated with the levels of GDNF in patients with mood disorders.

**[Methods]** We measured NCAM and GDNF levels in whole blood in remitted patients with mood disorders (n=56; major depressive disorders [MDD] 39, bipolar disorders [BD] 17) and controls (n=56). Soluble NCAM isoform (140kDa) was analyzed by Western blot and densitometric quantification. Total GDNF was assayed with the sandwich ELISA method.

**[Results]** The levels of soluble NCAM isoform (140kDa) were significantly higher in MDD and BD than in control subjects (p<0.001), while total GDNF levels were significantly lower in MDD and in BD than in control subjects (MDD; p<0.001, BD; p<0.05). Dosages of antidepressant and mood stabilizer did not affect on the NCAM levels. Interestingly, there was significant correlation between them in patients with mood disorders (p<0.01), while there was no correlation between the values of NCAM and GDNF levels in control subjects.

**[Conclusion]** Our study suggests that a pathway of GDNF signaling through NCAM might play a role in the pathophysiology of mood disorders.



### Higher Plasma Interleukin-6 (IL-6) Level is Associated with SSRI- or SNRI-resistant Depression

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Several cytokines and neurotrophic factors are involved in pathophysiology of depression or biological markers for response to antidepressants. We hypothesized that cytokines or neurotrophic factors are different between responders and nonresponders to antidepressants. To investigate this hypothesis, we compared plasma levels of interleukin-6 (IL-6), tumor necrosis factor $\alpha$  (TNF $\alpha$ ), and brain-derived neurotrophic factor (BDNF) among selective serotonin reuptake inhibitor (SSRI) or serotonin noradrenaline reuptake inhibitor (SNRI) responsive depressed patients (n=31), SSRI or SNRI resistant depressed patients (n=20), and healthy controls (n=30). The plasma levels of IL-6 and TNF $\alpha$  were significantly higher in depressed patients than in healthy controls. Treatment with antidepressants significantly reduced plasma levels of IL-6 and TNF $\alpha$ . In addition, the plasma IL-6 level, but not the plasma TNF $\alpha$  level, was higher in SSRI resistant than SSRI responsive depressed patients, and higher in SNRI resistant than SNRI responsive depressed patients. On the other hand, the plasma BDNF level was significantly lower in depressed patients than in healthy controls, whereas no difference was found in plasma BDNF levels between SSRI responsive and SSRI resistant depressed patients or between SNRI responsive and resistant depressed patients. These results indicate that higher plasma IL-6 activity is associated with the resistance of depression, and plasma IL-6 level is a biological marker for response to SSRIs or SNRI.

### HDAC5 and CREB mRNA Expressions in the Peripheral Leukocytes of Major Depression before and after SSRI Treatment

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Background: Gene expressions of the peripheral leukocytes in depressive patients might reflect the systemic dysfunction of major depression. We determined mRNA expression levels of Histone deacetylase 5 (HDAC5) gene and cyclic AMP response element-binding protein 1 (CREB) gene in the leukocyte of depressive patients. HDAC5 and CREB are reported to be important targets of antidepressants, the latter being located in the downstream of the former in lymphocyte calcium signaling. Methods: 25 patients with major depression and 25 age- and sex-matched healthy controls were included in this study. Twenty patients were able to be followed up until the 8 week-treatment. The mRNA levels were determined by a quantitative RT-PCR method. Result: Levels of HDAC5 and CREB mRNA were significantly higher in drug-free depressive patients than those of controls and the higher mRNA levels decreased to control levels after 8-week paroxetine treatment. There were positive correlation between levels of HDAC5 and CREB. Conclusion: Our results suggest the alteration of HDAC5 and CREB gene expression in the systemic pathophysiology of major depression.

### Serum Amyloid Beta Protein in Young and Elderly Depression

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Background: Depression may increase the risk of developing Alzheimer's disease (AD). Recent large cohort studies have also shown that a low plasma amyloid  $\beta$  (A $\beta$ )<sub>42</sub> level combined with a high A $\beta$ <sub>40</sub> level increases the risk of developing AD, suggesting plasma A $\beta$ <sub>42</sub>/40 ratio as useful for identifying risk of developing AD. Although several studies have examined A $\beta$  levels in the peripheral blood of elderly individuals with depression, results have been inconsistent. Furthermore, no results have been described for younger depression. Methods: Serum A $\beta$ <sub>40</sub>, A $\beta$ <sub>42</sub> level and A $\beta$ <sub>40</sub>/42 ratio were evaluated using ELISA in 60 patients with major depressive disorder (MDD) and 60 healthy controls. The results were analyzed in two age groups (young, <60 years; elderly,  $\geq$ 60 years). The study protocols were approved by the Medical Ethics Committee of Juntendo University. All participants provided written informed consent. Results: Serum A $\beta$ <sub>40</sub> level was significantly higher in young MDD patients compared to young controls (p<0.004), but it was not significantly different in elderly group. Serum A $\beta$ <sub>42</sub> level did not differ significantly in both young and elderly groups. A $\beta$ <sub>40</sub>/42 ratio was significantly higher in both young (p<0.001) and elderly (p<0.005) patients with MDD compared to controls. Conclusions: Serum A $\beta$ <sub>40</sub>/42 ratio was significantly higher in MDD patients than in controls, and this difference was seen for both elderly and young subjects. This may suggest that even young subjects with MDD undergo pathological changes in the very early stage of amyloid deposition.

### Creb as a Predictor of Therapeutic Response to Antidepressants

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**OBJECTIVE:** It takes 4-6 weeks to detect the maximal clinical effect of antidepressants. Such a time lag is due to biochemical and molecular changes such as messenger cascades causing alterations of gene expression. CREB (c-AMP response element binding protein) is known as a key mediator of the therapeutic response to antidepressants. We investigated the change of CREB at the early point of the fluoxetine treatment to find out it can be a predictor for antidepressant response.

**METHODS:** CREB-expression and phosphorylation were quantified via western blot, and binding activity between transcription factor and CRE-oligonucleotide via electrophoretic mobility shift assay (EMSA) in T-lymphocyte nuclear extracts from 20 depressed patients at 0 and 1th week during fluoxetine treatment (20 mg/day). Responders were defined as the > or =50% reduction of HAM-D score in 4 weeks. We compared the changes of CREB response at 0 and 1th week between responders and non-responders.

**RESULTS:** The responders showed a significant increase of CRE-DNA binding at week 1 compared with week 0. CRE-DNA binding of non-responders was decreased at week 1. (Mean, CRE-DNA: 14.56 vs. -1.64, p=0.043 by independent T-test) The drug responders showed a significant increase in changes of CREB and p-CREB compared to non-responders. (CREB: p=0.044 by Mann-Whitney U test; p-CREB: p=0.014 by Mann-Whitney U test) HAM-D difference between week 0 and 4 was positively correlated with the change of CREB response. (CREB: r=0.491, p=0.033 by Spearman's correlation; p-CREB: r= 0.593, p=0.010 by Spearman's correlation; CRE-DNA: r=0.438, p=0.037 by Pearson correlation)

**CONCLUSION:** These results suggest that the early change of CREB response in peripheral lymphocyte can predict the later response of antidepressant. The correlation showed CREB response directly reflects a response status to the antidepressant fluoxetine.

## The Effects of Valproate and Atypical Antipsychotics on Bone Metabolism in Female Bipolar Patients with Low Bone Mineral Density

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**Objective:** Long-term treatment of antipsychotics is known to be associated with low bone mineral density (BMD). However, studies on the association between valproate and bone density in bipolar patients are rather limited. Valproate is 1st choice as a mood stabilizer and mood stabilizers are frequently combined with antipsychotic in actual clinical practice. This report describes the biochemical markers of bone metabolism of nine premenopausal women with bipolar disorder who manifested osteopenia or osteoporosis under long-term treatment with valproate combined with low dose atypical antipsychotic. **Methods:** 9 premenopausal women with bipolar patients (DSM-IV) who showed osteoporosis or osteopenia receiving valproate combined with atypical antipsychotics for at least 2 years were evaluated. The BMD of the lumbar spine and at femur sites was measured by dual-energy X-ray absorptiometry (DEXA). The biochemical markers of bone formation and resorption including 25 (OH)-vitamin D, parathyroid hormone level, osteocalcin and urine deoxypyridinoline were measured. Circulating levels of gonadal hormones including prolactin, estradiol, luteinizing hormone, follicle-stimulating hormone, progesterone and testosterone were also assessed. **Results:** Two patients showed osteoporosis and seven patients showed osteopenia on DEXA scan with mean T-score -1.94. The mean age of subjects was 42.78±11.27 years and the body mass index was 23.38±3.04. They had longer length of valproate with atypical antipsychotic medications with 53.7 months and mean dose of valproate was 525mg. Biochemical markers of bone formation and resorption were changed. Six subjects of nine (66.7%) showed decreased level of Serum 25 (OH) vitamin D and two of nine (22.2%) showed decreased level of PTH which were the bone formation marker. Seven subjects of nine (77.8%) have increased level of ALP. Bone resorption markers such as osteocalcin and deoxypyridinoline were within normal levels. Eight subjects of nine (88.9%) showed decreased level of testosterone. However, prolactin and other circulating levels of gonadal hormones were within normal levels. **Conclusion:** We suggest that long-term treatment with valproate combined with atypical antipsychotic adversely affects the bone density and the biochemical markers of bone metabolism. The prospective studies with biochemical markers of bone metabolism are necessary to determine the effects of long-term valproate and low dose atypical antipsychotics treatment on bone metabolism.

## Impaired Negative Emotion Recognition in Bipolar Manic Patients: P300 Study

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Several studies reported the impairment in recognizing emotional stimuli in the bipolar patients. Bipolar manic patients had difficulties in negative stimuli recognition task. P300, an event related potentials, has been known that it reflects the stimuli evaluation, attention allocation and working memory. We aimed to observe the emotional bias in manic patients through measuring amplitudes and latencies of P300. We measured the P300 of 20 manic patients diagnosed with DSM-IV and Mini-International Neuropsychiatric Interview and 20 normal controls without psychiatric family and past history. Subjects were instructed to respond to the face emotion stimuli by pressing keypads and feel the emotion of face. We used standardized photos of Japanese in the 'Japanese and Caucasian Facial Expression of Emotion slides' set. The stimulus consisted of sadness, happiness, fear, disgust and neutrality. We measured demographics, YMRS, BDI, MADRS, BPRS and EEG through 64 channels. In manic patients, we observed the decrease in recognition rate of sad face relative to controls (66.5±37.8% vs 88.8±22.2%;  $t = -2.27$ ;  $p = 0.03$ ). 9(site) × 5(emotion) × 2(group) ANOVA revealed that interaction effect of emotion and group ( $F(4,148) = 7.66$ ;  $p < 0.001$ ). 2(emotion vs. neutral) × 2 (group) ANOVA revealed that there were significant interaction in sad condition ( $F(1,37) = 21.6$ ,  $p < 0.001$ ), disgust condition ( $F(1,37) = 7.6$ ,  $p = 0.009$ ) and fear condition ( $F(1,37) = 7.8$ ,  $p = 0.008$ ), but not in happy condition ( $F(1,37) = 1.4$ ,  $p = 0.24$ ). Compared to normal controls, manic patients showed different P300 amplitude pattern of neutrality and emotion interactions. This finding is consistent with the previous finding about impaired negative recognition in manic patients. Therefore this finding might be neurophysiologic evidence supporting the impairment in recognizing negative emotional stimuli in manic patients.

Keywords: bipolar disorder, P300, emotional stimulus

## A Follow-up Study on Features of Sensory Gating P50 in Treatment-Resistant Depression Patients

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**Backgrounds** Depressive disorder is a chronic, recurrent and disabling mental disease. At least 40% of depressed patients show only partial or no response to initial or even multiple antidepressants medication which are usually called treatment-resistant depression (TRD). The present work is to measure the features of sensory gating (SG) P50 in TRD patients and intend to understand the characteristics of this disease. **Methods** 50 TRD patients, 39 non treatment-resistant depression (NTRD) patients and 51 healthy controls (HC) were measured their auditory evoked potentials P50 using the conditioning/testing paradigm presented with auditory double clicks stimuli, and 36 TRD patients had a repeated measurement after an 8-week venlafaxine treatment duration. **Results** All the depressive disorder patients, including TRD and NTRD groups, were showed an increased testing stimulus wave (S2-P50) amplitude than that of controls ( $P < 0.01$  and  $P < 0.05$ ), but not differ significantly between the TRD and NTRD groups ( $P > 0.05$ ). There were significant differences in the ratio of testing stimulus (S2) and conditioning stimulus (S1) (S2/S1) or the value of 100 (1-S2/S1) among three groups. Compared to the baseline, TRD patients had no significant changes on features and different expressions of P50 after acute treatment ( $P > 0.05$ ). Meanwhile, a statistical significant positive correlation of S2/S1 with the scores of the 17-item Hamilton Rating Scale for Depression (HAM-D-17) ( $P < 0.01$ ), and a significantly negative correlation of S1-S2, 100 (1-S2/S1) with the scores of HAM-D-17 ( $P < 0.01$ ) were observed in the TRD patients' baseline measurement, but no correlation after venlafaxine treatment ( $P > 0.05$ ). **Conclusions** Both the TRD and NTRD patients had obvious SG deficits, with a more severe deficit in TRD patients. Though with a correlated relationship to the severity of depressive symptoms, SG P50 deficits might be suggested as trait markers of TRD, and combination of S2/S1 ratio, S1-S2 and 100 (1-S2/S1) was recommended for electrophysiological measurement in TRD patients.

## Different Patterns of Abnormal Gamma Oscillations in Bipolar and Unipolar Disorder Patients

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**Objectives:** The aim of this study was to investigate the patterns of regional gamma activities in patients with bipolar disorder (BD) and major depressive disorder (MDD). **Materials and Methods:** Three groups of twenty BD patients, twenty MDD patients, and twenty normal controls (NC) participated in this study. All patients met the DSM-IV criteria for clinical diagnosis and NC underwent MINI interview before the experiments to exclude possible morbidity of psychiatric illness. Three kinds of facial stimuli, including neutral, angry, and happy, were presented randomly. Subjects were asked to lift their finger for identifying gender of the face, (right index finger for female or left for male). For each subject, event-related magnetoencephalographic fields (ERMF) with sampling rate of 1000 Hz were recorded with a whole-head 306-channel neuromagnetometer (Vectorview; Elekta-Neuromag, Helsinki, Finland). Time-frequency map of the noise-free ERMFs were obtained by using Morlet wavelet analysis. A three-way ANOVA was used to test the effects of group, emotional facial expressions, and brain regions on relative gamma oscillations. The Wilcoxon rank-sum test was utilized to contrast each two groups. **Results:** The results showed that the BD patients had decreased gamma activities in the prefrontal and right frontal cognitive regions, and increased in the posterior visual regions. On the other hand, the MDD patients exhibited under-activation of cognitive areas (prefrontal, medial and right lateral parietal regions) and larger activation of the emotion-related areas (bilateral anterior temporal regions). **Conclusions:** Our findings demonstrated different neuropathological areas between two mood disorders, which implicate that the BD patients tend to have more cognitive impairments, especially attention dysfunction, and the MDD patients impaired both emotion processing and cognitive control dysfunction, especially working memory function.

## The Naturalistic Study of the Effects of EEG Biofeedback in Adult Patients with Psychiatric Disorders

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**Objectives:** The purpose of this study was to evaluate the characteristics and the effects of EEG biofeedback for adult patients with psychiatric disorders in naturalistic setting.

**Methods:** Fifty-seven adult patients with psychiatric disorders who were applied EEG biofeedback in university hospital, Korea from July, 2005 to July, 2008 were participated in this study. The demographic data (age, sex, educational level), characteristics of psychiatric disorders (diagnosis, duration of illness, presence of medication), and states of EEG biofeedback (total frequency, protocol) were analyzed. And the effects of EEG biofeedback were also evaluated before & after training using clinical global impression (CGI) and subjective self rating scale (provided by EEG Spectrum International, Inc.).

**Results:** Anxiety disorders were the most common psychiatric disorder who were applied EEG biofeedback (16 patients, 28.1%), and second were the depressive disorders (13 patients, 22.8%). Fifty-one patients (89.5%) were taken medicine. The average frequency of EEG biofeedback were 55 ±18.56, and 32 patients (56.1%) were applied EEG biofeedback more than ten times. Thirty-six patients (63.2%) were applied both  $\beta$ /SMR &  $\alpha$ / $\theta$  training. And discontinuation rate were 36.8% (21 patients). Significant change of CGI before and after training was noticed using covariance with frequency (<.001), and self rating scale also showed significant changes in depressive symptoms, anxiety, and inattention (<.001).

**Conclusion:** This is the naturalistic study in clinical setting, so there are several limitations such as absence of control group and validity of self rating scale, etc. But this study demonstrates the significant effects of EEG Biofeedback in objective & subjective rating scales for adult patients with certain psychiatric disorders. Prospective controlled studies are needed in the future.

## Differences in Brain Structural Abnormalities between Bipolar Disorder and Major Depressive Disorder

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**Background:** Morphometric brain imaging studies have revealed regional brain abnormalities in patients with mood disorder, which may play a role in illness pathophysiology. In the current study, we evaluated differences in brain structural abnormalities between two diagnostic groups, bipolar disorder and major depressive disorder. The purpose of current study is to investigate similarities and differences in structural brain abnormalities between bipolar and unipolar depression.

**Methods:** Fifty- three patients (26 bipolar I disorder, 27 bipolar II disorder) with bipolar disorder and 18 patients with major depressive disorder were recruited. Magnetic resonance images from patients were segmented into tissue volumes and compared with 34 images from healthy normal controls. All automated image processing was done using statistical parametrical mapping software (SPM2). Analysis followed the "optimized" voxel-based morphometry processing strategy.

**Results:** The patients with major depressive disorder showed a decreased gray matter volume in the medial frontal, anterior cingulate, posterior cingulate, bilateral hippocampal, left insula, and bilateral occipito-temporal regions. On the other hand, the patients with bipolar disorder showed a decreased gray matter volume in the medial frontal, anterior cingulate, right middle frontal, right inferior frontal regions, and the right caudate. CSF volume increase was specific to unipolar patients, while white matter volume changes in several regions were specific to bipolar patients.

**Conclusions:** These findings suggest that certain brain abnormalities like volume decreases in the medial frontal, anterior cingulate, and the insular regions are common to mood disorders, while the striatal and limbic structural changes are specific to diagnostic groups. Further studies to elucidate the role of those regions in the pathophysiology of mood disorders are needed.

**Key word:** bipolar disorder, major depressive disorder, MRI, structural abnormality

## Mood-Congruent Bias in Scenic Picture-based but not Word or Facial Picture-Based Affective Go/No-Go Performance of Patients with Mania: Comparison to Patients with Schizophrenia and Healthy Controls

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**Objective:** Patients with bipolar mania have difficulty in recognizing or attending to negatively affective stimuli and have an affective bias, which is congruent with the current mood. However, previous reports have adopted words or facial pictures, not scenic pictures as affective stimuli. On the word, face picture and scenic picture-based affective go-nogo tasks, this study investigated performance of patients with mania, which is compared to that of patients with schizophrenia and healthy controls. **Method:** Twenty patients with bipolar mania, 20 patients with schizophrenia, and 20 healthy comparison subjects, matched for age, gender and intelligence, performed affective go-nogo tasks which contained happy/sad words, facial pictures, and scenic pictures respectively. **Results:** On the scenic picture-based affective go-nogo task, a significant interaction between subject group and target valence emerged ( $F(2,57)=4.86, p<0.05$ ). Paired t test showed the manic patients required significantly more time to respond to sad than to happy stimuli ( $t=3.22, df=19, p<0.01$ ), but schizophrenia patients and healthy subjects did not differ in time to respond to happy or sad stimuli ( $t=1.95, df=19, p=0.07; t=-1.23, df=19, p=0.23$ ). **Conclusion:** Manic patients displayed a mood-congruent bias toward affective scenic pictures, but not toward affective word or facial pictures. This finding suggests that complex and scenic stimuli may influence more the affective arousal state and therefore increase the mood-congruent bias in manic patients. Key words: Bipolar disorder, mania, go-nogo task, mood-congruent bias

## A Biomarker to Differentiate Remitted Bipolar I vs. Bipolar II Disorder, Using Combined FDG-PET and Voxel-Based Morphometry

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**Objectives:** Using multiple neuroimaging modalities may help to delineate subtypes of bipolar disorders (BD). We aimed to investigate the structural morphometry using voxel-based (VBM) and metabolic difference <sup>18</sup>F-FDG (fluorodeoxyglucose) positron emission tomography (PET) in the brain between remitted BD I and BD II. **Methods:** Thirty-five remitted outpatients (BDI/BDII = 17/18) received VBM study, while twenty-four patients among them (BDI/BDII = 12/12) received another PET study. Remitted was defined as both 17-item Hamilton Depression Rating Scales kept lower than 7 and Young Mania Rating scales scores lower than 9 for at least 2 weeks after treatment. Well-matched healthy controls (n=28) without major medical and mental disorders were also recruited. T1-weighted magnetic resonance (MR) images were acquired by a 1.5 T GE scanner and PET images by a 64-slice PET/CT GE scanner. **Results:** Demographic and illness variables including age (40.8±12 vs. 41.7±13), gender (more female than males, ratio around 5/3), age at onset (30±10.7 vs. 32.9±12.6) and duration of illness (9.8±10.5 vs. 10.2±8.5) as well as episodes of mania (3±2.3 vs. 2.6±2.5) and depression (3.8±2.7 vs. 4.1±2.9), between BD I and BD II were comparable except M/D ratio (0.9±0.6 vs. 0.65±0.4) ( $p<0.05$ ) in both imaging studies. Compared to BD II and normal subjects, BD I patients presented decreased gray matter volume in right thalamus, right inferior frontal gyrus and left insula. BDII patients exhibited smaller right middle cingulum versus normal subjects, yet BD I was not. PET analyses showed significantly lower metabolism in BD I, including right thalamus, left superior frontal gyrus and right middle cingulum, as compared to BD II. **Conclusions:** Pathophysiology and neurocircuitry underlying subtypes of BD may be quite different and may account for more cognitive deficits and poorer outcome in BD I disorder. These results suggest a possible role of using neuroimaging studies to identify a biomarker in differentiating subtypes of BD, providing treatment direction and predicting clinical outcome.

## Treatment with SSRIs and Mirtazapine Results in Differential Brain Activation by Visual Erotic Stimuli in Patients with Major Depressive Disorder

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Mirtazapine, a noradrenergic and a specific serotonergic antidepressant, is reported to be less associated with sexual dysfunction compared with selective serotonin reuptake inhibitors (SSRI). The objective of this study was to identify patterns of brain activation elicited by erotic visual stimuli in patients treated with either SSRIs or mirtazapine.

Nine middle-aged men with major depressive disorder treated with an SSRI and ten middle-aged men with major depressive disorder treated with mirtazapine completed the trial. Ten subjects with no psychiatric illness were included as a control group. We conducted functional brain magnetic resonance imaging (fMRI) while a film alternatively played erotic and non-erotic contents for 14 minutes and 9 seconds.

The control group showed activation in the occipitotemporal area, anterior cingulate gyrus, insula, orbitofrontal cortex, and caudate nucleus. For subjects treated with SSRIs, the intensity of activity in these regions was much lower compared to the control group. Intensity of activation in the group treated with mirtazapine was less than the control group but greater than those treated with SSRIs. Using subtraction analysis, the SSRI group showed significantly lower activation than the mirtazapine group in the anterior cingulate gyrus and the caudate nucleus.

Our study suggests that the different rates of sexual side effects between the patients in the SSRI-treated group and the mirtazapine-treated group may be due to different effects on brain activation.

**Key words:** functional MRI; SSRI; mirtazapine; sexual dysfunction

## Brain Proton Magnetic Resonance Spectroscopic Study of Insight Among Elders with Late-Life Depression in Remission

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**Objective:** Insight refers to an awareness and attribution of disorders and attitude toward treatment. While neurocognitive studies indicate that insight is associated with frontal lobe dysfunction, little is known about the neurobiochemical profile of insight. We investigated the neurobiochemical characteristics of insight within the frontal lobe using proton magnetic resonance spectroscopy (<sup>1</sup>H MRS) among elderly people with major depressive disorders in remission.

**Methods:** Seventy-five elderly patients with major depressive disorder in remission underwent assessment of insight using the Mood Disorders Insight Scale (MDIS), including awareness, attribution, and need for treatment. Brain <sup>1</sup>H MRS spectra were acquired from voxels located in the left side of the frontal lobe. Ratios of N-acetylaspartate (NAA), choline, and myo-inositol reference to total creatine (tCr) were calculated. Correlations between these biochemical ratios and insight were examined. Secondary analyses included the association of biochemical ratios with each of the subscale of insight.

**Results:** Total score of MDIS correlated with NAA/tCr (spearman rho=0.31; p<0.006) at frontal lobe. Secondary analyses showed the depressive elders with inadequate attribution to their disease had lower level of NAA/tCr than those with full insight regarding attribution.

**Conclusions:** This is the first paper investigating the brain biochemical profiles of insight toward mental disorders. Our findings support the frontal lobe involving insight, and more specifically for disease attribution. Lower level of NAA/tCr suggested the neuronal dysfunction at frontal lobe is associated with inadequate insight in late-life depression.

## Aripiprazole Induced Gray Matter Growth on a Patient of Major Depressive Disorder with Panic Disorder

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**Objective:** Major depressive disorder (MDD) and panic disorder (PD) has been reported to be associated with GM deficits over amygdala, hippocampus, prefrontal cortex and anterior cingulate cortex in past brain structure analysis reports. Aripiprazole, a kind of D2 partial agonist antipsychotic, is approved for add-on therapy recently. It's believed to be related to its 5-HT1A partial agonist, 5-HT2C antagonist and 5-HT2A antagonist property. Here I want to present a case of MDD with panic disorder (PD) had improvement of symptoms after 6-week treatment. Magnetic resonance imaging (MRI) structural analysis also revealed gray matter (GM) growth and brain volume (BV) increase within 6 weeks.

**Method:** Hamilton Rating Scale for Depression (HAM-D) and Panic Disorder Severity Scale (PDSS) was rated at baseline, 3<sup>rd</sup> week and 6<sup>th</sup> week. Aripiprazole dose is 10 mg/day without concurrent medication therapy. 3T GE version scanner housed at Buddhist Tzu Chi Hospital, Taipei Branch. Scans with three-dimensional fast spoiled gradient-echo recovery (3D-FSPGR) T1W1 was performed at baseline and 6<sup>th</sup> week. Structural MRI was preprocessing with Structural Image Evaluation, using Normalization, of Atrophy (SIENAX) function of FSL (FMRIB Software Library) to calculate single time point GM and BV after registering and normalizing to template. The brain morphology change was estimated by SIENA function to calculate percentage BV change (PBVC).

**Result:** MDD and PD symptoms responded. The whole brain GM increased within 6 weeks and PBVC showed positive percentage after 6 week therapy, which suggested that BV increase after aripiprazole treatment.

**Conclusion:** Aripiprazole's short-term GM and BV increase in MDD and PD therapy might be a new research direction, though just a case report.

## Association Study of Brain-Derived Neurotrophic Factor (BDNF) Gene and Bipolar Disorder in Korea

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**BACKGROUND:** Brain-derived neurotrophic factor (BDNF) plays an important role in cell survival, differentiation, and cell death as well as in neural plasticity. Recent studies have suggested that BDNF is involved in the pathogenesis of bipolar disorder.

**OBJECTIVES:** The aim of this study was to investigate the association of the genetic variations of the BDNF gene with bipolar disorder in Korea. We also studied the possible association of these genetic variants with clinical features.

**METHODS:** The allelic and genotypic distributions of Val66Met polymorphism of the BDNF gene were analyzed using a polymerase chain reaction (PCR)-based method in 184 bipolar patients and 214 controls. Analysis was performed to investigate an association of the Val66Met polymorphism of the BDNF gene and the clinical features in bipolar disorder.

**RESULTS:** No significant difference was found between bipolar patients and controls in the genotype and allele frequencies for the investigated BDNF polymorphism. However, the age of onset of bipolar disorder among the Val/Val (25.57), Val/Met (30.42) and Met/Met (32.45) genotype groups were significantly different (p = 0.037).

**CONCLUSIONS:** This study suggests that Val66Met polymorphisms are unlikely to contribute to the genetic predisposition to bipolar disorder as a whole. But Val66Met polymorphism may be associated with age of onset of the disorder, further studies designed to investigate the relationship in a larger population may be warranted.

## The Role of Catechol-O-Methyltransferase (COMT) Gene in Male Patients with Major Depression

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Catechol-O-methyltransferase (COMT) has been suggested as an important factor in the pathogenesis of major depression (MD) because COMT catalyzes endogenous monoamines such as dopamine and norepinephrine. Allele and genotype frequencies of *COMT Val/met* polymorphism have been investigated for possible associations with MD in different populations, but these results have been inconsistent. Our goal was to investigate whether *Val/Met* polymorphisms of the *COMT* gene are associated either with MD or with different clinical subtypes of M D. The *COMT Val/Met* polymorphism was studied in 652 subjects (337 patients with MD and 315 unrelated controls) from a population of Han Chinese. All subjects were interviewed with identical methods, and mental disorders were diagnosed according to DSM-IV criteria. Individuals with MD were classified into 8 clinical subgroups to reduce clinical heterogeneity. The genetic variant of the *COMT Val/Met* polymorphism was associated with the subgroup of patient with MD with a positive family history, especially male subjects. However, no significant differences were found between controls and total case of MD, or between controls and other homogeneous subgroups of MD, both in males and females. Using multiple logistic regression analysis, we confirmed that these positive results were present only in male subjects. This study suggested that the *Val/Val* genotype of *COMT* gene might play a risk factor in increasing susceptibility to MD in Han Chinese males with a positive family history.

Key words: Catechol-O-methyltransferase; *COMT* gene; major depression

## Association between Serotonin Transporter Gene Promoter Polymorphism and Male Suicide Attempt in Han Chinese

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**Background:** Suicide behaviors bring enormous impacts on personal life, family, and the society. In addition to co-morbid depression or substance abuse, personality traits, selected socio-demographic variables, and previous suicide attempt, genetic factors also play a critical role in the susceptibility to suicide. Cumulative data have shown a significant association of genetic polymorphisms of serotonin transporter (5-HTT) with suicidal behavior, especially with violent suicide. Only a few studies examined the polymorphisms in Chinese subjects, which are inconclusive.

**Methods:** We compared 5-HTT gene promoter polymorphism (5-HTTLPR) between suicide attempters and healthy controls in Han Chinese. We also examined whether sex, psychiatric diagnosis, and the severity of suicide behavior will moderate the association.

**Results:** A marginal association was found between suicide attempters and the LL genotype ( $p=0.049$ ), compared with healthy controls. Moreover, the LL genotype was only associated with male ( $p=0.004$ ), not in female attempters ( $p=0.559$ ). Association with the LL genotype was also found when comparing male suicide attempters with non-attempters with mood disorder ( $p=0.008$ ), not in females with mood disorder. Association was not noted when focusing on suicide in schizophrenic patients, or moderated by the severity of suicide.

**Conclusions:** In this study, we found LL genotype in 5-HTTLPR is associated with suicide attempt in males, not in female. This result is inconsistent with those in most previous association studies about suicide, especially in Caucasian subjects. Ethnicity-specific or sex-specific moderating effects in mood regulation or impulse control of variants in serotonin transporter gene need further exploration.

## Catechol-O-methyl Transferase Gene, Monoamine Oxidase A Gene and Bipolar Disorder

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Bipolar disorder has reported to be associated with several monoamines such as serotonin, norepinephrine and dopamine. Therefore, it is postulated that catechol-O-methyl transferase gene (*COMT*) and monoamine oxidase A (*MAOA*), which are typically involved in metabolizing the monoamines, are associated with the onset of bipolar disorder or the clinical variables such as suicide attempt during the illness, family history and age at onset. This study investigated the genotype or allele frequency of *COMT* and *MAOA* gene in Korean bipolar disorder patients and compared the results to those of Korean healthy controls. We collected the blood of 184 bipolar patients and 216 healthy controls. *COMT val158Met* and *MAOA EcoRV/C1460T* were genotyped. For statistical analysis, independent sample t-test, ANOVA, and chi-square test were used. There was no significant association between *COMT val158Met* and *MAOA EcoRV/C1460T* and onset of bipolar disorder. In the bipolar patients group, there was no significant association between *COMT val158Met* and *MAOA EcoRV/C1460T* and clinical variables such as suicidal attempt during illness, family history and age at onset. In Korean population, there is no association between *COMT val158Met* and *MAOA EcoRV/C1460T* and onset of bipolar disorder or clinical variables such as suicidal attempt during illness, family history and age at onset.

## Association Between *GIRK2* Gene Polymorphisms and Postoperative Analgesic Requirements After Major Abdominal Surgery

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Opioids are commonly used as effective analgesics for the treatment of acute and chronic pain. However, considerable individual differences have been widely observed in sensitivity to opioids. We focused on a G-protein-activated inwardly rectifying potassium (*GIRK*) channel subunit, *GIRK2*, that is an important molecule in opioid transmission. In our initial polymorphism search, a total of nine single-nucleotide polymorphisms (SNPs) were identified in the whole exon, 5'-flanking, and exon-intron boundary regions of the *GIRK2* gene. A total of 129 patients who underwent major open abdominal surgery in hospitals were recruited as the subjects in the association study with written informed consent. The study protocol was approved by the Institutional Review Board at each related Institute. In an association study, the A/A genotype in the A1032G SNP and -1250G/1032A haplotype were significantly associated with increased postoperative analgesic requirements. Also, the *GIRK2* expression levels in the 1032A/A subjects were significantly decreased compared with the 1032A/G and 1032G/G subjects in a quantitative real-time PCR analysis using human brain tissues, suggesting that the 1032A/A subjects required more analgesics due to lower *GIRK2* expression levels and consequently insufficient analgesic effects. The results indicate that the A1032G SNP and G-1250A/A1032G haplotype could serve as markers that predict increased analgesic requirements. Our findings will provide valuable information for achieving satisfactory pain control and open new avenues for personalized pain treatment.

## An Association Study between Various Monoamine Transporter Gene Polymorphisms and Treatment Response to Mirtazapine in Major Depression

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**Background** Initial drug treatment fails in 30-40% of patients with major depression. A Genetic polymorphism between individuals may influence the response to antidepressant among patients suffering from depression. This study investigated a possible association of various monoamine transporter genetic polymorphism with treatment response to mirtazapine in major depressive patients in elderly. **Method** It was a 6-week naturalistic treatment study with blinded outcome evaluation of 100 Korean inpatient with major depression diagnosed by DSM-IV. Treatment response to mirtazapine was defined as  $\geq 50\%$  decrease in HAM-D score at 6 weeks. In this study three genetic polymorphism were selected: serotonin transporter 5-HTTLPR, serotonin transporter 5-HTT intron 2 VNTR, and norepinephrine transporter NET (G1287A). The genotype of patients were determined by the polymerase chain reaction. **Result** Our results showed that ss allele carriers were included more in responder group (ss allele in responder vs. non responder group; 70.0% vs. 30.0%). In addition, l-allele (sl/ll) carriers were included less in responder group (sl/ll allele in responder vs. non responder group; 42.3% vs. 57.6%). Multiple logistic regression analyses showed the 5-HTTLPR polymorphism as a predictor of the mirtazapine response (5HTTLPR ss allele carrier vs. l-allele (sl/ll) carrier; odds ratio: 3.72; 95% confidence interval [CI], 1.13-12.2;  $P=0.030$ ). However, 5-HTT intron 2 VNTR l/s ( $P=0.44$  by multiple logistic regression; [OR], 0.58; 95% [CI], 0.14-2.34), and NET (G1287A) G/A ( $P=0.51$  by multiple logistic regression; [OR], 1.45; 95% [CI], 0.47-4.42) showed no statistical significant influences on response rate. **Conclusion** Monoamine transporter gene polymorphisms were associated with response to Mirtazapine. The combinations of polymorphism may be informative for predicting the response and the non response to Mirtazapine. These findings could give a benefit for the refined antidepressant selection in treatment of depression patients. (This work was supported by Korea Science & Engineering Foundation through the NRL program(Grant 2007-0628-000))

## BDNF (Brain-Derived Neurotrophic Factor) Gene Polymorphism of Late-Onset Depression in Korean Population and Antidepressant Responsiveness

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**Introduction** Brain-derived neurotrophic factor (BDNF) has been studied, related to the neurogenesis of hippocampus after antidepressant administration in several studies using animal depression models. Also, the Val66Met polymorphism of BDNF gene was reported related to depression and antidepressant responsiveness, but these results controversial. Our purpose is to evaluate whether the polymorphism is associated to fluoxetine responsiveness in late-onset depressed patients.

**Methods** One hundred ten patients with late-onset depression were classified from genomic DNA for Val66Met polymorphism of the BDNF gene, using primer flanking exon 2 region. Patients then entered a 6 week clinical trial with an Serotonin selective reuptake inhibitor (SSRI), fluoxetine, with documentation of plasma drug concentrations. Responder was defined as the decrease of HAM-D score (%)  $> 50$  at 6 week after antidepressant treatment.

**Results** No differences were any characteristics of subjects such as age, gender, age of onset, duration of illness between responder and non-responder group. The association was in the polymorphisms between 54 responder group and 56 nonresponder ( $p=0.046$ , by Fisher exact test). However, the val/met heterozygotes were increased according decrease rate (%) of HAM-D score, compared to val/val and met/met homozygotes (11.2 $\pm$ 6.01 vs. -7.06 $\pm$ 5.79, mean $\pm$ SD,  $p=0.020$  by Mann-Whitney U test).

**Conclusions** Val66Met polymorphism of BDNF gene affect the changes of HAM-D score to SSRI drug in late-onset depressed patients. These results underscore the importance of study in evaluation of candidate genetic marker as predictor of response to treatment of late-onset depression.

## Gastrointestinal Symptoms Induced by an SSRI or an SNRI and Genetic Polymorphisms of CYP2C19 Enzyme, Serotonin 1A and 2A Receptors and Serotonin Transporter

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Gastrointestinal symptoms often occur in patients taking selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs). This study aims to clarify genetic background of the side effects. Subjects who were taking or used to take an SSRI or an SNRI were recruited. This study was approved by the ethics committee of Hirosaki University Graduate School of Medicine and written informed consent was obtained from all patients. Gastrointestinal symptoms were surveyed by inquiring to the patients and/or checking up the patients' record. Genetic polymorphisms determined include cytochrome P450 (CYP) 2C19 (\*2 and \*3 alleles), C-1019G substitution of serotonin (5-HT) 1A receptor, G-1438A substitution of 5-HT2A receptor and variable number of tandem repeats in the second intron of 5-HT transporter. A total of 102 patients participated in this study. Patients lacking functional allele of CYP2C19 gene showed significantly higher frequency of gastrointestinal symptoms (14/25) than those with one (11/42) or two functional alleles (8/35). The other genetic polymorphisms did not influence the frequency of the side effects. In sertraline-treated patients ( $n=32$ ), gastrointestinal symptoms were observed in 55% (6/11), 46% (6/13) and 0% (0/8) in the patients with zero, one and two functional alleles of CYP2C19 gene, respectively. In conclusion, CYP2C19 genotype was associated with gastrointestinal side effects in sertraline-treated patients. Further studies are desired to reveal other genetic background of gastrointestinal symptoms.

## Association Analysis of PROK2 and PROKR2 with the Fluvoxamine Therapeutic Response in Major Depressive Disorder in the Japanese Population

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**Introduction** Recently, we detected a significant association between prokineticin 2 receptor gene (PROKR2) and major depressive disorder (MDD) and bipolar disorder (BP) in the Japanese population. It might be that mood disorders and fluvoxamine therapeutic response in MDD have common susceptibility genes. In support of this hypothesis, we show recent evidence (BDNF gene). Therefore, we examined association between prokineticin 2 gene (PROK2) and PROKR2 and the efficacy of fluvoxamine treatment in 116 patients with Japanese major depressive disorder. **Methods** Scores on the 17 items of SIGH-D with MDD patients in this study were 12 or higher. We defined a clinical response as more than a 50% decreased in baseline SIGH-D within 8 weeks and clinical remission as less than a SIGH-D score of 7 at 8 weeks. Written informed consent was obtained from each subject. This study was approved by the ethics committees at Fujita Health University and Nagoya University Graduate School of Medicine. We selected four and five tagging SNPs in PROK2 or PROKR2, respectively, selected by HapMap database, for the following association analysis. **Results** We did not detect significant association of PROK2 or PROKR2 with the fluvoxamine therapeutic response in major depressive disorder in the allele/genotype-wise analysis and haplotype-wise analysis. **Conclusion** Our results suggest that PROK2 or PROKR2 do not play a role in the therapeutic response to fluvoxamine in Japanese major depressive disorder.

## Serotonin Transporter Gene Polymorphisms and Chronicity of Depression in Koreans

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**BACKGROUND:** Chronic depression has a considerable impact on social functioning, is difficult to treat and is associated with higher rates of history of suicide attempt.

The serotonin transporter gene is one of the most studied genes for depression. Previous studies showed that serotonin transporter gene polymorphisms are associated with antidepressant response.

We examined the association of serotonin transporter gene polymorphisms with chronicity of depression in a Korean population

**METHODS:** This cross-sectional study involved 283 patients with major depression who fulfilled the DSM-IV criteria for major depressive episode. Clinical data was collected by structured interview with patient and at least 1 family member.

Patients were genotyped for s/l polymorphisms in 5-HTT promoter region (5-HTTLPR), s/l variation in second intron of the 5-HTT gene.

Chronicity in duration was defined as duration of current episode was not less than 24 months. Chronicity in episode number was defined as no fewer than 2 episodes.

All statistical analyses were performed using SPSS 17.0

**RESULTS:** Chronicity in duration was associated with 5-HTTLPR. Patients with l/l (N=25) had higher rate of chronicity in duration than the other patients (N=258). (l/l vs. s/l or ss, 32.0% vs. 12.4%; Odds ratio [OR], 0.288; 95% confidence interval [CI], 0.105-0.787; p=0.0152; logistic regression analysis) Chronicity in episode number was not associated with 5-HTTLPR. Chronicity in duration and chronicity in episode number were not associated with polymorphism of second intron of the 5-HTT gene.

**CONCLUSION:** These results suggest that chronicity in duration is associated with 5-HTTLPR. Confirmation of this preliminary finding would help to predict the clinical course of depression by genetic evaluation.

## 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 forty-nine patients with DSM-IV OCD underwent mean 18-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.

## Adult-onset Citrullinemia with Repeated Stereotyped Behavior: A Pitfall for Antiepileptic Drug Usage

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The adult-onset citrullinemia (type II) is caused by mutations of citrin gene encoding the mitochondrial aspartate-glutamate carrier protein, which plays a key role in urea cycle function. Most of the patients have particular fondness for foods rich in arginine: beans, peas, and peanuts; strict dietary restriction is usually required to prevent hyperammonemic encephalopathy. We report a female case of citrullinemia onset at 21 years old as repeated stereotyped behavioral abnormalities. An antiepileptic drug prescribed in another hospital had further exacerbated her symptoms. Over 30 years, EEG abnormalities and slightly high blood ammonia concentration were continuously detected. Nevertheless, the patient has not shown a disturbance in consciousness for the past 20 years. We found a homozygotic single nucleotide mutation of the gene at a splicing donor site resulting in a 53-amino acid deletion of the mitochondrial aspartate-glutamate carrier. Benign outcome and mild liver damage in this case may reflect a genetic subtype of citrin gene mutation. Under occasional misdiagnosis as prolonged epileptic automatisms in patients of citrullinemia and other urea cycle disorders, treatment with antiepileptics (e.g., sodium valproate) may cause severe ammoniemia and deteriorate general condition. The high frequency of mutations of citrin gene among the Asian population should be taken into consideration. This study was approved by the ethics committee of the University, and the written informed consent was provided by the patient for the participation in the study.

## Symptom Based Cluster Typology of OCD and Their Drug Response Differences

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**Objective:** There have been a few attempts to make typology of heterogeneous OCD patients, but nearly all of the studies used factor analysis not the cluster analysis. Our aim was to identify symptom based cluster typology of OCD patients. For validation of that typology, we compared drug response differences.

**Method:** Cluster analysis was performed on the 13 main categories of Y-BOCS symptom check list scores of 354 OCD patients to identify a valid cluster solution. From the pooled data of 150 non depressed OCD patients in 6 double-blind placebo-controlled trials with SRIs, outcome measures of drug treatment were compared to evaluate the predictive validity of cluster solution.

**Results:** 5 cluster solution was identified (Precision/Completeness, Contamination/Cleaning, Safety/Checking, Pure Obsessions, and Hoarding). Each cluster was characterized by its own unique symptom patterns, and was robust to replication. It also had good descriptive and construct validity. For external and predictive validity, we applied two way ANOVA (cluster x Drug-placebo) using % reduction of the scores on the Y-BOCS as a dependent variables. There were some drug treatment differences among clusters. Especially hoarding cluster showed the worst drug response.

**Conclusions:** The identified 5 cluster solution was stable and valid. Multiple clinical measures including drug responses were largely congruent with the earlier reports. The provided classification equation would be a useful tool for identifying a symptomatic taxonomy of OCD in the future researches including drug response studies.

## Korean Medication Algorithm for Generalized Anxiety Disorder 2009: Consensus of Treatment Strategy in Case of Partial Response or Non-response

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**Objective:** This study was performed to investigate the consensus of treatment strategy in case of partial response or non-response in the treatment of generalized anxiety disorder (GAD) that is one of the subjects of Korean medication algorithm project for GAD 2009. **Method:** Based on the guidelines or algorithms and clinical trial studies published formerly in foreign country, the executive committee developed the questionnaires about the treatment strategy for patients with GAD. In this study we analyzed the treatment strategy in case of partial response or non-response in the treatment of GAD. 55 (64%) of 86 experts of review committee of GAD answered the questionnaires. We classified the consensus of expert opinion to 3 categories (the 1st line, the 2nd line, and the 3rd line) and the treatment of choice by the 95% confidence interval and  $\chi^2$ -test. **Results:** For the consensus of treatment strategy in case of partial response or non-response in the treatment of GAD, the items of 'switch from a selective serotonin reuptake inhibitor (SSRI) to a serotonin and noradrenaline reuptake inhibitor (SNRI) or buspirone or vice versa' and 'clonazepam or alprazolam can be combined with another drug even from the initial period' were recommended as 1st line strategy. As the next step 2, the items of 'augment with atypical antipsychotics or add a benzodiazepine or antihistamine' and as the step 3, the items of 'switch to another combination that includes SSRI, SNRI, mirtazapine or tricyclic antidepressant' were also recommended as 1st line strategy. As the last step 4, the items of 'add a third drug of different class from other two drugs that is used in step 3' were recommended as 2nd line strategy. **Conclusion:** This study provided the informations about Korean experts consensus of treatment strategy in case of partial response or non-response in the treatment of GAD. This Korean medication algorithm will be helpful to Korean clinician in the treatment of GAD.

## Sequel on Children After Earthquake in Bantul - Yogyakarta Review of Neuroplasticity Aspect

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**Background:** A few researches about sequel consequences from *Post traumatic Stress Disorder* (PTSD) in Indonesia, whereas many traumatized events has happened to people, especially disasters, one of them is earthquake in Bantul - Yogyakarta in 2006. Sequel of PTSD may happens to everybody which victims of earthquake, especially children which susceptible age for mental disorder. Sequel of mental disorder in children after earthquake in Bantul may be review from one of aspects, it is neuroplasticity aspect. Large of stress level and suddenly event on earthquake in Bantul, neuroplasticity of children should be tolerant that traumatized event to protect sequel after 3 years post earthquake.

**Aim:** The aim of this research is to analyze sequelae from children after earthquake which review from neuroplasticity aspect.

**Methodology:** This research using descriptive analytic. The research will do in Bantul - Yogyakarta with children in elementary school. Measurement sequelae of PTSD using Check List Early Detection Behaviors Tendency to PTSD for Children Based on DSM-IV Criteria. Data which are collected will be investigated base on review of neuroplasticity aspect.

**Result:** The expectation from this research is show sequel from children after earthquake because of large of stress level and suddenly event.

**Benefit:** Because of sequel after earthquake will assist the efforts comprehensive and continuous treatments for children.

**Key Words:** Sequel - Children after Earthquake - Neuroplasticity Aspect.

## The Impact of Panic Disorder on Productivity in Workers: A Preliminary Study Using WHO-HPQ (Health and Work Performance Questionnaire)

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Panic disorder (PD) correlate with poor quality of life, and poor functional outcomes, including high rates of welfare and disability (27%). We aimed to identify the LPT for patients in Korea with PD using the World Health Organization's Health and Work Performance Questionnaire (HPQ), to establish the relative costs to an employer. Additionally, we provided eight weeks of treatment with SSRI's and routine psychotherapy, and assessed post-treatment productivity via HPQ, while comparing to a sample of healthy working controls. 120 patients seeking treatment for the first time at an outpatient psychiatric clinic were recruited as test subjects, using a consecutive sampling technique. A group of age and sex-matched subjects were recruited through advertisement to serve as controls. Actual hours worked per week were 38.7 and 43.6 for the PD and control groups, respectively, with a p value of 0.77. Expected work hours per week were 50.4 and 41.1, with a p value or 0.12. The difference in absent days due to health problems as statistically significant, with the PD group reporting 1.92 days missed in the past four weeks, while the control group reported 0.07 missed days ( $p < 0.01$ ). Of the initial 108 employees in the PD group, 41 completed eight weeks of treatment, as well as the HPQ, PDSS, and HAM-D at both zero and eight weeks. Comparing these 41 subjects at baseline versus eight weeks, there was a statistically significant difference in several categories. The PDSS scores decreased from 16.5 at baseline to 3.7 ( $p = 0.002$ ). HAM-D scores decreased from 18.1 to 4.7 ( $p = 0.001$ ). Reported actual work hours per week increased from 37.4 to 50.2 ( $p < 0.001$ ), while expected hours per week did as well (49.9 to 51.8,  $p < 0.001$ ). The average cost of presenteeism is calculated at \$6451 per employee per year. The PD group's average yearly cost of absenteeism per employee is calculated as \$10,611, while the cost of presenteeism is projected as \$12,895. The total cost of LPT per employee per year is (total for controls) for the control group versus \$23,506 for the PD group.

## Survival Rates of Maintenance Treatment with Venlafaxine ER in Patients with Somatic Symptoms

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**Objective:** To evaluate the efficacy of venlafaxine ER in patients with somatic symptoms, we investigated the clinical factors that affects maintenance periods of patients with venlafaxine ER treatment and presented a comparison in patients who complain of somatic symptoms and not. **Methods:** The recruitment was conducted within outpatients who had received psychiatric treatment with venlafaxine ER. Patients were excluded who used psychotropic agents except venlafaxine ER and benzodiazepines. It was assessed whether the subjects complained somatic symptoms or not at the point of initiation of venlafaxine ER treatment. The duration from initiation to the point when medication was changed due to recurrence of any symptoms and side effects was assessed and compared in two groups. The maintenance periods of the two groups were analyzed using Kaplan-Meier method, and relations with several clinical variables of subjects were with Cox's proportional hazard model. **Results:** Forty eight patients fulfilled inclusion criteria during the study periods. 27 patients (56.3%) were divided to 'with' somatic symptoms group and 21 patients were 'without' somatic symptoms group. Survival rates of 'with' somatic symptoms group (median survival time =79 weeks) were higher than that of 'without' somatic symptoms group (median survival time =12weeks; Breslow test,  $p = 0.036$ ). When analyzed by multivariate analysis used Cox's proportional hazard model, it also showed that somatic symptoms affected survival rates of maintenance treatment significantly (odd ratio=2.837,  $p=0.024$ ). **Conclusion:** Subjects with somatic symptoms had longer maintenance period without recurrence than subjects without somatic symptoms in venlafaxine ER treatment. Subjects with depression showed the trend of long maintenance periods without recurrence, but it was not statistically significant. Subjects with somatic symptoms had longer maintenance period without recurrence than subjects without somatic symptoms in venlafaxine ER treatment. **Key Words:** Venlafaxine ER, Somatic symptoms, Maintenance periods

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## Evaluation of Tiredness in University Students Using a New Multi-dimensional Inventory: A Possible Correlation Between the Severity of Tiredness and Egogram

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We propose a multidimensional inventory covering emotional, physical, anxious, and apathetic dimensions for evaluating the severity of tiredness in university students. Using this inventory and egogram, we investigated the correlation between severity of tiredness and type of personality. We examined 239 students (average age 20.4) and determined the di-mensional structure statistically using confirmatory factor analysis. The questionnaire for tiredness composed 36 items (9 questions each) and student scores the severity of each item using a seven-point SD scale. The hypothesized four-factor model appeared to fit the data in all samples tested (CFI=0.78, GFI=0.72) and had good internal consistency, with an average Cronbach's  $\alpha$  coefficient of 0.86. The severity of tiredness was significantly high in students who did not have enough time to rest, comparing to the students with much time. The students, who felt anxious on their health, showed significantly high tiredness score in physical and apathetic dimensions. Among 5 types of personality determined by egogram, students who were categorized in "Adapted Child (AC)" type had a significant high score in emotional, anxious, and apathetic dimensions of tiredness. Canonical correlation analysis indicated that there were correlations between factors of the tiredness inventory and types of personality ( $\lambda = 0.582$ ): AC type strongly affected to emotional, anxious, and apathetic dimensions. Our findings suggest that type of personality might be an important correlates for evaluating the severity of tiredness in students.

## Developing a Training Program for Clinical Research and Research Ethics at the National Center of Neurology and Psychiatry, Japan

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The aim of clinical research is to improve methods of preventing, diagnosing, and treating diseases, to gain better understanding of the etiology of individual diseases, and to improve the quality of life of patients. Therefore, there is increased attention to translate basic research into human studies, and to develop validate tests and treatments that can improve clinical practice. Furthermore, translating these new medical discoveries into daily clinical practice is crucial. A potential solution to these problems is the enhancement of patient-oriented clinical research. During this past decade, a number of medical schools and teaching hospitals in the US and Europe have initiated clinical research training programs. However, there are only few facilities that provide clinical research training programs in Japan.

Translational Medical Center, National Center of Neurology and Psychiatry is currently developing future leaders and also enhancing present researchers and healthcare professionals into the growing field of clinical research through the Clinical Research and Ethics Training Program. Clinical Research and Ethics Training Program is an ongoing program consisted with didactic seminars and other format to advance individual's degree of knowledge in clinical research design, methods and ethics, and to help them to develop and execute a research project. We believe this program will enhance researchers and related professionals who can work creatively and collaboratively with their colleagues in other disciplines to generate new knowledge to improve healthcare.

## Involvement of Gender Differences in the Effectiveness of Indonesian Version of Life Skills Training

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**Introduction:** Adolescent is one of the critical period in human development. This period is at risk for adolescents in developing mental health problems, especially nowadays where globalization is a quite serious issue. Indonesian version of life-skill training is serial modules of training which help children to gain some psychosocial competence, such as conflict resolution, dealing with emotion and handling peer pressure. These modules were modified from WHO modules of life skills education by Mental Health Directorate, Indonesian Ministry of Health. Gender differences in coping behavior have been reported in many studies. Men are more likely to use problem-focused behavior, which consist of action and preparation. Women are more likely to use emotion-focused strategies, that involve cognitive and emotion. **Objectives:** Evaluating the involvement of gender differences in the effectiveness of Indonesian version of life skills training for adolescent students in one junior high school which was located in Central of Jakarta. **Method:** 40 junior high school students age 11-15 year old, were randomly selected in participating the study. This was the one group pre and post test design. Subjects were enrolled in a five weeks life skills training which were consisted into 5 modules, i.e. enhancing self-esteem, coping with emotions, coping with stress, coping with peer pressures, and conflict resolution. Gender differences behavior was assessed after analyzing the effectiveness of the training by using Strength and Difficulties Questionnaire (SDQ) self-rated and Rosenberg's self-image questionnaire, before and 2 weeks following the training. Statistical analysis is done by using SPSS Wilcoxon Rank test and *Mann-Whitney test*. **Result:** There were significantly change in mean of total difficulties score ( $p=0,009$ ), emotional symptoms ( $p=0,001$ ), hyperactivity ( $0,029$ ) dan prosocial scale ( $0,004$ ) in female students, whereas in male students there was no significantly change in all domains of strength and difficulties before and after life skills training. There were also significantly changes in all domains of self-image questionnaire for female students, which were *self consciousness* ( $p=0,000$ ), *instability* ( $p=0,003$ ), *low self esteem* ( $p=0,001$ ) dan *negative perceived self* ( $p=0,018$ ). In male students only one domain, instability that showed significantly difference ( $p=0,014$ ). Analysis with *Mann-Whitney Test* revealed there was significantly difference between male and female students only in the strength or prosocial score after life skills training ( $p=0,007$ ). **Conclusion:** Gender differences are assumed to have association in effectiveness of five weeks life skills training. **Key words:** gender, life skills, adolescent

## Depersonalization as a Side Effect of Entacapone

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### Background

Depersonalization is a non-pathognomotic symptom seen both as idiopathic and as secondary to various conditions. But medication-induced depersonalization is rarely reported.

### Method

A case study of medication induced depersonalization with non-systematic review of literatures.

### Results

A 65 yrs old male of Parkinson's disease with depression and hypochondria got depersonalized by adding entacapone: catechol-O-methyltransferase (COMT) inhibitor. He has no prior history of dissociative disorder nor posttraumatic stress disorder (PTSD). As he often called ambulances for the hypochondriac symptoms, sertraline was administered to calm the symptoms. His depersonalization and hypochondria had been gradually subsided with adding sertraline. The severity of depression was unchanged between before and after the emergence of depersonalization. But his depersonalization got started soon after the administration of entacapone. With literature search, no case of depersonalization by entacapone was reported.

### Conclusion

Depersonalization induced by medications are seldom seen in clinical practice. It is often missed or confused as a symptom of other conditions. In this case, there is no other cause of depersonalization but COMT inhibitor for Parkinson's disease.

## Default Mode Functional Connectivity in Obsessive-Compulsive Disorder

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**OBJECTIVE:** Resting state functional connectivity is a relatively novel functional magnetic resonance imaging (fMRI) approach that analyzes the temporal correlation of blood oxygen level-dependent (BOLD) signal fluctuations in different brain areas that is not attributable to specific inputs and outputs. There have been no studies regarding functional connectivity during resting state in the patients with obsessive-compulsive disorder (OCD). The aim of the current study was to determine whether functional connectivity in default mode network was altered in patients with OCD during resting state. It was hypothesized that OCD patients would show abnormal spatial and/or temporal patterns in default mode network.

**METHOD:** Twenty two patients with OCD (16 drug-naive, and 6 drug-free at least 4 weeks), and 22 age-, and sex-matched healthy comparison subjects were included in this study. All subjects underwent 4.68-min resting state functional scanning runs in eyes closed conditions. The posterior cingulate cortex (PCC) region was chosen as the seed region for the connectivity analysis. Correlations between temporal connectivity with the PCC seed region in each regions of interest were assessed.

**RESULTS:** The patients with OCD demonstrated lesser default mode network activity compared to the comparison subjects in the anterior cingulate cortex, putamen, and prefrontal cortex. In addition, connectivity between the PCC seed region and the putamen was negatively correlated with the severity of anxiety.

**CONCLUSIONS:** The authors detected decreases in default mode activity in the anterior cingulate cortex, putamen, and prefrontal cortex, which are components of the fronto-subcortical circuitry in OCD. These data provide evidence for fronto-subcortical dysfunction in patients with OCD.

## Neural Correlates of Impaired Response Inhibition in Obsessive-Compulsive Disorder

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**Objective:** Impairment in response inhibitions have been reported in patients with obsessive-compulsive disorder (OCD). However, there have been no reports regarding neural correlates of response inhibition in unmedicated OCD patients. In the present study, we used event-related functional magnetic resonance imaging (fMRI) to investigate the fronto-striato-thalamo-cortical (FSTC) circuit dysfunction in unmedicated OCD patients during the response inhibition process. **Method:** Eighteen unmedicated patients with OCD and 18 age-, sex-, and IQ-matched healthy control subjects underwent event-related fMRI during the stop-signal task that incorporated elements of a response inhibition function. Measurements were taken repeatedly before and after 4 months of treatment in OCD patients. Correlations between brain activation and clinical measures were also assessed. **Results:** In the comparison of stop success minus go contrasts, the OCD patients showed lesser activation of the FSTC circuitry, which included the bilateral inferior cortex, right medial frontal cortex, right posterior cingulate, right caudate, right putamen, left pre-supplementary motor area, and left subthalamic nucleus. In the comparison of successful inhibitory with unsuccessful inhibitory events, patients with OCD had greater activation of the distributed frontal regions, including the right superior frontal cortex, right middle frontal cortex, and right anterior cingulate cortex. These activations were mostly normalized after 4-month treatment. Obsessive symptom scores showed a significant negative correlation ( $r = -0.75$ ,  $p < 0.01$ ) with the activation of the right caudate, and compulsive symptom scores revealed a significant negative correlation ( $r = -0.46$ ,  $p = 0.05$ ) with the activation of the right putamen during stop success minus go contrast trials. **Conclusions:** Our results suggest that a dysfunction of the FSTC loop is responsible for the response inhibition impairment and raise a possibility of action monitoring circuit recruitments as compensation in OCD patients. These aberrant activations are also possibly reversible.

## Midsagittal Structural Difference of Corpus Callosum in Obsessive-Compulsive Disorder

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**Objectives:** The aim of this study was to investigate morphometric difference of corpus callosum (CC) using midsagittal area and thickness on magnetic resonance (MR) images in patients with obsessive-compulsive disorder (OCD) compared to normal controls.

**Methods:** MR images of CC were acquired from 69 patients with OCD and 69 matched normal controls. Midsagittal areas including five subregional areas and 100-point midsagittal thickness were obtained from midsagittal MR images. We compared midsagittal areas and thickness of CC between OCD patients and normal controls. Their correlations with clinical variables and neurocognitive function were also analyzed.

**Results:** The absolute total area of CC was significantly larger in OCD patients than in normal controls when brain size, age, gender and intelligence quotient (IQ) were controlled ( $F=7.858$ ,  $p=0.006$ ). Significant enlargements in CC1 ( $F=9.469$ ,  $p=0.012$ ), CC2 ( $F=4.087$ ,  $p=0.045$ ) and CC5 ( $F=5.765$ ,  $p=0.018$ ) were seen in OCD patients compared to normal controls. OCD patients had thicker midbody and splenium than normal controls controlling brain size ( $p<0.05$ ). However only splenium remained a thicker region in OCD than in normal controls when IQ was added as another covariate ( $p<0.05$ ). There were no significant correlations with clinical variables and cognitive function.

**Conclusion:** The findings suggested that OCD patients would have structural difference of CC and abnormal interhemispheric hyperconnection.

## Neurodevelopmental Anomaly of the Anterior Cingulate Cortex in Obsessive-Compulsive Disorder

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Anterior cingulate cortex (ACC) abnormalities have been consistently implicated in the pathophysiology of obsessive-compulsive disorder (OCD), yet it remains unclear whether these abnormalities originated during early neurodevelopment. In this study, we examined the ACC sulcal/gyral patterns to investigate whether neurodevelopmental anomalies of the ACC were present in patients with OCD. Magnetic resonance imaging of 169 healthy volunteers and 110 patients with OCD was used to examine the paracingulate sulcus (PCS) and cingulate sulcus (CS). Cortical folding patterns were assessed according to established classification criteria. Three categories of PCS morphology were constructed according to the presence and antero-posterior extent of the PCS: "prominent," "present," and "absent". The CS was classified as "interrupted" or "continuous" according to the interruptions in its course. ACC sulcal asymmetry was also evaluated based on inter-hemispheric comparisons of PCS morphology. Analyses revealed that patients with OCD were significantly less likely than controls to show a well-developed left PCS, but we found no differences in regard to CS continuity. Patients also showed the same leftward ACC sulcal asymmetry as was demonstrated by controls. In conclusion, these findings imply a subtle deviation in the early neurodevelopment of the ACC in OCD patients, but the extent to which these anomalies contributed to the pathogenesis of OCD remains unclear. We postulate that several other factors may interact with early neurodevelopment in the pathogenesis of this disorder.

Key word: Obsessive-Compulsive disorder; cingulate; sulci; gyri; neurodevelopment.

## Are Males or Females More Sensitive? -Correlation between Life Event Scale (LES) and Serum Cholesterol Level

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### Background:

Previous researches have documented the relationship between serum cholesterol metabolism and stress. Gender differences are also widely investigated regarding the hormones' effect on serum cholesterol level. However, the result of gender difference is inconsistent. This study reveals the gender differences of correlations between the serum lipid profile and life stress.

### Methods:

Eighty healthy volunteers (40 males, 40 females; mean age = 31.66 years old (SD=10.10) from the community were recruited via advertisement. The Ethical Committee for Human Research at the National Cheng Kung University Hospital had approved the study protocols, and the informed consent was obtained while they were enrolled in this study. Serum lipid profile measurements were taken at the beginning of this study. In addition, all participants were required to finish the questionnaire of life event scale.

### Results:

Significantly positive correlations were shown between LES and either total serum cholesterol or Low-density lipoprotein (LDL) in males.

### Conclusions:

The results of this study suggest that there are significant correlations between serum lipid profiles (total serum cholesterol, low-density lipoprotein) and LES in males. Our findings raise the issue that male serum lipid profiles are more vulnerable to stressors reaction, while lipid serum profiles of males and females are both affected by life stresses.

## Association between Glutamate N-methyl-d-aspartate 2b Subunit Receptor Gene and Age of Onset of Obsessive-Compulsive Disorder

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**Objective:** The definite cause of obsessive-compulsive disorder (OCD) is still unknown. There is strong evidence from family and twin studies that genetic determinants play an important role in the etiology of OCD. Specially, an early age at onset of OC symptoms in family studies is strongly associated with a more familial form of OCD. Also, many researches suggest that early- and late-onset OCD represent separate subtypes of the disorder. The aim of this study was to investigate the associations between glutamate receptor, ionotropic, n-methyl-d-aspartate (NMDA) subunit 2B gene (GRIN2B) polymorphisms and onset of OCD in Korean.

**Methods:** We recruited 109 OCD patients and classified them into an early-onset group (age of onset <18 years) and a late onset-group (age of onset ≥ 18). Genomic DNA was extracted from their blood then comparison of the genotypes and allele frequencies of the two polymorphisms (5072T/G and 5988T/C) in GRIN2B between groups. We also compared between child-onset group (age of onset ≤ 15) and adult-onset group (age of onset ≥ 19)

**Results:** There were no significant differences between an early-onset group and a late onset-group in genotype. Moreover, we could not find any differences between child-onset group and adult-onset group.

**Conclusion:** Our study suggest that GRIN2B polymorphisms (5072T/G and 5988T/C) does not affect the onset of OCD in Korean. But this finding is the result from preliminary study. Therefore, further investigations will be needed by using a larger sample size.

## Plasma BDNF Levels in Patients with Panic Disorder and its Relation with Clinical Characteristics

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**Purpose:** Brain-derived neurotrophic factor (BDNF), one of the most abundant and important neurotrophins, is known to be involved in the development, survival, maintenance and plasticity of neurons in the nervous system. Some studies have suggested that BDNF may play a role in the pathophysiology of several psychiatric illnesses such as depression and schizophrenia. Similarly, it is likely that alteration of BDNF may be associated with the neuromodulation that contributes to the development of anxiety disorder. The purpose of this study was to determine whether there is an abnormality of plasma BDNF levels in patients with panic disorder, and its relation with clinical characteristics. **Methods:** The 101 patients with panic disorder (mean age: 39.95 ± 10.16 years, 53 males, 48 females) who fulfilled the DSM-IV criteria for panic disorder and 101 healthy controls (mean age: 38.45 ± 10.10 years, 52 males, 49 females) were enrolled in the study. BDNF was assayed using the DuoSet ELISA Development System (R&D Systems, DY248). The clinical characteristics of the panic patients were evaluated by Panic Disorder Severity Scale (PDSS), Acute Panic Inventory (API), Agoraphobic Cognition Questionnaire (ACQ), Hamilton Anxiety Rating Scale (HAMA), duration of illness, presence of agoraphobia, insomnia, early or recent stressful events, and history about alcohol or smoking. The difference in the plasma BDNF levels between two groups and subgroup analysis were analyzed by non-parametric Mann-Whitney test, and the correlations between the BDNF level and clinical characteristics were examined by Spearman correlation coefficient using the SPSS 12.0 ( $p < 0.05$ ). **Results:** The mean plasma BDNF levels of 101 panic patients were significantly lower compared with those of controls (146.55 ± 138.72 pg/ml vs. 788.89 ± 500.94 pg/ml,  $Z = -10.06$ ,  $p < 0.001$ ). The HAMA score ( $r = -0.31$ ,  $P < 0.05$ ) and duration of illness ( $r = -0.33$ ,  $P < 0.05$ ) were negatively correlated with the BDNF level in panic patients. And, mean plasma BDNF level in panic patients with the recent stressful event were higher than without that (188.61 ± 166.94 pg/ml vs. 116.61 ± 106.23 pg/ml,  $Z = 2.67$ ,  $p < 0.005$ ). However, other variables did not reveal any significant correlations with BDNF levels. **Conclusion:** These results suggest that BDNF may play a role in the pathophysiology of panic disorder. Further studies are needed to clarify the more precise role of BDNF in panic disorder, and its interaction with other vulnerable factors on anxiety disorder. **Index Words:** Panic disorder, BDNF, Neurotrophin

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## Association Between Beta-adrenergic Receptor Gene Polymorphisms and Personality Traits in Healthy Japanese Subjects

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There are 3 subtypes in beta adrenergic receptor, beta-1, beta-2, and beta-3. To date, it has been reported that the beta adrenergic receptor genes (*ADRB1*, *ADRB2* and *ADRB3*) are associated with the resting heart rate, obesity, and thermogenesis. On the other hand, there is a self-rating scale called Temperament and Character Inventory (TCI) developed based on a psychological model of personality. As for the Cloninger's theory, personality consists of temperament and character, and it is assumed that the temperament is associated with dopamine, serotonin, and noradrenaline. We examined the correlation between five polymorphisms, which cause amino-acid substitution, in the beta adrenergic receptor genes (*ADRB1*, *ADRB2* and *ADRB3*) and the personality traits, measured with the TCI, in 500 healthy Japanese subjects. In the results, the *ADRB1* Ser49Gly (rs1801252) polymorphism was significantly associated with Harm Avoidance (total,  $p = 0.0186$ ; female,  $p = 0.0326$ ), Cooperativeness (total,  $p = 0.0440$ ), and Self-Transcendence (total,  $p = 0.0475$ ; male,  $p = 0.0290$ ), and the individuals with the 49Gly allele showed lower scores than those without the 49Gly allele. The *ADRB2* Gln27Glu (rs1042714) polymorphism was also significantly associated with Persistence (female,  $p = 0.0173$ ) and Self-Transcendence (male,  $p = 0.0151$ ), and the individuals with the 27Glu allele showed higher scores than those without the 27Glu allele. Our results suggest that the variations in the *ADRB1* Ser49Gly and the *ADRB2* Gln27Glu gene polymorphisms influence the personality traits of both temperament and character dimensions.

## Interaction between Serotonin Transporter Promoter and Dopamine D4 Receptor Polymorphisms on Decision Making

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Appropriate decision making is an important brain function to maintain our lives. The Iowa Gambling Task (IGT) is a tool for decision making under ambiguity. The aims of this study were to evaluate the influence of serotonin transporter linked polymorphic region (5-HTTLPR) and dopamine receptor D4 (DRD4) polymorphisms and their interaction on IGT performance. One hundred fifty-nine normal subjects were involved in this study. All subjects performed the IGT and were genotyped for the triallelic 5-HTTLPR and DRD4 48 bp u-VNTR polymorphisms. After controlling for the gender, age, and impulsiveness, there were no main effects of 5-HTTLPR and DRD4 gene polymorphisms on total IGT scores. However, there was a significant effect on the interaction between 5-HTTLPR and DRD4 on total IGT scores. In the presence of the 5-HTTLPR S'S' (SS+SLG+LGLG), subjects with the DRD4 2R- (2 repeat non-carrier) had higher total IGT scores compared to those with the DRD4 2R+. In contrast, in the absence of the 5-HTTLPR S'S', subjects with the DRD4 2R+ had higher total IGT scores than those with the DRD4 2R-. When we divided IGT scores into the first and second half trials, the 5-HTTLPR x DRD4 interaction effects were stronger in the second half block (decision under risk) than the first half block (decision under ambiguity). In conclusion, the DRD4 genotypes might influence decision-making performance differently according to the background genotypes of 5-HTTLPR.

## Differences in the Clinical Characteristics of Response and Non-Response Groups with Once-Daily OROS-Methylphenidate Treatment of Attention-Deficit/Hyperactivity Disorder

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**Objective:** Attention-deficit/hyperactivity disorder (ADHD) is a common, life-long condition associated with major functional impairment. The purpose of this study was to identify differences in the clinical characteristics of response and non-response groups composed of Korean children and adolescents with ADHD. **Methods:** Sixty-three children and adolescents diagnosed with ADHD according to the Kiddie-Schedule for Affective Disorders and Schizophrenia for School-age Children-Present and Lifetime Version-Korean Version were included in the study. The study design was an 8-week, open-label trial of OROS-methylphenidate (OROS-MPH) monotherapy. The subjects were assessed using the Korean ADHD Rating Scale (K-ARS), Korean version Conners parent rating scale (K-CPRS), Clinical Global Impression of Severity (CGI-5), Clinical Global Impression of Improvement (CGI-I), and Barkley Side Effect Rating Scale at baseline and 1, 2, 4, and 8 weeks after starting OROS-MPH treatment and Wechsler Intelligence Scale for Children at base line. **Results:** No differences were observed in the age, sex, severity of symptoms, IQ, reported by the parent, comorbidities at baseline, or doses of OROS-MPH at each evaluation point between groups but only difference was observed in weight. However, the non-responder had heavy weight & body mass index at baseline than the responder. No difference in intellectual function between the two groups was observed at the base line of the trial, and the responder was more likely to have side effects at first and forth week. **Conclusion:** The results suggest that individual biological diversity may mediate different treatment responses to OROS-MPH. Interventions other than medication are needed to achieve response and to restore proper functioning of patients with ADHD in the non-response group.

## The Relationship between Prolactin Level in Static State and Brain Response to Erotic Stimuli

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Many studies have showed that excess or lack of sexual hormones, such as prolactin and testosterone, induced the sexual dysfunction in humans. Little, however, is known about the role of sexual hormones showing normal range in, especially, the static state unexposed to any sexual stimulation. We hypothesized sexual hormones in the static state may affect sexual behavior. We investigated the association of the sexual hormones level in the static hormonal release state before visual sexual stimulation with the sexual response-related brain activity during the stimulation. Twelve heterosexual men were recorded the functional MRI signals of their brain activation elicited by passive viewing erotic (ERO), happy-faced (HA) couple, food and nature pictures. Both plasma prolactin and testosterone concentrations were measured before functional MR scanning. A voxel wise regression analyses were performed to investigate the relationship between the concentration of sexual hormones in static release state and brain activity elicited by ERO vs. HA, not food vs. nature, contrast. The plasma concentration of prolactin in static release state showed positive association with the activity of the brain involving cognitive component of sexual behavior including the left middle frontal gyrus, paracingulate/superior frontal/anterior cingulate gyri, bilateral parietal lobule, right angular, bilateral precuneus and right cerebellum. Testosterone in static release state was positively associated with the brain activity of the bilateral supplementary motor area which related with motivational component of sexual behavior. Our results suggested sexual hormones in static release state may have their specific target regions or network associated with sexual response.

## Factors Associated with the Persistence of Treatment in the Setting of ADHD

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### Introduction

ADHD results common problems in social functioning. Identifying factors of long-term adherence to treatment is important. To investigate the factors, we decided to define the initial point as when the patient visits clinic for the first time, and the end point as when the patient drops out of the clinic. It is different, compared to other studies that identify continuity of medication treatment.

### Method

Retrospective chart review for 318 ADHD patients. Enrolled period is from 2005 to 2008. Time of first treatment is defined as the date of first visit to clinic and time to a first treatment discontinuation is defined as the date of the last prescription. Subjects are divided into two groups; the first group as non-persistence group (follow-up periods < 6 months), the other group as persistence group (follow-up period > 6 months). Examine epidemiologic factors.

### Results

Non-persistence group (n=167) includes 82 never-medicated. Compared with non-persistent group, persistence group showed more severe symptoms in Conner's score and continuous performance test. Higher paternal education and higher IQ score of patients were inversely related. If mother had difficulty in parenting, it positively.

### Conclusion

1) High proportion of patients are discontinuing even before starting medication treatment. 2) Long term persistence is associated with maternal psychological distress, lower patient's IQ scores, and more severe ADHD symptoms.

## Treadmill Exercise Alleviates the Symptoms of Attention Deficit Hyperactivity Disorder (ADHD) through Enhancing of Dopamine Synthesis and Neuronal Activity in Rats

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Attention deficit hyperactivity disorder (ADHD) affects 8-12% of children and is characterized by inattention, hyperactivity, and impulsivity. The exact underlying mechanisms of ADHD are not clarified, however, impairment of dopaminergic system in the pre-frontal cortex was suggested one of the possible mechanisms of ADHD. Tyrosine hydroxylase (TH) is the rate-limiting enzyme that is involved in the synthesis of dopamine. The expression of c-Fos has been used as a marker of neuronal activity, and increased expression of c-Fos in neurons represents enhanced neuronal activity. Spontaneous hypertensive rats have been used as the animal model for ADHD. Physical exercise has been known to restore the brain functions disrupted by several neurodegenerative and psychiatric disorders. In the present study, we investigated whether treadmill exercise exerts therapeutic effects on ADHD. In this study, open field test for the determination of activity and radial 8-arm maze test for the evaluation of leaning ability were performed using spontaneous hypertensive rats. TH and c-Fos expression in the substantia nigra and striatum were evaluated using immunohistochemistry. In the present results, the rats of ADHD model showed hyperactivity and impaired leaning ability. TH and c-Fos expressions were decreased in the rats of ADHD model. Treadmill exercise alleviated hyperactivity and improved leaning ability in the ADHD rats. TH and c-Fos expressions of the ADHD rats were also enhanced by treadmill exercise. Here in this study, we showed that treadmill exercise effectively alleviates the ADHD-induced symptoms through enhancing of dopamine synthesis and neuronal activity. Key Words: Attention deficit hyperactivity disorder; Activity, Learning ability; Dopamine; c-Fos; Treadmill exercise; Spontaneous hypertensive rats

## Determinants for Discriminating Child with and without Autism Using Multidimensional Inventory and Discriminant Analysis

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Autism is classified as one of the developmental disorders, and is characterized by disability of social communications and stereotyped patterns of behavior. Ever since the first report by Kanner (1943) a variety of rating scales for evaluating symptoms of autism have been developed. Most of them, however, need special skills to evaluate the severity of autism. From the behavioral viewpoints, we proposed a new multidimensional inventory for determining the severity of the behavioral disorder (Bekku and Yoshimura, 2008), one that does not require any specific skill. This inventory covers the social, emotional, cognitive, stereotypical, perceptual, and autism-specific behavioral dimensions (ten questions each) and was verified statistically. During childhood (3 to 14 years old), however, healthy child also displays something complicated behavior, and it appears that comparison of behavioral characteristics between healthy and autism children is important to establish the inventory. In this study, the mother scored the severity of each item using a five-point scale (233 mothers who had a child with autism and 240 mothers who had a child without autism). We extracted ten behavioral elements, based on the incidence and severity of behavioral disorder between two groups. Using these elements, discriminant analysis revealed that the discrimination hit ratio was approximately 83.7%, while the misclassification ratio was approximately 16.3%. We suggest that these ten behavioral elements are essential for discriminating between children with and without autism.

## Follow Up Study of Using OROS MPH in ADHD Children and Adolescents: Preliminary Report

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**Background:** OROS MPH (Concerta) is the only long-acting slow release MPH available in Taiwan. The once-daily dosing preparation has been reported to improve compliance and enhance the effectiveness in treatment of ADHD. We attempt to investigate the long term efficacy, side effects, and compliance of OROS MPH in treating ADHD children and adolescents,

**Method:** A follow up study with 7 visits within 40 weeks after patients were initiated OROS MPH. Dosage was adjusted according clinical response and side effects by clinician's judgment.

**Results:** 69 patients & their caretakers participated. Half of them finished 28 weeks and one thirds finished 40 weeks follow up. The improvement in ADHD symptoms were observed since visit 1 and lasted throughout the whole observation weeks in CGI-I or SNAP-IV rating. Compliance had been improved markedly after shift to OROS MPH from IR MPH (Ritalin). However, the compliance gradual decreased as the duration of treatment increased. There were 40% of patients never missed the dosage during visit 1 but only 20% during visit 4 (20 weeks). The dosage of OROS MPH was around 1.1mg/kg/day. However, there was no dose related to the degree of CGI-I change. The side effects are similar to the short term treatment and the most common side effects including poor appetite& insomnia. Poor appetite was prominent at initial few weeks and persisted through the whole period. The severity decreased gradually after 8-12 weeks of treatment. Caretaker's anxiety and depression by SCL-90 were decreased as the treatment continuing. During the initial few visits, parental anxiety & depression were correlated to the scores of children's ADHD symptoms in SNAP-IV.

**Conclusion:** OROS MPH is effective and safe in the treatment of ADHD for about 10 months. It improved both the compliance and effectiveness, and also decreased the parental anxiety and depression.

## Effect of Low-dose Clorgyline on Methamphetamine-induced Conditioned Place Preference in Rats

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The effect of subchronic treatment of rats with clorgyline, an irreversible monoamine oxidase-A (MAO-A) inhibitor, on methamphetamine (METH)-induced conditioned place preference (CPP) was investigated. Administration of rats with METH (1.0 mg/kg, i.p.) for every other day during two conditioning sessions (i.e. saline/METH conditioning with no clorgyline pretreatment) induced a significant CPP index compared with saline/saline conditioning. Pretreatment of the rats with clorgyline at a dose of 0.1 mg/kg (i.p.), but not 1.0 or 10 mg/kg, attenuated METH-induced CPP. Neurochemical analysis by high-performance liquid chromatography revealed that tissue levels of monoamines and their metabolites were not significantly affected by treatment with 0.1 mg/kg clorgyline except the levels of 3-methoxy-4-hydroxyphenylglycol (MHPG) in the regions of the striatum and nucleus accumbens. Clorgyline at doses of 1.0 and 10 mg/kg significantly affected the tissue levels of 3,4-dihydroxyphenylacetic acid, norepinephrine (NE), MHPG, and 5-hydroxytryptamine in the cerebral cortex and of all monoamines and the metabolites examined in the region of the striatum and nucleus accumbens. A significant decrease in the MHPG/NE ratio was apparent in the rats pretreated subchronic clorgyline (0.1 mg/kg). Overall, the present study demonstrated that low-dose of clorgyline attenuated METH-induced CPP in rats.

### Attenuation by L-histidine of Methamphetamine-induced Stereotypical Biting in Mice

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Administration of methamphetamine (METH; 10 mg/kg, i.p.) to male ICR mice induced bizarre behavior including persistent locomotion and stereotypical behaviors, which were classified into four categories: stereotyped head-bobbing, circling, sniffing, and biting. Pretreatment with L-histidine (750 mg/kg, i.p.) significantly decreased the stereotypical biting induced by METH and significantly increased persistent locomotion. This effect of L-histidine on behavior was completely abolished by simultaneous administration of pyrilamine or ketotifen (brain-penetrating histamine H<sub>1</sub> receptor antagonists; 10 mg/kg each, i.p.), but not that of fexofenadine (a non-sedating histamine H<sub>1</sub> receptor antagonist that does not cross the blood-brain barrier), zolantidine (a brain-penetrating histamine H<sub>2</sub> receptor antagonist), thioperamide, or clobenpropit (brain-penetrating histamine H<sub>2</sub> receptor antagonists; 20 mg/kg for fexofenadine and 10 mg/kg for other drugs, i.p.). L-histidine pretreatment significantly increased the hypothalamic histamine content compared with saline pretreatment. L-histidine plus thioperamide pretreatment significantly increased the hypothalamic N<sup>7</sup>-methylhistamine content compared with saline pretreatment. These data suggest that L-histidine modifies the effects of METH through central histamine H<sub>1</sub> receptors.

### Riluzole Rapidly Activates a MEK/ERK/CREB Pathway in Glial Cells: A Role for GDNF Expression

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[Background] Riluzole, which reduces glutamatergic overstimulation, is currently approved for the treatment of amyotrophic lateral sclerosis. Recent clinical studies reported that riluzole, either as monotherapy or as augmentation therapy, is also effective in patients with depression. We previously reported that blood level of glial cell line-derived neurotrophic factor (GDNF) was lower in patients with depression than in control subjects and that antidepressants induced GDNF expression in a rapid activation of MEK/ERK/CREB pathway-dependent manner in normal human astrocyte and rat C6 glioma cells (C6 cells). Therefore, GDNF is suggested to be involved in the effect of antidepressants in glia. Because it was reported that riluzole induced GDNF expression, we hypothesized that riluzole, as well as antidepressants, could activate a common pathway of GDNF expression in glial cells. In this study, we investigated the effect of riluzole on the GDNF expression pathway, especially on the CREB phosphorylation in C6 cells. [Results] We found that riluzole rapidly induced CREB phosphorylation, which increased within 5 min and peaked at 1 h after the treatment. Furthermore, the riluzole-induced rapid CREB phosphorylation was inhibited by U0126, a MEK inhibitor. These results suggest that riluzole rapidly activates a MEK/ERK/CREB pathway. [Conclusion] Our data suggests that riluzole resembled antidepressants in its rapid action on a MEK/ERK/CREB pathway, which is involved in the antidepressants-induced GDNF expression in glial cells.

### Effect of Yokukansan on the BPSD-like Behavior Induced by Repeated Cerebral Ischemia in Rats Via Serotonergic Nervous Systems

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Yokukansan (YKS) is a traditional Japanese medicine which was reported to improve behavioral and psychological symptoms of dementia (BPSD) such as hallucinations, aggressiveness, and anxiety in the patients with cerebrovascular dementia and other forms of senile dementia. Moreover, abnormalities of the serotonin (5-HT) system such as 5-HT<sub>2A</sub> receptors have been reported to be associated with BPSD of dementia patients. But neuropathological background of these effects remains unknown. In the present study, we investigated the effects of YKS on impairments of BPSD-like behavior by repeated cerebral ischemia (RI) in rats.

Repeated oral administration of YKS significantly improved anxiety-like behavior in the light/dark box test and the elevated plus-maze task which was induced by RI. In addition, YKS significantly suppressed the wet-dog shake response induced by 2,5-dimethoxy-4-iodoamphetamine (5 mg/kg, i.p.) in RI rats which is 5-HT<sub>2A</sub> receptors mediated a behavioral response.

These findings suggest that the improvement of BPSD-like behavior by YKS may be mediated, in part, by altered expression of 5-HT<sub>2A</sub> receptors in the prefrontal cortex, which suggests the involvement of the 5-HT system in psychopharmacological effects of YKS.

### Add-on Aripiprazole Potentiates Fluoxetine-induced Monoamine Release in Rat Prefrontal Cortex

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#### Background:

Treatment-resistant depression is a common occurrence in clinical practice. Second generation antipsychotics (SGA) have been reported to augment the effect of SSRI therapy in treatment-resistant depression. In particular, aripiprazole has shown efficacy as an augmentation option. In the present study, we evaluated the effects of perospirone, risperidone and aripiprazole in combination with fluoxetine in a preclinical study

#### Method:

Male Wistar rats weighing 200-250g were used in this study. A microdialysis probe was placed in the right medial frontal cortex. Two days postoperatively, perospirone, risperidone and aripiprazole with fluoxetine were administered intraperitoneally to rats. The dopamine and serotonin levels in the medial frontal cortex were measured.

#### Results:

The 5-HT/DA ratio of co-administration of perospirone with fluoxetine, risperidone with fluoxetine, and aripiprazole with fluoxetine were 0.44, 0.68 and 2.56 fold of the pre-administration level, respectively.

#### Conclusions:

Aripiprazole is a second generation antipsychotic. But it is a unique antipsychotic because it is a partial agonist of the dopamine D<sub>2</sub> and 5-HT<sub>1A</sub> receptors and an antagonist of the serotonin 5-HT<sub>2A</sub> receptor. The 5-HT/DA ratio of aripiprazole with fluoxetine is different from that of perospirone with fluoxetine or risperidone with fluoxetine. The property of receptor affinities of aripiprazole may be related to the characteristic 5-HT/DA ratio.

### Effects of GDNF on Adult Dentate Gyrus-Derived Neural Precursor Cells

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It has been shown that neurogenesis in dentate gyrus is decreased in adult rodents' models for mood disorders and that antidepressants increase adult neurogenesis. These follow that the increase of adult neurogenesis might be beneficial to the treatment of mood disorders. However, it is poorly understood how antidepressants affect neurogenesis in adult dentate gyrus. We have already established the culture system of adult rat dentate gyrus-derived neural precursor cell (ADP). Using ADP, we investigated the direct effects of antidepressants on ADP and showed that antidepressants have no direct effects on proliferation, apoptosis and differentiation of ADP. Therefore, we hypothesized that antidepressants increased neurogenesis in adult dentate gyrus with unknown indirect mechanism. Recent studies have shown that antidepressants increase the expression and the secretion of glial cell line derived neurotrophic factor (GDNF) in C6 glioma cell derived from rat astrocyte (Hisaoka et al, J.Neurochem, 2001). It suggests that antidepressants might affect neurogenesis through increasing the secretion of GDNF from astrocyte. Therefore, we investigated the effects of GDNF on proliferation, apoptosis, differentiation of ADP. ADP proliferation was examined with Alamar Blue assay with or without of 5  $\mu$ M dexamethasone, an agonist of glucocorticoid receptor. GDNF had no effect on ADP proliferation both in the presence and absence of 5  $\mu$ M dexamethasone. ADP apoptosis was induced by 300 nM staurosporine and estimated with TUNEL staining. GDNF had no effect on 300 nM staurosporine-induced ADP apoptosis. ADP differentiation was induced by 1 $\mu$ M retinoic acid and estimated with immunocytochemistry of Tuj1 (a marker of neuron) and GFAP (a marker of astrocyte). Retinoic acid differentiated ADP into both neuron and astrocyte. GDNF decreased ADP differentiation into neuron and increased it into astrocyte. These results suggest that GDNF may not be involved in the proliferation and apoptosis but differentiation steps on neurogenesis with antidepressants.

### Effect of Co-administration of Mirtazapine with Citalopram in Rat Contextual Conditioned Fear Stress Model

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Mirtazapine introduced newly as an antidepressant in Japan has an anxiolytic property in clinical trials and preclinical animal experiments (Kakui et al., Pharmacol Biochem Behav 92:393-8, 2009). In addition, mirtazapine addition to selective serotonin reuptake inhibitors (SSRIs) is proven to be effective for depression resistant to SSRIs. Accordingly, combination of SSRIs and mirtazapine may have better efficacies for anxiety disorders. In this study, we examined the combined effects of mirtazapine and citalopram, an SSRI, on freezing behavior induced by contextual conditioned fear as an index of anxiety or fear. Male Sprague Dawley rats individually received footshocks in a shock chamber, and 24 hours later, they were given citalopram and/or mirtazapine injections. One hour after citalopram and 30 min after mirtazapine administration, freezing behavior was analyzed in the same shock chamber without shocks. Mirtazapine decreased freezing dose-dependently consistent with a previous report, and enhanced an anxiolytic effect of both low and high doses (3 and 30 mg/kg) of citalopram. Because mirtazapine blocks  $\alpha_2$  adrenoreceptors, the combined effect of atipamezole, a selective  $\alpha_2$  receptor antagonist, with citalopram was also examined. Similar to mirtazapine, atipamezole reduced freezing dose-dependently but the enhancement of citalopram's effects by atipamezole is less clear than that by mirtazapine. The present findings suggest that mirtazapine is anxiolytic and enhances the anxiolytic effect of SSRI, but this enhancement may not be explained only by its anti- $\alpha_2$  property.

### Sertraline Inhibits Endocytosis Via Suppression for Dynamin GTPase

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The phospholipid is a main component of the plasma membrane and has a hydrophilic region and a hydrophobic region in a molecule. The phospholipid makes bilayer membrane that consists of two regions: a hydrophilic region and a hydrophobic region locate outside and inside of bilayer membrane respectively. The uptake of small molecules together with the bilayer membrane is called endocytosis except that nutritional factors or antigens are selectively transferred by specific membrane protein or glycolipid. Endocytosis is a primitive and a conservative phenomenon widely distributing throughout receptor mediated signal transduction and the lymphocyte phagocytosis. For instance, the signal transduction such as neurotransmitters are modulated by the down-regulation that internalized the cell surface receptors. Dynamin (Dyn) family has GTPase and pleckstrin homology (PH) domains. A major role of Dyn GTPase activity in endocytosis is to produce a mechanical force for membrane fission during vesicle budding, either by constriction or expansion of the collar surrounding the neck of the invaginated vesicle. The plasma membrane binds the PH domain of Dyn, stimulates its GTPase activity, and induces cooperative helix assembly. Mammalian has three Dyn isoforms with different tissue distributions. Dyn 1 is only expressed in brain. Dyn 1 KO mice leads to inhibition of synaptic vesicle recycling with strong stimulation. We previously reported that sertraline potently inhibited Dyn GTPase activity *in vitro*. In this study, we report the uptake of endocytosis marker under sertraline stimulation.

### Dynamin 1 Depletion and Memory Deficits in Rats Treated with Beta-amyloid and Cerebral Ischemia

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Alzheimer's disease (AD) is progressive dementia with senile plaques composed of beta-amyloid (A $\beta$ ). Recent studies suggest that synaptic dysfunction is one of the earliest events in the pathogenesis of AD. Here, we provide the first experimental evidence that a change in the level of dynamin 1 induced by A $\beta$  correlates with memory impairment *in vivo*. We treated rats with transient cerebral ischemia with oligomeric forms of A $\beta$  (A $\beta$  oligomers), including dimers, trimers and tetramers intracerebrally. The combination of A $\beta$  oligomers and cerebral ischemia, but not A $\beta$  oligomers or cerebral ischemia alone, significantly impaired memory and decreased the level of dynamin 1, which plays a critical role in synaptic vesicle recycling, but did not affect the levels of other synaptic proteins, such as synaptophysin and synaptobrevin, in the hippocampus. Furthermore, the N-methyl-D-aspartate (NMDA) receptor antagonist memantine prevented memory impairment and dynamin 1 degradation, suggesting that these changes might be mediated by NMDA receptors. These results suggest that A $\beta$  oligomers induce memory impairment via dynamin 1 degradation, which may explain the synaptic dysfunction in the early phase of AD.

### Seizure-evoked Brain Fos Expression in Noda Epileptic Rat (NER)

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Noda Epileptic Rat (NER) is a genetic rat model of epilepsy that exhibits spontaneous generalized tonic-clonic (GTC) seizures. In the present study, we analyzed the brain Fos expression following GTC seizures in NER to explore the regions involved in the seizure generation. NER was placed in an observation box for 30 min and the incidence of seizures was monitored. NER which exhibited GTC seizures during the observation were deeply anesthetized 2 hours after the seizure, and the brains were removed for immunohistochemical examination. NER rats which did not show any seizure were used as the control. The staining of Fos like-immunoreactivity (Fos-IR) was performed by the ABC methods and the number of Fos-IR positive nuclei was counted. Six out of 11 NER examined exhibited GTC seizures during the 30 min-observation. Control level of Fos expression in NER (no GTC) was very low in all brain areas examined. GTC seizures elicited Fos expression with high densities in cerebral cortices such as in the motor cortex, piriform cortex, perirhinal-entorhinal cortex, agranular insular cortex, auditory cortex. In the limbic region, GTC seizures in NER specifically induced Fos expression in the amygdala, cingulate gyrus and hippocampus (i.e., dentate gyrus and CA3). However, Fos expression in the basal ganglia (e.g., accumbens and striatum), diencephalon (e.g., thalamus and hypothalamus) and pons-medulla oblongata were very low. These results suggest that GTC seizures in NER are of forebrain origin and are evoked by activation of the limbic and/or cortical seizure circuits.

### Regional Distribution of the Forebrain Fos Expression in Tremor Rats, a Novel Model of Human Essential Tremor

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Tremor rat (TRM) is a mutant lacking the aspartoacylase gene and exhibits intensive tremor at a young age (~8 weeks). We performed pharmacological analysis of tremor in TRM and showed that TRM is useful as a novel model of human essential tremor. In this study, we analyzed the regional distribution of the forebrain Fos expression in TRM to explore the brain regions involved in the tremor generation. After an observation of tremor, TRM was deeply anesthetized with pentobarbital, transcardially perfused with 4% formaldehyde, and the brain was removed. Immunohistochemical staining of Fos protein was performed by the ABC methods and the number of Fos-immunoreactivity (Fos-IR) positive cells was counted. Wild type rats with no tremor showed only marginal Fos expression in all brain areas examined. TRM with continuous tremor exhibited a marked Fos expression in various regions of the cerebral cortices including the motor cortex, sensory cortices and auditory cortex. In addition, increases in Fos expression were also found in some regions of the parahippocampal gyrus (e.g., piriform cortex and insular cortex) and of the hypothalamus (e.g., tuberal and dorsomedial hypothalamus). In contrast, the level of Fos-IR positive cells was very low in other regions including the limbic areas (e.g., hippocampus and amygdala), basal ganglia (e.g., striatum and globus pallidus) or the thalamus. These results suggest that neural excitation in the cerebral cortices and parahippocampal gyrus are closely associated with the expression of tremor in TRM.

### Behavioral and Pharmacological Analysis of Tremor Rats, a Novel Model of Human Essential Tremor

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Tremor rat (TRM) is a mutant originally found in the Kyoto:Wistar colony and exhibits intensive tremor at a young age (~8 weeks). In order to assess a phenotypic relevance of TRM, we examined the effects of various anti-tremor agents on the incidence and magnitude of tremor in TRM. TRM of either sex (4-5 weeks old) were used. Animals were treated with various anti-tremor agents as follows, propranolol and pindolol (non-selective  $\beta$  antagonists, 30 and 60 mg/kg, i.p.), diazepam (a benzodiazepine anxiolytic, 1 and 3 mg/kg, i.p.), and trihexyphenidyl (THP: a muscarinic acetylcholine (mACh) agonist, 3 mg/kg, i.p.). Total duration of tremor and its intensity were measured for 1 min, before and 15, 30, 45, 60 min after the injection of an anti-tremor agent. In addition, THP was also tested for oxotremorine (OXO: mACh agonist, 0.5 mg/kg, s.c.)-induced tremor in male ddY mice. Before the drug treatment, TRM exhibited intensive tremor for most time (50-60 sec) of each observation (1 min each). However, both total duration and intensity of tremor were significantly reduced by propranolol and pindolol in a dose-related manner. Diazepam (3 mg/kg) also improved the tremor of TRM. In contrast, the antiparkinsonian agent THP failed to affect the incidence of tremor in TRM, while it suppressed OXO-induced tremor. These results suggest that TRM is useful as a novel animal model of human essential tremor.

### Kangenkaryu Improves Aging-related Memory Deficit by Normalizing NMDA Receptor-mediated Signaling in the Brain

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Kangenkaryu (KK), a traditional Chinese prescription consisting of six different herbs, has been reported to improve learning and memory deficits in animal models of dementia. This study aimed to clarify the mechanism underlying the effect of KK using senescence accelerated prone mice (SAMP8) and the mice with temporal brain ischemia. Twenty-week-old SAMP8 (P8) received transient two vessel occlusion (P8-2VO) or sham operation (P8-sham) at day 0. Age-matched senescence-resistant inbred strain (SAMR1, R1) and 8-week-old SAMP8 (young P8) mice were also used as controls. P8-2VO and P8-sham mice received daily administration of KK (100 mg/kg, p.o.) or water for 21 days from day 3. Compared to R1 and young P8, P8-sham and -2VO mice exhibited learning and memory deficit in the object recognition and object location tests conducted from day 17. 2VO tended to exacerbate the deficit in P8 but the effect was insignificant. KK administration improved learning and memory deficits in P8-2VO and P8-sham. The expression levels of phosphorylated N-methyl-D-aspartate (NMDA) receptor 1, phosphorylated CaM kinase II, phosphorylated cyclic AMP-responsive element-binding protein in the cerebral cortices of P8-2VO and -sham were significantly reduced compared to the levels in the cerebral cortices of R1 and young P8. KK significantly normalized the expression levels of these proteins. These findings suggest that KK-induced improvement of learning and memory deficit in P8-2VO and -sham is mediated by normalization of impaired NMDA receptor function in the brain.



### Chronic Treatment with a Selective Opioid-delta Agonist SNC80 Affects the Expression of Excitatory Amino-acid Transporter Genes in Frontal Cortex of Olfactory Bulbectomized Rat

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The olfactory bulbectomized (OBX) rat is considered to be one of the important animal models for depression in terms of face/predictive validity. Previously, we reported that OBX-induced behavioral abnormalities were completely rescued by 7-day subchronic treatment with SNC80, a selective opioid- $\delta$  agonist, as well as with imipramine, a classical monoaminergic antidepressants. In addition, we suggested that these drugs commonly induced changes in expression of several genes that regulate glutamate levels in OBX rat frontal cortex (FCX) using a GeneChip rat Genome oligonucleotide array. The present study examined whether SNC80 or imipramine influence the expression of excitatory amino-acid transporter (EAAT) genes in FCX of OBX rat. Total RNA was extracted from FCX of OBX rat after emotional response measurements. Real-time quantitative PCR was performed to quantify EAAT1/EAAT2 mRNA expression using an ABI PRISM 7000 instrument. There was no significant difference in EAAT1 mRNA expression levels between sham and OBX rat. SNC80 treatment increased EAAT1 mRNA expression in OBX rat. On the other hand, EAAT2 mRNA expression in OBX rat was significantly less than that of sham rat. Interestingly, SNC80 and imipramine commonly and significantly increased in expression of EAAT2 mRNA in OBX rat. Our results suggest that chronic treatment with SNC80 and imipramine increase the expression of EAAT genes in OBX rat. Also it is suggested that opioid- $\delta$  agonist induced antidepressant-like effects in OBX rat may be mediated by mechanism that regulate synaptic glutamate levels in FCX.

### Effects of Quetiapine on Radial Maze Learning Deficits in Rats Neonatally Treated with MK-801

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Neonatal antagonism of N-methyl-D-aspartate (NMDA) receptors, a subtype of glutamate receptors, by repeated MK-801 (dizocilpine) treatment is known to produce learning and/or performance deficits in several kinds of working memory tasks such as radial maze and delayed nonmatching-to-position. Thus chronic neonatal NMDA receptor antagonism has been suggested as an animal model of schizophrenia. In this study we investigated if quetiapine, an atypical antipsychotic agent, alleviated radial maze learning deficits induced by neonatal MK-801 treatment. Wistar-Imamichi rats were injected with MK-801 (0.4 mg/kg s.c.) or saline twice daily on postnatal days 7-20. From the age of 7-8 weeks they were trained in an eight-arm radial maze to run down the maze for food reward efficiently without revisiting the same arms one trial a day, until they reached a criterion of 7-8 correct choices out of the first 8 choices in five consecutive trials. Rats were administered with quetiapine 5-10 mg/kg (i.p.) or vehicle 15 min before the trial every day. Number of trials to criterion, number of errors in each trial and running time per choice were compared among groups (neonatal treatment x pretrial drug treatment in adulthood). Results are discussed in terms of the predictive validity of neonatal MK-801 treatment as an animal model of schizophrenia.

### Antidepressant-like Effects of Glucagon-like Peptide-2 in Forced Swimming Test of Mice

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In this study, we investigated whether glucagon-like peptide-2 (GLP-2) had antidepressant-like effects in mice, and whether these activities were associated with monoamine systems. Antidepressant-like effects were evaluated based on the immobility time in the forced-swim test. GLP-2 (1.5-6  $\mu$ g/mouse, i.c.v.) significantly reduced the immobility time in a dose-dependent manner without affecting locomotor activity in the wheel running test and memory function in the step-down passive avoidance test. These effects were inhibited by pretreatment with metergoline (an antagonist of non-specific 5-HT receptors), parachlorophenylalanine (an inhibitor of 5-HT synthase), NAN-190 (an antagonist of 5-HT<sub>1A</sub> receptors), yohimbine (an antagonist of  $\alpha_2$  adrenoceptors), atenolol (an antagonist of  $\beta_1$  receptors), and raclopride (an antagonist of D<sub>2</sub> receptors), but not by prazosin (an antagonist of  $\alpha_1$  adrenoceptors), ICI118551 (an antagonist of  $\beta_2$  adrenoceptors), and SCH23394 (an antagonist of D<sub>1</sub> receptors). These results suggest that GLP-2 exerts antidepressant-like effects in the forced-swim test in mice that are associated with 5-HT<sub>1A</sub>,  $\alpha_2$ ,  $\beta_1$ , and D<sub>2</sub> receptors.

### Development of Tolerance to Nicotine-induced Corticosterone Increase and Antinociception in Mice

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It is well known that nicotine produces serum corticosterone (SCS) increase and antinociception in rodents. Moreover, endogenous opioid system is involved in nicotine-induced antinociception, but not SCS increase. In this study, we investigated the development of tolerance to nicotine-induced SCS increase and antinociception in ICR mice. SCS level was quantified by fluorometrical assay. Antinociceptive effect was evaluated by tail-pinch test. For the development of tolerance, morphine (40 mg/kg, s.c.) or nicotine (5 mg/kg, s.c.) was administered twice a day for 4 or 5 days, respectively. SCS was increased by nicotine (0.3 - 5 mg/kg, 30 min after injection), dose-dependently. Nicotine (5 mg/kg, s.c.)-induced SCS increase was antagonized by mecamylamine (nicotinic ACh receptor antagonist; MEC; 1 mg/kg, s.c.), but not by naloxone (opioid receptor antagonist; NLX; 1 mg/kg, s.c.), whereas nicotine-induced antinociception was antagonized by both MEC and NLX. In chronic morphine-treated mice, not only morphine but also nicotine-induced antinociception were attenuated, suggesting the development of cross-tolerance. However, in chronic nicotine treated mice, nicotine-induced SCS increase and antinociception were attenuated, while morphine-induced SCS increase and antinociception were not affected by chronic nicotine. These results suggest that 1) the reduced sensitivity of nicotinic ACh receptor may involve in the development of nicotine tolerance and 2) the endogenous opioid system does not clearly participate in the development of tolerance to nicotine-induced antinociception.

### Inhibition of Morphine Tolerance Under the Several Pain Conditions in Mice

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Although morphine is widely used as a useful analgesic, long-term treatment often causes analgesic tolerance. Growing evidence suggests that morphine tolerance is prevented under the pain condition. In this study, we investigated the modulations of morphine tolerance under the several pain conditions, using ICR mice. To induce inflammatory pain, 1% carrageenan, which was dissolved in PBS, was injected into the intraplantar surface of both hind paws. To produce neuropathic pain, sciatic nerves of both hind limbs were exposed under pentobarbital anesthesia and 1/3 of the nerves were ligated with a silk suture. Morphine (10 mg/kg) was subcutaneously injected once a day for 5 days, and analgesic effect of morphine during 2 h after morphine injection was evaluated by tail-pinch test on days 1, 3, and 5. In all pain model and control mice, morphine (10 mg/kg, s.c.) showed significant analgesic effects, which almost disappeared within 2 h, and the magnitude of morphine analgesia in all group were similar degree. The magnitude of morphine analgesia was significantly attenuated on days 3 and 5 in control mice, indicating the development of morphine tolerance. In carrageenan-treated mice, magnitude of morphine analgesia was significantly greater than that in PBS-treated mice on days 3 and 5. On the other hand, in nerve-injured mice, magnitude of morphine analgesia was significantly greater than that in sham-operated mice on day 5. These results suggest that not only inflammatory pain but also neuropathic pain inhibits the development of tolerance to morphine analgesia.

### Depression of Synaptic Vesicular Release and Functional Impairment Induced by Glial Overexpression of APP

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Amyloid precursor protein (APP) is a critical protein in Alzheimer's disease (AD) as APP processing produces amyloid $\beta$ (A $\beta$ ), a pathological hallmark of AD. Recent study revealed that overexpression of APP in hippocampal neurons elicited a depression of the excitatory synaptic transmission resulting from production of neural A $\beta$ . Although APP is abundant in neurons, it is not clear whether functional APP is distributed in astrocytes. We found that APP is expressed in cultured cortical astrocytes, which consequently secreted A $\beta$ . Using autaptic cultures of normal hippocampal neurons on a micro island of cortical astrocytes cultured from Tg2576 mouse, a model of AD, astroglial overexpression of APP leads to depression of synaptic vesicular release and functional impairment. Our findings suggest that A $\beta$  derived from astroglial APP plays severe role for the synaptic dysfunctions in AD pathological pathway.

### Activation of Microglia and Migration of Brain Pericytes are Involved in Disruption of the Blood-brain Barrier Caused by Lipopolysaccharide

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Pathogenesis of the neuroinflammatory disease are known to be associated with neuroinflammation and blood-brain barrier (BBB) disruption. The BBB is primarily formed by brain microvascular endothelial cells. This endothelial functions are regulated by pericytes, astrocytes, microglia and neurons. The present study aimed to evaluate the role of pericytes and microglia in the mediation of BBB disruption using a lipopolysaccharide (LPS)-induced model of septic encephalopathy. Mice were injected intraperitoneally with LPS. Sodium fluorescein (Na-F) accumulated in the hippocampus after LPS injection; this hyperpermeability was supported by detecting the extravasation of fibrinogen. Microglia were activated and the number of microglia increased after LPS injection. LPS-treated mice exhibited a broken basal lamina and pericyte detachment from the basal lamina after LPS injection. To test whether activation of microglia is linked to BBB dysfunction, we evaluated the effects of LPS on BBB functions in an in vitro co-culture system with rat brain microvascular endothelial cells (RBEC) and microglia. In the presence of LPS-activated microglia, permeability to Na-F was increased in RBEC. LPS-increased Na-F permeability was blocked by the NADPH oxidase inhibitor. In conclusion, microglial activation and pericyte detachment from the basal lamina appear to contribute to BBB impairment due to inflammatory responses. The production of reactive oxygen species through NADPH oxidase in activated microglia may be involved in the process of this inflammatory BBB dysfunction.

### Effects of Psychotropic Drugs and a Pericentrin Mutation on Neuronal Primary Cilia

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Almost all vertebrate cells have an immotile primary cilium that singly extends like an antenna into the environment surrounding the cell and transduces sensory stimuli to the cell body. In the rodent brain, each neuron has a solitary primary cilium for nearly all regions, although the biological roles played by the neuronal primary cilia remain unclear. In the mouse brain, adenylyl cyclase 3 and certain subtypes of somatostatin and melanin-concentrating hormone (MCH) receptors have been found to be localized in primary cilia of neuronal cells, and it might then be possible that a G protein/cAMP signaling cascade in neuronal primary cilia transduces the extracellular neuropeptide stimuli to the neuronal cell body. The MCH system is thought to play an important role in the regulation of feeding and emotional processing, and to negatively modulate dopaminergic function. In this study, a possible involvement of signaling via neuronal primary cilia in psychiatric diseases was explored by characterizing the effects of psychotropic drugs and a hypomorphic mutation of the pericentrin gene on neuronal primary cilia in the mouse brain. Administration of some psychotropic drugs to mice altered the architecture of the neuronal cilia in several brain regions. The pericentrin mutant mice displayed a shortened time of immobility in the forced swimming test and the tail suspension test as well as disturbed localization of cilia-related components. These results suggest that cilia-dependent signaling may be involved in neurobiological mechanisms underlying psychiatric diseases.

### Neuroprotection of Parkinsonian Dopaminergic Dysfunction by DJ-1-binding Modulator

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DJ-1 was recently identified as the causative gene of familial Parkinson's disease, PARK7. DJ-1 protein has three cysteine residues at amino acid numbers 46, 53, and 106. Among these three cysteine residues, cysteine 106 (C106) is considered to be the most sensitive to oxidative stress and excess oxidation leads to loss-of-function. We performed virtual screening (in silico) for compounds which bind to the region at C106 from a compound library (about 30,000 chemicals), and then we identified some DJ-1-binding modulators. Among them, compound B has a structure with the highest docking score to the C106 region of oxidized SO<sub>2</sub>H form of DJ-1 protein. This DJ-1-binding compound prevented oxidative stress-induced death of SH-SY5Y cells and primary cultured dopaminergic neurons of the rat ventral mesencephalon, but not in DJ-1-knockdown SH-SY5Y cells, indicating that this compound specifically affects to endogenous DJ-1. In addition, this compound prevented dopaminergic neuronal death in the substantia nigra and restored movement abnormality in 6-hydroxydopamine-injected hemiparkinsonian rats. These results suggest that DJ-1-binding modulator interacts with endogenous DJ-1 and then induces neuroprotective episodes, possibly mediated by anti-oxidative and/or anti-apoptotic pathway(s). Thus, these findings suggest that DJ-1-binding modulators may also be useful for treating oxidative-stress-mediated neurodegenerative disorders, including Parkinson's disease.

### Expression of Runt Related Factor-2 by Astrocytes

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We have previously shown the expression of mRNA and corresponding protein for the master regulator of osteoblast differentiation runt related factor-2 (Runx2) in cultured rat astrocytes and C6 glioma cells. Cultured astrocytes were transiently transfected with expression vector of Runx2 for microarray analysis. Marked upregulation was seen for Runx2 and several target genes, whereas downregulation was found for particular astrocyte- and reactive astrocyte-related genes. In C6 glioma cells stably overexpressing the dominant negative Runx2, a significant decrease was found in luciferase activity for the wild type reporter containing 6 tandem copies of Runx2 binding element linked to the luciferase reporter plasmid. These results suggest that Runx2 may be functionally expressed by astrocytes in terms of transcriptional regulation of particular astrocyte-related genes.

### Myosin VI Expressed by Neural Progenitors

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We have found that mRNA for Myosin VI (Myo6) is selectively expressed in the murine hippocampus within 24 h in response to a traumatic stress experience prior to a drastic but transient decrease in proliferation of progenitors in the dentate gyrus. Western blotting analysis clearly revealed a significant increase in the expression of Myo6 protein in the murine hippocampus within 24 h after the flashback experience by forced swimming in mice previously exposed to traumatic stress 9 days ago. Transient overexpression of Myo6 led to a significant decrease in the size of clustered aggregates without affecting cell viability in mouse embryonal carcinoma P19 cells cultured with retinoic acid. These results suggest that Myo6 may play a pivotal role in the mechanism underlying the suppression of neurogenesis relevant to hippocampal atrophy seen in patients with posttraumatic stress disorder.

### Involvement of Mineralocorticoid Receptor on Trimethyltin-induced Neuronal Cell Damage in the Dentate Gyrus of Mouse Brain

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The systemic administration of trimethyltin (TMT) is known to induce granule cell death in the dentate gyrus of mice. We have previously shown that the neuronal damage induced by TMT at the dose of 2.0 mg/kg was enhanced by adrenalectomy (ADX), with glucocorticoid receptor (GR) agonist dexamethasone being capable of abolishing enhancement by ADX. However, little has been known about the role of mineralocorticoid receptor (MR) in the TMT-induced neuronal death. In this study, we examined the effects of MR agonist and antagonist on TMT-induced damage in the dentate granule neurons. Male mice at age of 4-5 weeks were anesthetized and then the dorsal skin was cut and fascia opened to reveal the kidney. The adrenal gland were removed and sutured. ADX and sham-operated animals were given TMT on day 7 after surgery. TMT-induced neuronal damage was assessed by the immunohistochemical analysis of single-stranded DNA. ADX and sham-operated animals were given MR agonist aldosterone (0.1 mg/kg, s.c.) every 12 h for 2 day (4 time) after TMT injection. Aldosterone exacerbated neuronal damage induced by TMT in the dentate gyrus of both ADX and sham-operated animals. GR antagonist mifepristone had the ability to enhance TMT-induced neuronal damage, whereas MR antagonist spironolactone was effective in protecting against the neuronal damage. These results suggest that the activation of MR promotes TMT-induced neuronal damage in the dentate gyrus.

### Altered Expression of Genes Involved in DNA Methylation and Chromatin Modification in Rodent Frontal Cortex after Chronic Treatment with Antipsychotic Drugs

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Valproic acid is an anticonvulsant and a mood stabilizer for the treatment of mania. It was shown to be an inhibitor of histone deacetylase, suggesting that epigenetic process is involved in its pharmacological mechanism of action. All the antipsychotic drugs have indications for the treatment of manic symptoms, thus it is interesting to know whether epigenetics is involved in the mechanism of action of antipsychotic drugs. To address this issue, we measured the mRNA level of several genes responsible for DNA methylation and chromatin modification, including DNA (cytosine-5-)-methyltransferase 1 (Dnmt1), DNA methyltransferase 3A, transcript variant 1 (Dnmt3a), DNA methyltransferase 3B (Dnmt3b), methyl CpG binding protein 2 (Mecp2), histone deacetylase 1 (Hdac1) and histone deacetylase 2 (Hdac2) in rodent frontal cortex after four weeks' treatment of several antipsychotic drugs, such as risperidone, olanzapine, haloperidol, clozapine and aripiprazole, respectively. Using real-time quantitative PCR, we found that the mRNA level of Dnmt1 was significantly suppressed by olanzapine (2 mg/kg) compared to vehicle, while the mRNA level of Dnmt3b was significantly reduced by risperidone (1 mg/kg) at rat frontal cortex as compared to vehicle. The expression of Hdac1 was significantly decreased by haloperidol and olanzapine as compared to vehicle, while the expression of Hdac2 was increased significantly by clozapine (20 mg/kg) at rat frontal cortex as compared to controls. Using western blotting, we found that Hdac1 protein was significantly down-regulated in frontal cortex of mice treated with olanzapine (2 mg/kg) treated mice compared to control groups. Our preliminary results support the hypothesis that long-term administration of certain antipsychotic drugs may affect the epigenetic programming on regulating gene expression in the brain, and further elucidation of such mechanism may bring new insight into the therapeutic efficacy of antipsychotic drugs.

### Expression of Runt Related Factor-2 in Mouse Brain

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Runt related factor-2 (Runx2) is the master regulator of osteoblast differentiation. In this study, we investigated the possible expression of Runx2 in the murine brain. Adult male mice were anesthetized and perfused with 4% paraformaldehyde for in situ hybridization using a DIG-labeled cRNA probe. In sagittal sections, Runx2 mRNA was highly expressed in the hippocampal pyramidal cell layer, hippocampal dentate granular cell layer and cerebellar granular cell layer, respectively. Although distribution of mRNA for NSE, one of the neuronal markers, was similarly seen with that of mRNA for Runx2 in hippocampal sections, distribution of mRNA for the astroglia marker GFAP was different from that of mRNA for Runx2. These results suggest that Runx2, a master regulator of osteoblast differentiation, is preferentially expressed in particular neuronal cells rather than astroglial cells in the murine brain.

### Expression of Irf1 by Neural Progenitors in Adult Mouse Hippocampus

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We have previously identified the gene differentially expressed in neural progenitors between adult and embryonic mouse hippocampi as interferon-related developmental regulator-1 (Irf1). In this study, we attempted to evaluate the functionality of Irf1. In neural progenitors of adult mouse hippocampus, more than 7-fold higher expression was seen for Irf1 mRNA than in embryonic mouse hippocampus. We next used the mouse embryonic carcinoma P19 cells endowed to differentiate into neuronal and astroglial cells. In P19 cells with transient overexpression of Irf1, a significant decrease was seen in MAP2 mRNA expression and numbers of MAP2-expressing cells. These results suggest that spontaneous cellular differentiation would undergo into astroglia rather than neurons through a mechanism relevant to constitutive expression of Irf1 in hippocampal neural progenitors during adult neurogenesis.

### Involvement of 5'-AMP-activated Protein Kinase in Proliferation and Survival of Neural Progenitor Cell

○Shohei Sano, Nobuyuki Kuramoto, Masanori Yoneyama, Reiko Nagashima, Koichi Kawada, Kiyokazu Ogita  
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Neural stem/progenitor cells (NPCs), which are defined by their ability to self-renew and differentiate into the three major cell types, neurons, astrocytes, and oligodendrocytes, play a key role in the development and maturation of the central nervous system. 5'-AMP-activated protein kinase (AMPK) acts as an efficient sensor for cellular energy state. To elucidate roles of AMPK in proliferation of NPCs, in this study, we evaluated the effect of an activator and inhibitor for AMPK on proliferative activity in NPCs derived from the neocortex of embryonic mice. Neurospheres were prepared from the neocortex of 15-days-old embryonic mice by primary culturing in DMEM/F12 medium with EGF and bFGF for 9 days in vitro (DIV). After replating, the cells were further cultured for 6 DIV under the same condition in the absence or presence of metformin (AMPK activator) and compound C (AMPK inhibitor). Immunoblot analysis revealed that the level of phospho-AMPK (p-AMPK), but not AMPK, was progressively increased in a culture time-dependent manner. Treatment with metformin produced enhancement of the proliferative activity and survival of neurospheres during culture, as well as an increase in the level of p-AMPK. In contrast, treatments with compound C produced a decrease in the proliferative activity and survival of neurospheres during culture. In addition, compound C was the ability to facilitate cell damage. These results suggest that AMPK is involved in the proliferation and survival in NPCs of embryonic mouse neocortex.

### Excitatory Signals Induce Phosphorylation of Inhibitory GABA<sub>B</sub> Receptor Subunit

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GABA<sub>B</sub> receptors mediate slow and prolonged synaptic inhibition in the brain, and are members of the G protein-coupled receptor (GPCR) superfamily. To date 2 GABA<sub>B</sub> receptor subunits have been identified, GABA<sub>B</sub>R1 and GABA<sub>B</sub>R2 (R2), and unlike other members of the GPCR superfamily, functional GABA<sub>B</sub> receptors are heterodimers formed between these 2 proteins. We have studied metabolic sensor 5'-AMP activated protein kinase (AMPK) association to GABA<sub>B</sub> receptors intracellular domains and phosphorylate at serine 783 (S783) of R2. While AMPK phosphorylates both R1 and R2 subunits, R2 phosphorylation by AMPK might extend GABA<sub>B</sub> heterodimers functions. Although it is classically believed that AMPK is activated by intracellular 5'-AMP accumulated via ATP consumption, it has been appeared that calmodulin kinase kinase (CaMKK) activates AMPK directly. In this presentation, we, thus, investigated whether GABA<sub>B</sub> R2 phosphorylation by AMPK is regulated by intracellular calcium levels via opening of NMDA receptors. In cortical neurons, AMPK was phosphorylated at threonine 172 by exposing to NMDA for 15 minutes. The phosphorylation at S783 on GABA<sub>B</sub> receptor R2 subunit (p783) was also increased. The p783 increase was blocked by competitive antagonist AP5 or uncompetitive antagonist MK-801. These data, therefore, suggests that facilitation of excitatory transmission and/or increase of intracellular calcium level modulate GABA<sub>B</sub> receptors functions.

### Protection of Neurons by Astroglial Glutamine Transporter from Glutamate Excitotoxicity

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We have shown the functional expression of glutamine transporter (GlnT) by astroglia prepared from rat brains. In this study, we attempted to evaluate the possible role of astroglial GlnT in glutamate neurotoxicity. Cultured rat hippocampal neurons were exposed to glutamate for 1 h, followed by further culture in the presence of conditioned medium from C6 glioma cells overexpressing GlnT for 24 h. Exposure to glutamate led to a significant decrease in MTT reduction in hippocampal neurons, while the decreased viability was significantly prevented by conditioned medium from stable GlnT transfectants. In these stable transfectants, a significant increase was seen in mRNA expression of particular neurotrophic factors such as neurotrophin-4/5. These results suggest that GlnT may be a determinant of the vulnerability to glutamate neurotoxicity through promotion of particular neurotrophic factor expression in astrocytes.

### NMDA Receptor Channels Artificially Expressed in HEK293 Cells

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Glutamate toxicity is mediated by massive influx of Ca<sup>2+</sup> across NMDAR channels in neurons. In the present study, we evaluated properties of acquired NMDAR channels artificially orchestrated in HEK293 cells. Cells were transfected with either an NR2A or NR2B expression vector, together with the expression vectors of GFP and NR1 subunit. Exposure to 0.1 mM NMDA similarly decreased the number of fluorescent cells with GFP expression in a manner sensitive to blockade by the NMDAR antagonist MK-801 in HEK293 cells with acquired expression of NMDAR composed of NR1/NR2A and NR1/NR2B subunits, where NMDA was also effective in significantly increasing intracellular and mitochondrial free Ca<sup>2+</sup> levels determined by Fluo-3 and Rhod-2, respectively. These results suggest that acquired channels are quite useful for elucidation of the mechanisms underlying Ca<sup>2+</sup> influx across membrane NMDAR channels.

### Studies on Pain Control System (Rept. 111): Functional Change in Sensory Neurons Under Caerulein-induced Acute Pancreatitis Pain in Mice

○Kazuhiko Miyashita, Minoru Narita, Sadayoshi Furuta, Shigeto Hirayama, Satoshi Imai, Michiko Narita, Naoko Kuzumaki, Tsutomu Suzuki

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Pain management in acute pancreatitis represents a major clinical challenge and influences the clinical outcome of the disease. The aim of the present study was to investigate the peripheral and central mechanisms of the acute pancreatitis pain-like state in mice. After repeated injection of caerulein, a cholecystokinin analogue, mice showed pancreatic tissue damage characterized by edema, acinar cell necrosis and increased blood concentrations of pancreatic enzymes compared to those observed in saline-injected mice. Under this condition, repeated treatment with caerulein caused the hypersensitivity to tactile stimuli at the upper abdominal region in mice. The whole-cell patch clamp analysis revealed that action potential firing rate in dorsal root ganglion (DRG) neurons of mice was increased following repeated treatment with caerulein. Furthermore, we evaluated possible contribution of transient receptor potential vanilloid 1 (TRPV1) to a pain-like state in caerulein-treated mice. Interestingly, a selective TRPV1 antagonist N-(4-t-Butylphenyl)-4-(3-chloropyridin-2-yl) tetrahydropyrazine-1(2H)-carboxamide (BCTC) attenuated hypersensitivity to tactile stimuli and increased excitation of DRG neurons in mice following repeated treatment with caerulein. These results suggest that the model made by caerulein-treated is useful for better understanding the molecular mechanisms underlying acute pancreatitis-induced hyperalgesia. Furthermore, the activation of TRPV1 in the mouse DRG may contribute to the development of a pain-like state in mice with acute pancreatitis.

## The Effects of Atypical Antipsychotic Drugs on Regulation of Cell Cycle Against MPP<sup>+</sup>-Induced Apoptosis in PC12 Cells

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**Purpose:** Growing evidence showed that atypical antipsychotics trigger neurogenesis in the adult rat brain. To confirm these findings, we examined the effect of atypical antipsychotic drugs on cell proliferation and G1/S-phase cell cycle regulators, cyclinD1, pRetinoblastoma (pRb), and p27 against N-methyl-4-phenylpyridinium ion (MPP<sup>+</sup>) cytotoxicity in PC12 cells. **Methods:** PC12 cells were cultured with atypical antipsychotics (olanzapine, ziprasidone and clozapine) in medium with or without MPP<sup>+</sup> for 72 hr. Haloperidol, typical antipsychotics, was used for comparison. Cell proliferation was investigated using bromodeoxyuridine (BrdU), a thymidine analog. The changes in the levels of cyclinD1, pRb, and p27 expression were measured by Western blot analysis. **Results:** MPP<sup>+</sup> (1mM) reduced cell proliferation to about 70% (p<0.01). Olanzapine (10-100μM) significantly increased cell proliferation under MPP<sup>+</sup>-free conditions (35-45%, p<0.01). On the other hand, ziprasidone (0.1-10μM) effectively increased the MPP<sup>+</sup>-induced decreases in cell proliferation (20%, p<0.01). However, clozapine (10-100μM) and haloperidol (10-100μM) produced a dose-dependent reduction in BrdU incorporation in PC12 cells with or without MPP<sup>+</sup> treatment. Olanzapine significantly increased the levels of cyclinD1 under MPP<sup>+</sup>-free conditions, but did not affect the MPP<sup>+</sup>-induced reduction in cyclinD1 expression. Moreover, olanzapine (100μM) increased the levels of pRb expression in dose-dependent manner in media with or without MPP<sup>+</sup> (45-50%, p<0.01), and alleviated the levels of p27 expression in both conditions (30-40%, p<0.01). Ziprasidone prevented the MPP<sup>+</sup>-induced decrease in cyclinD1 and pRb levels in a dose dependent manner (30-80%, p<0.01) and ameliorated the levels of p27 expression in media with (30%, P<0.01) or without MPP<sup>+</sup> (20%, p<0.05). **Conclusions:** Olanzapine and ziprasidone, but not clozapine and haloperidol have mitogenic effects against MPP<sup>+</sup>-induced apoptosis in PC12 cells. These results might suggest that olanzapine and ziprasidone may play an important role in the regulation of cell cycle progression for neurogenesis. **Key words:** antipsychotic drugs, PC12 cell, MPP<sup>+</sup>, cell proliferation, cyclinD1, pRb, p27

## Activation of NMDA Receptor Regulates Proliferative Activity of Neural Progenitor Cells in Hippocampal Dentate Gyrus after Neuronal Cell Damage

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We evaluated the effects of the NMDA receptor antagonists on neural progenitor cells in the hippocampal dentate gyrus after the damage induced by trimethyltin chloride (TMT). TMT-treated mice were given either MK-801, SM31900 or ifenprodil with 5-bromo-2'-deoxyuridine (BrdU) every 12 h for 2 days from day 2 to day 4, and then decapitated to determine BrdU-positive cells in the hippocampus at 12 h after the final injection of drugs. Hippocampi were isolated from mice day 3 after injection of TMT and then cell suspensions were maintained in DMEM/F-12 supplemented with epidermal growth factor (EGF) and basic fibroblast growth factor (bFGF). TMT led to neuronal loss in the granule cells of the hippocampus on day 2 post-treatment, followed by a marked increase in BrdU-positive cells in the dentate gyrus on day 3 to 4 post-treatment. TMT-induced increase in BrdU-positive cells was significantly prevented in the subgranular zone by NMDA antagonists such as MK-801, ifenprodil, and SM31900. Cells were prepared from dentate gyrus of mouse sacrificed on day 3 after TMT injection and subsequently cultured in DMEM/F-12 medium containing EGF/bFGF resulted in the formation of round spheres immunoreactive to nestin at 30 days in vitro. The number of neurosphere was significantly increased compared with that derived from naive animals. Additionally, MK-801 and SM31900 markedly decreased the number of neurospheres. Our results suggest that NMDA receptors positively regulate proliferative activity of neural progenitor cells in the hippocampal dentate gyrus after neuronal damage.

## Possible Regulation of Synaptic Activity-dependent Phosphorylation of GABA<sub>B</sub>R2 Subunit

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GABA<sub>B</sub> receptors mediate slow and prolonged synaptic inhibition in the brain, and are members of the G protein-coupled receptor (GPCR) superfamily. To date 2 GABA<sub>B</sub> receptor subunits have been identified as GABA<sub>B</sub>R1 and GABA<sub>B</sub>R2 (R2), and unlike other members of the GPCR superfamily, functional GABA<sub>B</sub> receptors are heterodimers formed between these 2 proteins. Among the 2 subunits, R2 is highly phosphorylated at serine 892 by protein kinase A. Similar to the other proteins, phosphorylated and dephosphorylated states of R2 are crucially regulated and are probably important for stabilities, localizations, and functions of GABA<sub>B</sub> receptors. Therefore, we examined the basal phosphorylation of R2 in the mouse brain and explored possible mechanisms to dephosphorylate the R2. While R2 and phosphorylated R2 (p892) were strongly detected in cerebral cortex, hippocampus, and cerebellum, relative phosphorylation of p892 against total R2 was constant among the brain regions. In cultured cortical neuron, the phosphorylation was increased by treatment with forskolin or okadaic acid, but not with cyclosporine A, sodium fluoride nor orthovanadate. In vitro dephosphorylation analysis revealed that p892 dephosphorylated by PP1α or PP2A, but not PP2B nor PP2C. Moreover, p892 decreased by tetrodotoxin treatment in cultured neurons and acute hippocampal slices. These data suggest that GABA<sub>B</sub> receptors function is regulated by 2 phosphatases including PP1α and PP2A.

## Effects of Nitric Oxide on the Proliferation of Neural Stem/progenitor Cells in Embryonic Hippocampus

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It is widely known that nitric oxide (NO) inhibits cell proliferation and induces cell death in neural stem/progenitor cells (NPCs) derived from adult mice. In this study, we evaluated the effects of NO on proliferative activity in the NPCs of the hippocampus in embryonic mice. Neurosphere was prepared from the hippocampus of 15-days-old embryonic mice by primary culturing in DMEM/F12 medium with EGF and bFGF for 9 days in vitro (DIV). After replating, the cells were cultured for 4 DIV under the same conditions in the absence or presence of N-nitro-L-arginine methyl ester (L-NAME, NO synthase inhibitor), 1H-[1,2,4]oxadiazolo [4,3-a]quinoxalin-1-one (ODQ, soluble guanylyl cyclase inhibitor), 8-bromocyclic GMP (8-Br-cGMP, cGMP analogue), 3-morpholininosydnonimine (SIN-1, peroxyxynitrite generator) or KT5823 (protein kinase G inhibitor) for a period of 9-13 DIV. Treatment with L-NAME significantly led to a decrease in NO<sub>2</sub> level in the culture medium and intracellular cGMP level after 24-h treatment. ELISA of 5-bromo-2-deoxyuridine (BrdU) revealed that a marked decrease in the proliferative activity was seen by L-NAME, ODQ, and KT5823. Moreover, treatment with SIN-1 led to an increase in the proliferative activity. 8-Br-cGMP partially abolished the decrease in BrdU incorporation induced by L-NAME. In addition, L-NAME and ODQ prevented the phosphorylation of Akt, without affecting that of EGF receptor and ERK. These results suggest that endogenous NO-cGMP pathway is essential for proliferative activity through the activation of Akt in NPCs of embryonic mouse hippocampus.

**Transferrin Receptors Expressed in Brain**

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Iron is shown to be accumulated in particular brain regions in patients suffering from neurodegenerative diseases such as Parkinson's disease. In this study, we evaluated expression profiles of different genes related to iron mobilization in neurons. Marked mRNA expression was seen for ferritin, transferrin and transferrin receptor-1 (TfR1) in mouse neocortical neurons. In neuronal Neuro2A cells, neurite outgrowth was seen together with increased expression of both mRNA and corresponding protein for TfR1. In mouse embryonal carcinoma P19 cells, exposure to RA led to neurite outgrowth toward neuronal differentiation along with a significant increase in TfR1 mRNA expression. However, TfR1 mRNA expression was significantly decreased in response to subsequent differentiation into an astroglial lineage in P19 cells. These results suggest that TfR1 would be highly expressed in neurons rather than astroglia in the brain.

**GABA<sub>B</sub>R Signaling in Neural Progenitors**

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We have previously shown the modulation by signals mediated by ionotropic GABA<sub>A</sub> receptors (GABA<sub>A</sub>R) of cellular proliferation and differentiation in neural progenitors prepared from embryonic mouse brains. In neural progenitors, mRNA expression was found for metabotropic GABA<sub>B</sub>R1 and GABA<sub>B</sub>R2 subunits. A significant increase was induced in the neurosphere size and MTT reduction in cells exposed to the GABA<sub>B</sub>R agonist baclofen. On spontaneous differentiation, prior exposure to baclofen led a significant increase in the number of cells immunoreactive to MAP2 with a decrease in that to GFAP. In cells prepared from mice defective of GABA<sub>B</sub>R1 subunit, a significant increase was seen in the number of cells immunoreactive to GFAP with a decrease in that to MAP2. These results suggest that GABA<sub>B</sub>R signals may promote proliferation for self-replication and differentiation into a neuronal lineage in undifferentiated neural progenitors.

**Clozapine Inhibits Strychnine-sensitive Glycine Receptors in Rat Hippocampal Neurons**

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Clozapine (Clo) is a widely used antipsychotic for the treatment of schizophrenia, especially for the treatment-resistant schizophrenia. However, severe side effects of it should be noted, especially seizure. Until now, the mechanism of seizure associated with Clo therapy is not completely clear. Strychnine-sensitive glycine receptors (GlyRs) play an important role in regulating the excitability in the hippocampus. In the present study, we investigated the effect of Clo on GlyRs in cultured hippocampal neurons of rats. Clo reversibly inhibited the glycine-induced chloride currents ( $I_{Cl_{gly}}$ ) in a concentration-dependent manner. And it should be noted that Clo binding ahead of channel open is necessary to its inhibition of GlyR. The half-maximal effect concentration ( $EC_{50}$ ) for glycine alone was  $25.6 \pm 0.7 \mu\text{M}$  with the Hill coefficient  $1.5 \pm 0.1$ ; in the presence of Clo, the  $EC_{50}$  and the Hill coefficient were  $28.9 \pm 6.3 \mu\text{M}$  and  $1.2 \pm 0.3$  respectively, which were not significantly affected by Clo. In addition, the inhibitory effect of Clo on  $I_{Cl_{gly}}$  was voltage-independent, but not influenced by blocking D<sub>1</sub> and D<sub>2</sub> dopamine receptors with haloperidol (Hal). Taken together, these results suggest that Clo is a non-competitive antagonist of GlyR independent of its activation of dopamine receptors, which may contribute to seizure associated with Clo therapy.

**The Role of Nucleoside Transporters on Oxidative Stress Injury in Cultured Astrocytes**○Koh-Ichi Tanaka<sup>1,2,3</sup>, Nobue Kitanaka<sup>2</sup>, Junichi Kitanaka<sup>2</sup>, Tomoaki Sato<sup>3</sup>, Takashige Nishikawa<sup>3</sup>, Motohiko Takemura<sup>2</sup>, Nobuyoshi Nishiyama<sup>1</sup><sup>1</sup>Division of Pharmacology, Department of Pharmacy, School of Pharmacy, Hyogo University of Health Sciences, Kobe, Hyogo, Japan, <sup>2</sup>Department of Pharmacology, Hyogo College of Medicine, Nishinomiya, Hyogo, Japan, <sup>3</sup>Department of Applied Pharmacology, Kagoshima University Graduate School of Medical and Dental Sciences, Kagoshima, Japan

We have found that astrocytes pretreated with *N*<sup>6</sup>, 2'-*O*-dibutyryl adenosine 3',5'-cyclic monophosphate (DBcAMP), a permeable analogue of cAMP, but not astrocytes pretreated without DBcAMP, have the ability to incorporate thymidine specifically in the presence of hydrogen peroxide ( $\text{H}_2\text{O}_2$ ) at an early time.

Thymidine is incorporated via equilibrative and concentrative nucleoside transporters (ENT and CNT).

We studied the role of nucleoside transporters on thymidine incorporation and delayed cell death induced by  $\text{H}_2\text{O}_2$  in cultured astrocytes pretreated with DBcAMP.

We concerned that cultured astrocytes expressed ENT1, ENT2 and CNT2, but not CNT1 by RT-PCR. [<sup>3</sup>H]Thymidine incorporation into cultured astrocytes in the presence and absence of  $\text{H}_2\text{O}_2$  were suppressed by NBMPR, dilazep and dipyridamole, ENT inhibitors, in the concentration dependent manner. And [<sup>3</sup>H]thymidine incorporation into cultured astrocytes in the presence and absence of  $\text{H}_2\text{O}_2$  were suppressed by the removal of extracellular  $\text{Na}^+$ .

$\text{H}_2\text{O}_2$ -induced delayed cell death was promoted by the treatment of ENT inhibitors or the removal of extracellular  $\text{Na}^+$ .

These findings indicate that the decrease of  $\text{H}_2\text{O}_2$ -induced thymidine incorporation via ENT and CNT might be relative to delayed cell death in cultured astrocytes.

### Clock Genes Expressed by Microglial Cells

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In order to evaluate expression profiles of clock genes by different cells other than neurons in the brain, we attempted to demonstrate the possible expression of particular clock genes in microglial cells. In the mouse microglial cell line BV-2 cells, marked expression was found with mRNA for a variety of clock genes on RT-PCR analysis. In primary cultured rat microglia, similarly marked expression was seen with Per1 mRNA. In HEK293 cells transfected with Per1 promoter linked to the luciferase reporter plasmid, co-introduction of both Bmal1 and NPAS2 expression vectors led to a more than 8-fold increase in the luciferase activity. Further transfection with Per1 expression vector significantly prevented the increase by both Bmal1 and NPAS2 in HEK293 cells. These results suggest that clock genes may be functionally expressed by the microglial cell line BV-2 cells and rat microglial culture.

### Implication of Epigenetic Control in the Abnormal Glial Differentiation Induced by the Prenatal and Neonatal Exposure to Environmental Endocrine Disrupters

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Bisphenol-A (BPA), one of the most common environmental endocrine disrupters, has been extensively evaluated for toxicity in a variety of tests in rodents. However, the exact mechanism remains unclear. In the present study, we documented that exposure to BPA decreased the immunoreactivity (IR) for doublecortin and the number of NeuroD-positive cells in the dentate gyrus (DG) of the mouse hippocampus. We also found that prenatal and neonatal exposure to BPA dramatically increased both GFAP-IR and MAG-IR in the hippocampus. It has been widely accepted that epigenetic mechanisms result in the silencing of genes without a change in their coding sequence. Thus, early developmental exposure is considered to involve its modifications. Therefore, we analyzed GFAP DNA methylation status in the mouse whole brain at E14.5 by methylation-specific PCR (MSP). As a result, GFAP DNA methylation status was highly methylated in mice with and without prenatally exposed to BPA. In addition, histone acetylation/deacetylation mechanisms control modifications of chromatin structure that results in the regulation of gene transcription. In this study, prenatal and neonatal exposure to BPA decreased histone deacetylase 5 (HDAC5) function in the hippocampus, which allows for increased histone acetylation and transcription of HDAC5 targeted genes. These findings suggest that prenatal and neonatal exposure to BPA could disrupt the adult neurogenesis associated with the epigenetic abnormalities.