Methods: Here, we report preliminary data on the possible efficacy of tiagabine (Gabitril), which is a selective uptake inhibitor of the GABA (gamma-aminobutyric acid) transporter GAT-1, in the treatment of recent-onset schizophrenia. Subjects were randomized to receive either tiagabine or placebo added on to their antipsychotic regimen.
Results: Our data suggest that treatment with tiagabine during the early course of the illness can modulate PFC activation, as demonstrated by functional magnetic resonance imaging during working memory, and improve negative symptoms.
Discussion: Taken together, the proposed treatment strategy represents an effort to actively translate preclinical findings in SZ research into clinically testable hypotheses. This kind of translational approach, we believe, will ultimately lead to breakthrough in the treatment and possible prevention of SZ.

F44. AN ADD-ON TRIAL WITH N-ACETYL-CYSTEINE (NAC) IN EARLY PSYCHOSIS PATIENTS: TOWARDS BIOMARKER GUIDED TREATMENT

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Background: Oxidative stress, coupled with dysregulation of inflammation, NMDAR and dopamine, is involved in schizophrenia (SZ) pathophysiology. Earlier add-on clinical trials showed in chronic SZ patients that NAC, a precursor of glutathione (GSH), an important cerebral antioxidant, improved negative symptoms, mismatch negativity and local synchronization. We hypothesized that NAC at an earlier stage of illness would have a greater impact.
Methods: Early psychosis patients (EP, less than 5 years of illness, N=63; NAC=32, placebo=31) were supplemented with NAC (2.7g/day, 6 months) in a double-blind randomized placebo-controlled trial. Outcome measures: PANSS and neurocognition (MATRICS Consensus Cognitive Battery; n=36); quantification of medial prefronfal cortex glutathione (GSHmPFC) by 1H-magnetic-resonance-spectroscopy, of white matter diffusion properties estimated by generalized fractional anisotropy (gFA) computed from diffusion spectrum imaging (DSI), of blood cells GSH (GSHBC) and GSH peroxidase activity (GPxBC) at start and end of trial
Results: While PANSS negative and positive were not affected by NAC, NAC improved Processing Speed (NAC > Placebo; $F(1, 30)=5.849$, $p=.022$), favoring 2 of 3 processing speed tasks (Trail Making A, $F(1, 30)=4.279$, $p=.048$ & Verbal Fluency, $F(1, 30)=5.749$, $p=.023$). GSHmPFC (+23%, $p=0.005$) and GSHBC (+19%, $p=0.05$) were increased following NAC treatment. In patients with high-baseline GPxBC (>22.3U/gHb), subgroup explorations revealed an improvement of PANSS positive compared to placebo ($p=0.02$). The change of PANSS positive correlated negatively with that of GPxBC activity, showing that the improvement paralleled the restoration of redox status. NAC group showed 11% increase in fornix white matter integrity as measured by gFA, correlating with an increase in GSHmPFC over the 6-months period.
Discussion: This is the first clinical trial assessing the impact of NAC treatment in a sample of EP and the potential predictive role of peripheral biomarkers of redox dysregulation. The hypothesis that NAC would be beneficial to negative symptoms in EP was not confirmed in this small sample, most likely in reason of their very low level at baseline. The NAC induced GSHmPFC increase demonstrates its target engagement. NAC improved Processing Speed showing a therapeutic enhancement of cognitive functions. Most importantly, NAC improved fornix integrity, in association with brain GSH elevation, demonstrating for the first time that a redox regulator can enhance structural connectivity. Peripheral redox status allows identifying a subgroup of patients with improved positive symptoms. Future biomarker guided antioxidant interventions in larger EP samples should replicate these findings.

F45. THE EFFICACY AND SAFETY OF BLONASERIN AFTER SWITCHING FROM OTHER ATYPICAL ANTIPSYCHOTICS IN SCHIZOPHRENIC INPATIENTS: AN OPEN-LABEL, MULTI-CENTER TRIAL

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Background: The aim of this study was to investigate the efficacy and safety of blonanserin treatment after switching from other atypical antipsychotics in schizophrenic inpatients who showed inadequate efficacy and poor tolerability.
Methods: A total of 63 schizophrenic inpatients (inadequate response group=45 and poor tolerability group=18) were included in this study. They were already treated with atypical antipsychotics except blonanserin and not favored due to inadequate responses or intolerable adverse effects. Blonanserin was administered during 12 weeks after switching from their previous antispsychotics. Treatment response was evaluated with Brief Psychiatric Rating Scale (BPRS) and CGI-S, and safety profile were measured with Abnormal Involuntary Movement Scale (AIMS), Simpson-Angus Extrapyramidal Side effects Scale (SAR)S and Barnes Akathisia Rating Scale (BARS). Drug Attitude Inventory (DAI-10) and Subjective Well-being Under Neuroleptic Treatment (SWN) were used for subjective estimates. Assessments were done at baseline, 1, 2, 4, 8 and 12 weeks after blonanserin treatment. Repeated measures of ANOVA were done to analyze the group (inadequate vs. intolerable group) and time effects.
Results: CGI and BPRS were showed significant treatment responses after switching to Blonaserin. Time effects were significant at 2, 4, 8, 12 weeks after switching and group by time effect were also significant at that time. Mean changes of AIMS, SARS and BARS scores were not significant throughout test trial. Although SWN was significantly improved after switching to Blonaserin, it was not found significant group by time effect.
Discussion: The results suggest that blonanserin may be effective and well tolerable in schizophrenic patients who showed inadequate treatment response or poor tolerability.

F46. LUMATEPERONE (ITI-007): FAVORABLE SAFETY PROFILE IN AN OPEN LABEL SAFETY SWITCHING STUDY FROM STANDARD-OF-CARE ANTIPSYCHOTIC THERAPY IN PATIENTS WITH SCHIZOPHRENIA

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Background: Lumateperone (ITI-007) is a first-in-class investigational agent in development for the treatment of schizophrenia. Acting synergistically through serotonergic, dopaminergic and glutamatergic systems, lumateperone represents a new approach to the treatment of schizophrenia and other neuropsychiatric disorders. Lumateperone is a potent antagonist at 5-HT2A receptors and exhibits serotonin reuptake inhibition. Lumateperone also binds to dopamine D1 and D2 receptors acting as a mesolimbic/mesocortical dopamine phosphoprotein modulator (DPPM) with pre-synaptic partial agonism and post-synaptic antagonism at D2 receptors and as an indirect glutamatergic (GluN2B) phosphoprotein modulator with D1-dependent enhancement of both NMDA and AMPA currents via the mTOR protein pathway. Lumateperone demonstrated antipsychotic efficacy in two well-controlled clinical trials and was found to be well tolerated with a safety profile similar to placebo in all trials conducted to date.
Methods: In an open-label safety study, 302 patients with schizophrenia were switched from standard-of-care (SOC) antipsychotic therapy to 6 weeks treatment with lumateperone (ITI-007 60 mg, equivalent to 42 mg active base) QPM with no dose titration, then switched back to SOC for 2 weeks. The primary objective was to determine the safety of lumateperone, assessed by adverse events, body weight, 12-lead electrocardiograms, vital signs, clinical laboratory tests, motor assessments, and the Columbia-Suicide Severity Rating Scale. The secondary objectives were to determine the effectiveness of lumateperone to improve psychopathology as measured by the PANSS, social functioning as measured by the PANSS Pro-Social Factor and the Personal and Social Performance Scale (PSP), and depression as measured by the Calgary Depression Scale for Schizophrenia.
Results: Lumateperone was generally well-tolerated with a favorable safety profile. There was no drug related serious adverse event. In comparison to treatment with SOC antipsychotics at baseline, mean body weight decreased with lumateperone treatment. Lumateperone also demonstrated a favorable cardiometabolic and endocrine safety profile. Mean levels of cholesterol, triglycerides and prolactin improved with lumateperone treatment and worsened again when patients returned to SOC. The cardiovascular safety of lumateperone was favorable including no QTc interval prolongation. While efficacy data in an open-label study should be interpreted cautiously due to the absence of a parallel control group, improvements were observed in change from baseline of the PANSS total scores. Improvements were also seen in the Positive symptom subscale score, General Psychopathology subscale score, Marder Negative Factor score, and Prosocial Factor score as well as in the PSP scale. Greater improvements were observed in subgroups of patients with elevated symptomatology such as those with comorbid symptoms of depression and those with prominent negative symptoms.
Discussion: Lumateperone represents a novel approach to the treatment of schizophrenia with a favorable safety profile. The lack of metabolic, motor and cardiovascular safety issues presents a safety profile differentiated from standard-of-care antipsychotic therapy. Patients with stable symptoms on other antipsychotics may further improve when switched to lumateperone, with no dose titration needed. These data may warrant further investigation in placebo-controlled trials in patients with prominent negative symptoms and, separately, in patients with comorbid depression to demonstrate efficacy in these populations.

F47. COGNITIVE REMEDIATION AND PHYSICAL EXERCISE IN MULTI-EPISODE SCHIZOPHRENIA: STUDY PROTOCOL FOR A RANDOMISED CONTROLLED TRIAL

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Background: Cognitive remediation (CR) and physical exercise have separately shown promising results in schizophrenia cognitive improvement, despite this, the impact on daily functionality is still limited. Physical exercise increases Brain Derived Neurotrophic Factor (BDNF) levels, promoting neuronal and cognitive plasticity, which can maximize the impact of CR. We are conducting a randomised controlled trial to determine the efficacy of an intensive program that combines CR and physical exercise on cognition and related outcomes for patients with schizophrenia. In addition, we investigate functional and structural brain effects of this intervention and its association to BDNF.
Methods: This study protocol describes a randomized controlled trial in which 74 patients are randomly assigned to either CR and physical exercise or CR and health promotion. The interventions are 12-week long and consist of three weekly sessions (90 min of CR and 40 min of either aerobic exercise or health promotion). To be included in the study, patients must be diagnosed with schizophrenia or schizoaffective disorder, aged 28–60 years, and do low physical activity, as measured by International Physical Activity Questionnaire, IPAQ. Exclusion Criteria for participation in the study are the presence of neurological or substance use disorders, IQ < 70 and somatic illnesses that contraindicate physical exercise. Healthy control participants (n=18) are screened for the presence of lifetime Axis I psychotic disorders and for the presence of a first-degree relative with schizophrenia. Primary outcome measures are cognitive performance, functional outcome, negative symptoms, BDNF levels and neuroimaging measures. Secondary outcome measures are quality of life and metabolic parameters. All measures are blindly assessed at baseline, at 3 months follow up and at 15 months follow up.
This trial was approved by the Comité Ètic d'Investigació Clínica de l'Hospital del Mar (CEIC) 2015/6209/I
Results: This poster is a study protocol. We will correct data from now on.
Discussion: The results of this trial will provide valuable information about whether cognitive remediation efficacy for patients with schizophrenia can be enhanced by aerobic exercise-induced BDNF upregulation.
TRIAL REGISTRATION:
The trial is registered at www.clinicaltrials.gov (NCT02864576)

F48. RANDOMISED CONTROLLED TRIAL OF SOCIAL COGNITION INTERACTION TRAINING

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Background: Enthusiasm for the importance of social cognition in schizophrenia has grown as research has revealed that it is more strongly related to functional outcomes than neurocognition. A promising therapy developed