and neurobiology of schizophrenia have not been fully established and validated in this species. MK-801, an NMDA receptor antagonist, is frequently used to recapitulate schizophrenia symptoms in rodent models. We thus aimed to evaluate the effects of a concentration curve of MK-801 on locomotor activity, social interaction, and neurochemical parameters related to oxidative stress in adult zebrafish.
Methods: Wild-type male and female zebrafish (50:50 ratio) were randomly allocated to 4 groups: control; 1 µM MK-801; 5 µM MK-801 or 10 µM MK-801 (n = 12). In the locomotor activity test animals were individually and sequentially placed in (1) a beaker with 200 mL of water for 20 min, (2) test aquarium for 30 min to assess basal locomotor activity, (3) beaker with water or MK-801 at the different concentrations for 20 min, and (4) test aquarium for 60 min. Locomotor and exploratory parameters (total distance traveled and upper zone time) were automatically analyzed using ANY-Maze software. In the social interaction test animals were individually exposed to water or MK-801 for 20 min and then placed for 7 min in a tank flanked by two identical tanks either empty or containing 10 zebrafish serving as social stimuli. Distance traveled was automatically tracked while social interaction time was manually and blindly scored using Boris software; only the last 5 minutes were analyzed. Oxidative damage in the brain was assessed by the levels of thiobarbituric acid reactive substances (TBARS). Data were analyzed by ANOVA followed by Tukey post hoc test.
Results: Exposure to 5 µM MK-801 decreased the total distance traveled in the locomotor activity test. In the social interaction test, exposure to 5 and 10 µM MK-801 significantly increased the total distance traveled while reduced the time of social interaction with the stimulus animals. No differences in TBARS levels were found between the groups.
Discussion: Unlike what is observed in rodents after MK-801 administration, zebrafish did not show hyperlocomotion at the concentrations tested. Other studies point to the context-dependent effect of this drug, as an increase in locomotor activity is only observed when animals are tested in a novel environment. In the social interaction test, on the other hand, animals were tested in a novel context with social stimulus and zebrafish exhibited hyperlocomotion and decreased social interaction, similar to what is observed in rodents. In contrast to chronic animal models and patients with schizophrenia, there were no differences in TBARS levels after acute exposure to MK-801. These preliminary results reinforce that zebrafish is an alternative model organism useful to the study of psychotic disorders. More behavioral and biochemical tests are needed to achieve reproducible tests and models to study multiple schizophrenia domains in zebrafish.

S31. ENHANCEMENT OF SYNAPTIC PLASTICITY BY COMBINATION OF PDE2 AND PDE9 INHIBITION PRESUMABLY VIA PRE- AND POST-SYNAPTIC MECHANISMS

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Background: Evidence from clinical and preclinical studies has led to the hypothesis that impaired glutamatergic transmission and NMDA receptor hypofunction play an important role in cognitive impairment associated with schizophrenia (CIAS). Second messenger pathways depending on cAMP and/or cGMP are key regulators of glutamatergic transmission and NMDA receptor related pathways. Therefore, the specific cyclic nucleotide phosphodiesterases (PDEs) PDE2 and PDE9, expressed in cognition relevant brain regions such as cortex and hippocampus, are putative targets for cognition enhancement in neuropsychiatric disorders (Dorner-Ciossek et al., 2017; Zhang et al., 2017). In fact, it has previously been shown that either PDE2 or PDE9 inhibition increases synaptic plasticity, as determined by hippocampal long-term potentiation (LTP), and improves memory performance in animal cognition tasks. However, the exact sub-cellular localization of PDE2 and PDE9 enzymes in neurons is not fully established. Thus, in the present study, co-localization studies of PDE2 and PDE9 with pre- and post-synaptic markers were performed by double immunofluorescence staining. Moreover, the PDE2 inhibitor PF-05180999 (Helal et al., 2018) was characterized regarding enhancement of hippocampal LTP and further investigated in combination with the PDE9 inhibitor Bay 73–6691 (Wunder et al., 2005) for potential synergistic effects on LTP.
Methods: Brains of adult rats were fixed with formalin and sliced for double immunofluorescence staining of PDE2 or PDE9 enzymes with pre-/post-synaptic markers. Analysis of staining was performed by confocal microscopy. Effects of the PDE2 inhibitor PF-05180999 alone and in combination with the PDE9 inhibitor Bay 73–6691 on synaptic plasticity were evaluated in rat hippocampal slices by using a protein-synthesis independent early LTP paradigm.
Results: Double immunofluorescence analysis revealed co-localization of PDE2 predominantly with pre-synaptic, but not post-synaptic, markers and mainly in glutamatergic neurons. In contrast, PDE9 showed co-localization with post-synaptic markers. Inhibition of PDE2 by PF-05180999 led to a concentration-dependent enhancement of early LTP. Combination of PF-05180999 with a subthreshold concentration of the PDE9 inhibitor Bay 73–6691 caused a transformation from early LTP into protein-synthesis dependent late LTP.
Discussion: Immunofluorescence staining suggests that PDE2 is localized pre-synaptically in glutamatergic neurons. This might indicate an involvement of PDE2 in neurotransmitter release via regulating cGMP/cAMP levels at pre-synaptic terminals, whereas PDE9 is located post-synaptically presumably involved in the NMDA receptor signaling cascade via regulation of cGMP. Corroborating previous findings, PDE2 inhibition improves synaptic plasticity as shown by enhanced LTP. Moreover, for the first time, we could show that the combination of a PDE2 with a PDE9 inhibitor acts synergistically on improvement of synaptic plasticity as demonstrated by the shift from early into late LTP, which is considered to be a crucial mechanism for memory formation.

References

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S32. ARE SELECTIVE ESTROGEN RECEPTOR BETA AGONISTS POTENTIAL THERAPEUTICS FOR SCHIZOPHRENIA?

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Background: Estrogen therapies, such as estradiol, have shown promise as therapeutics for schizophrenia; however, safety and tolerability concerns, including feminization effects in men and cancer and stroke risk in premenopausal women, may limit their broader use. Estradiol binds to both the estrogen alpha (ERA) and beta (ERB) receptors. ERB receptors appear not to mediate many of the concerning side effects of estrogen therapies. In addition, beta receptors have unique localization in cortical regions (i.e., hippocampus), and improve social behaviors and cognition in some animal models, which has led to interests in these compounds for testing in schizophrenia. To our knowledge, there have been no previous clinical trials of selective ERB agonists in schizophrenia. LY500307 is a highly selective agent

for beta receptors without effects on estrogen alpha receptors when doses are constrained. Doses that are too high may engage alpha receptors but the alpha engaging threshold dose has not been fully determined in patient groups. The purpose of this dose-response study was to determine: ERB selectivity doses of LY500307 (i.e., without engaging alpha receptors); safety and tolerability; brain target engagement; and effects on cognition and symptoms.
Methods: A two-staged, double-blind, 8-week, adjunctive to APDs, adaptive phase 1b/2a trial design was conducted in men with schizophrenia (women were not included because of the lack of toxicology, safety, phase 1 and clinical data supporting use in this population). Three LY500307 doses and placebo were evaluated: 25 mg/day, 75 mg/day, and 150 mg/day. The primary markers for estrogen beta receptor selectivity was lack of effects on total testosterone levels (TT) and no feminization signs. Target engagement was assessed with an N-back working memory fMRI task and the electrophysiology measure mismatch negativity (MMN). Cognitive effects were assessed by the MCCB Composite score. Negative and total symptoms were assessed by the NSA-16 and PANSS, respectively. The primary analyses included all subjects and compared the slope from the three LY500307 dosing arms to the placebo slope in order to evaluate the dose responses. The linear mixed model with random intercept was employed and secondary analyses assessed differences between mean changes of the two higher dose arms combined (75 mg and 150 mg) versus placebo.
Results: Ninety-four patients were randomized across the placebo and three LY500307 dosing arms. There were no effects on plasma TT levels and no evidence of feminization, suggesting all doses were selective for the beta receptor. No significant adverse events were observed. There were no significant differences between the slopes of the three drug doses versus placebo on the brain target engagement variables (fMRI/N-back: F=0.24, p=0.868; MMN (Duration): F=1.08, p=0.358; MMN (Frequency): F=0.89, p=0.446) or on the cognitive/symptom measures (MCCB composite: F=0.87, p=0.458; NSA-16: F=1.79, p=0.148; and PANSS Total: F=0.69, p=0.558.) Secondary analyses also failed to show any significant effects of LY500307 versus placebo on any of the study variables.
Discussion: Conclusions: This study indicates that the ERB agonist LY500307 was selective, safe, and well tolerated in patients with schizophrenia. This selective ERB agonist, however, failed to demonstrate any significant effects on brain targets, cognition, negative and total symptoms. Potential issues related to dosing and characteristics of the patient population will be discussed. These data suggest that estrogen alpha receptor activation may be necessary to yield positive results in this patient population. Future studies are needed to confirm these findings.

S33. RELATIVES IN RESOURCE GROUP ASSERTIVE COMMUNITY TREATMENT (RACT): RELATIVES' EXPERIENCES

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Background: Relatives often provide extensive support to their next of kin suffering from psychotic disorders. However, they often experience lack of support from psychiatric services. While cooperation with relatives is a central component in Resource Group Assertive Community Treatment (RACT), little is known about relatives' experiences of RACT. The aim was to investigate relatives' experiences of encountering psychiatric care with and without RACT, in relation to quality of life, family burden and family stigma.
Methods: A total of 139 relatives of individuals suffering from psychotic disorders in the Region Västra Götaland, Sweden filled out the self-report instruments Family Involvement and Alienation Questionnaire – Revised (FIAQ-R), the Burden Inventory for Relatives of Persons with Psychotic Disturbances, the Inventory of Stigmatizing Experiences (family version), and RAND-36.
Results: Participants included 79 relatives with experience of RACT and 60 without. In the total group 70% were women. Mean age was 63 years (SD 12.4). A majority came from Sweden (91%), had >12 years of education (61%) and did not live together with the patient (76%). A majority were parents, (70%). These demographic characteristics did not differ in those with and without RACT. We found that relatives who participated RACT experienced a more positive approach from the healthcare professionals compared to those without RACT (p=.001). Furthermore, relatives who participated in RACT felt to a lower extent that they were alienated from the provision of care than did other relatives (p=.005). Relatives who did not participate in resource group were significantly more afraid that their ill next of kin would hurt someone. The association remained after adjustment for experience of approach and feeling of alienation. No other differences in family burden variables were found. Findings regarding mental Quality of Life scores and experiences of family stigmatization were similar in those both with and without RACT.
Discussion: The results suggest that participating in RACT may contribute to a higher level of satisfaction for relatives in their encounter with healthcare professionals.

S34. EFFECTIVENESS OF INDIVIDUAL METACOGNITIVE TRAINING (MCT+) IN FIRST-EPISODE PSYCHOSIS

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Background: The individual Metacognitive Training (MCT+) is useful to reduce positive symptoms in people with schizophrenia, however less is known in people with first-episode psychosis (FEP). The aim of the study is to assess the effectiveness of MCT+ in FEP regarding symptoms and cognitive insight.
Methods: A random clinical trial was performed with people with FEP from 10 clinical centers of Spain. One group received ten sessions of MCT+ and the other group received TAU. A total of 75 patients were included in the study, however only 40 finished the final assessment. Patients were assessed before treatment, post-treatment and 6 month follow-up. The assessment includes a battery of instruments for the main aims the Positive and Negative Syndrome Scale (PANSS) and the Beck Cognitive Insight (BCIS) will be analyzed. Repeated measures statistical test were used in order to assess differences between groups.