review aims to investigate whether melatonin or melatonin agonists significantly attenuate metabolic side effects among psychiatric populations treated with atypical antipsychotics.
Methods: Four randomized controlled trials were identified through a comprehensive literature search using MEDLINE, EMBASE, and the Cochrane Library on 22 October 2015. These four trials (including three melatonin studies and one ramelteon study) included 138 patients, of whom 71 were treated with melatonin or ramelteon and 67 were treated with a placebo. Because of high heterogeneity, we did not carry out a meta analysis.
Results: Melatonin was beneficial in lowering blood pressure among bipolar disorder patients; this blood pressure-lowering effect was not prominent among schizophrenic patients. Melatonin appeared to improve lipid profiles and body composition and attenuated weight gain among both schizophrenic and bipolar disorder patients. Ramelteon showed a significant efficacy in lowering total cholesterol level.
Discussion: Despite the few studies included, this systematic review provided promising evidence of the potential benefits of melatonin and its agonists in attenuating one or more components of metabolic syndrome among psychiatric patients using atypical antipsychotics.

T220. THE GLUTAMINASE INHIBITOR EBSELEN PREVENTS AMPHETAMINE SENSITIZATION IN MICE

Lior Heffetz-Giterman[1], Sharon S. Lander[1], Reut Cohen[1], Amit Gross[1], Inna Gaisler-Salomon*[,1]
[1]*University of Haifa*

Background: Dysregulated glutamatergic neurotransmission has been strongly implicated in the pathology of schizophrenia (SZ). Glutaminase 1 (GLS1) plays a critical role in the recycling of glutamate. GLS1 deficient mice were previously shown to display an attenuated response to the acute and chronic effects of the dopamine-releasing psychotomimetic drug amphetamine and have a pro-cognitive profile. A recent large-scale drug screening study identified ebselen as a potent CNS-available GLS1 inhibitor. Here, we asked whether ebselen (10 mg/kg) would attenuate sensitization to amphetamine (4 mg/kg) and induce pro-cognitive behavior.
Methods: Sensitization to amphetamine (4mg/kg) was tested in the open field. Mice received either saline, amphetamine or amphetamine+ebselen (10mg/kg) i.p. on 4 consecutive days. Seven days later, mice were challenged with amphetamine, amphetamine+ebselen or saline. We further assessed the effect of ebselen administration on Gls1 mRNA in the hippocampus, prefrontal cortex and striatum, and on dopamine receptor expression in the striatum. Finally, we measured social preference and recognition in genetically modified GLS1 deficient mice and in ebselen (10mg/kg)-treated wild-type mice.
Results: We found decreased sensitization to amphetamine in mice that received pre-treatment with ebselen. Gene expression studies revealed reduced Gls1 expression in hippocampus, and altered expression of dopamine markers in the striatum of ebselen-treated mice. Finally, ebselen-treated mice show enhanced social recognition, similarly to GLS1 deficient mice.
Discussion: Similarly to genetically modified GLS1 deficient mice, ebselen-treated mice demnstrate resilience to the sensitizing effects of the pro-psychotic drug amphetamine and a pro-cognitive phenotype. These findings provide evidence for the potential of GLS1 inhibition in addressing some of the central clinical features of SZ and related pathology.

T221. LURASIDONE DISPLAYS ANTIDEPRESSANT AND PRO-COGNITIVE EFFECTS IN THE CHRONIC MILD STRESS MODEL: A ROLE FOR REDOX MECHANISMS AND PARVALBUMIN EXPRESSION

Andrea Carlo Rossetti[1], Maria Serena Paladini[1], Paola Brivio[1], Giulia Sbrini[1], Mariusz Papp[2], Francesca Calabrese[1], Raffaella Molteni[1], Marco Andrea Riva*[,1]
[1]*University of Milan;* [2]*Polish Academy of Sciences, Krakow*

Background: Exposure of rodents to chronic stress is able to recapitulate a number of functional alterations that are associated with psychiatric disorders, including anhedonia and cognitive impairment. Stress-based experimental models are also useful to investigate the ability of pharmacological intervention in normalizing such defects as well as the molecular alterations associated with the behavioral phenotype. On these bases, the aim of the present study was to investigate the ability of a chronic treatment with the multi-receptor modulator lurasidone in normalizing behavioral changes produced by chronic mild stress (CMS) in rats. Moreover, we investigated the potential contribution of parvalbumin expression and of redox mechanisms in the alterations brought about by CMS exposure.
Methods: Adult male Wistar rats were exposed to CMS for 2 weeks and sucrose consumption was used to identify rats that were susceptible to the stressful manipulation. Control and CMS-susceptible rats were then randomized to receive chronic vehicle or the multi-receptor modulator lurasidone (3 mg/kg/day) for 5 more weeks, while continuing the stress procedure. Animals were tested for anhedonia, using the sucrose intake test, and for cognitive impairment, using the novel object recognition (NOR) test. Rats were sacrificed at the end of the procedures and the brain regions of interest were dissected and used for the molecular analyses.
Results: Exposure to CMS produced a persistent anhedonic phenotype as well as a significant deficit in the NOR test. Both behavioral abnormalities were normalized by chronic lurasidone treatment. Rats exposed to CMS display a marked and selective reduction in the expression of parvalbumin, which identifies a subpopulation of GABAergic interneurons, in dorsal (but not ventral) hippocampus, an effect that was normalized by chronic lurasidone administration. CMS rats also show a significant up-regulation of (NADPH) oxidase 2 (NOX2), which is critically involved in oxidative stress, as well as a down-regulation of Nrf-2, a master regulator of antioxidant defense. These alterations in dorsal hippocampus were normalized in animals that received chronic lurasidone treatment that was also capable of reducing the levels of Keap-1, an important player that exerts a repressive control over Nrf-2.
Discussion: Our results demonstrate the ability of lurasidone in normalizing anhedonia and cognitive deficits associated with CMS exposure, suggesting its effectiveness on different 'domains' (RDoC) that characterize psychiatric disorders. Lurasidone was also able to normalize the effects produced by CMS exposure on parvalbumin expression, possibly through its ability in promoting anti-oxidative mechanisms within the dorsal hippocampus. All in all, these effects may promote resilience toward the alterations produced by adverse environmental conditions, such as stress, which represents a major vulnerability element in the etiology of psychiatric disorders.

T222. EARLY TREATMENT RESISTANCE IN A LATIN-AMERICAN COHORT OF PATIENTS WITH SCHIZOPHRENIA

Cristian Mena[1], Alfonso Gonzalez-Valderrama[1], Barbara Iruretagoyena[2], Juan Undurraga[1], Nicolas Crossley*[,2]
[1]*J. Horwitz Psychiatric Institute;* [2]*Universidad Católica de Chile*

Background: Failure to respond to antipsychotic medication in schizophrenia is a common clinical scenario with significant morbidity. Recent studies have highlighted that many patients present treatment-resistance from disease onset. We here present an analysis of clozapine prescription patterns, used as a real-world proxy marker for treatment-resistance, in a cohort of 1195patients with schizophrenia from a Latin-American cohort, to explore the timing of treatment resistance during the course of the disease and possible subgroup differences.
Methods: We used survival analysis from national databases of clozapine monitoring system, national disease notification registers, and discharges from an early intervention ward.

Results: Echoing previous studies, we found that around 1 in 5 patients diagnosed with schizophrenia were eventually prescribed clozapine, with an over-representation of males and those with a younger onset of psychosis. The annual probability of being prescribed clozapine was highest within the first year (probability of 0.11, 95% confidence interval of 0.093–0.13), compared to 0.018 (0.012–0.024) between years 1 and 5, and 0.006 (0–0.019) after 5 years. There were no differences in age at psychosis onset or gender related to the onset of treatment resistance. A similar pattern was observed in a subgroup of 230 patients discharged from an early intervention ward with a diagnosis of non-affective first episode of psychosis.
Discussion: Our results highlight that treatment resistance is frequently present from the onset of psychosis. Future studies will shed light on the possible different clinical and neurobiological characteristics of this subtype of psychosis.

T223. REAL WORLD EFFECTIVENESS OF ANTIPSYCHOTIC DRUGS IN PATIENTS WITH SCHIZOPHRENIA: A 10-YEARS RETROSPECTIVE STUDY

Tae Young Lee*[,1], Minah Kim[1], Junhee Lee[1], Jun Soo Kwon[1]
[1]*Seoul National University College of Medicine*

Background: Discontinuation of antipsychotics in patients with schizophrenia has increasing attention as a representative treatment effectiveness of the medication. The objective of present study is to determine which antipsychotic medication is highly effective in a real-world clinical setting considering adjuvant pharmacotherapy over a 10-year follow-up period.
Methods: A total of 2300 patients with schizophrenia were recruited at the Seoul National University Hospital, and participants received amisulpride, aripiprazole, clozapine, haloperidol, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone for up to 10-years. Time-to-discontinuation of antipsychotic medications was analyzed using Kaplan-Meier survival analyses. Group differences were compared using log-rank tests.
Results: The most frequently used drugs were Risperidone, Aripiprazole, Olanzapine in the antipsychotic drug, Valproate, Lamotrigine, Topiramate in the anticonvulsant agents, Escitalopram, Sertraline, Milnacipran in antidepressants, Lorazepam, Clonazepam, Zolpidem in anxiolytics or sedatives, Propranolol, Benztropine, Trihexyphenidyl in antiparkinson drugs. About half of the patients discontinued taking antipsychotics before 1.5 years. Clozapine showed significantly longer time to discontinuations compared to other antipsychotic drugs. Aripiprazole also showed a lower incidence of discontinuation except for Clozapine and Olanzapine.
Discussion: Clozapine was found to be the most effective antipsychotics in terms of time to discontinuations. Aripiprazole is the most highly recommended 1st line antipsychotics.

T224. THE FUNCTIONAL CONNECTIVITY DERIVED WITH BIVARIATE ANALYSIS, COHERENCE AND PHASE LOCKING VALUE IN PATIENTS WITH SCHIZOPHRENIA UNDER CLOZAPINE

Yong Sik Kim*[,1], In Won Chung[1], Hee Yeong Jung[2], Tak Youn[1], Se Hyun Kim[1], Nam Young Lee[1], Seong Hoon Jeong[3], Kyung Tae Park[4], Sang Hoon Yi[4], Yong Min Ahn[2]
[1]*Dongguk University School of Medicine;* [2]*Seoul National University;* [3]*Eulji University Hospital;* [4]*Inje University*

Background: Coherence (COH) and Phase Locking Value (PLV) may have considerable potentials for investigating anomalies of functional connectivity in schizophrenia but results are still conflicting. This study is aimed to investigate relationships between plasma levels of clozapine (p-CZP) and norclozapine (p-NCZP), and total and cognitive factor scores of Positive and Negative Syndrome Scale (PANSS-T, -C), and functional connectivity by COH and PLV.
Methods: Fifty-eight patients who were diagnosed as schizophrenia with DSM-5 criteria and under CZP were recruited (duration of illness, 15.5 ± 8.0 years; duration of CZP, 6.8 ± 4.6 years; mean daily dose of CZP, 233.6 ± 88.4 mg). COH and PLV were calculated with Neurophysiological Biomarker Toolbox from qEEG and were averaged from the signals of electrodes in the designated brain regions, frontal (F), temporal (T), central (C) and occipitoparietal (OP). For interhemispheric connectivity, electrodes except all midline channels were combined into Odd (O) and Even (E). The results were presented at ≥0.30 of Spearman correlation.
Results: 1) Correlation coefficient between p-CZP and p-NCZP was 0.84, and those of CZP dose with p-CZP and p-NCZP were 0.38 and 0.53, respectively. 2) p-CZP showed correlations with OCEC in delta and alpha, OTEC in delta, OCEOP in theta, OTEF in alpha, and OOPEF in gamma band in COH, and OOPEOP in beta band in PLV. 3) p-NCZP showed correlations with ETEOP in delta, theta, and gamma, OCEC in delta and alpha, OFOC and OCEOP in delta, OFET and OTET in alpha, OCEF in beta, OOPEC in gamma band in COH, and with ETEOP in delta, theta, and beta, OTET and OCEC in alpha, OCEF in beta band in PLV. 4) CZP dose showed correlations with ETEC in beta and gamma, ETEOP in theta, OCEF in alpha, OTET in beta, OOPEF and OOPET in gamma band in COH, and with OTET in alpha and beta, ETEOP in theta, OTEOP in alpha, ETEC in beta, OFOC in gamma band in PLV. 5) PANSS-T showed correlations with OFEOP and EFEOP in alpha, OCEOP in beta, OTOC and OTEF in gamma band in COH, and with OTEF in beta and gamma, OFET in delta, OOPEF in beta, OTOC and OCEOP in gamma band in PLV. 6) PANSS-C showed correlations with EFEOP in delta, theta, alpha, and beta, OOPEOP in delta, alpha, and beta, OFET and OTEF both in alpha and beta, OOPEF in delta, OFEOP in alpha, OFEC and OCEOP in beta, OTOC in gamma band in COH, and with EFEOP in theta, alpha, and beta, OFEOP and OOPEOP both in alpha and beta, OFET in delta and beta, OTOC, OOPEF, OOPEOP in beta, OTOC and OCEOP in PLV. 7) PANSS-T and -C showed no correlations with p-CZP, p-NCZP and CZP dose. 8) However, the clinical and drug variables showed significant simultaneous correlation with certain functional connectivity, but sometimes the direction correlation was opposite.
Discussion: The relationship between functional connectivity and clozapine parameters seems to demonstrate inter- and intra-hemispheric connections in brain regions. However, there were same and/or opposite directions of correlations between COH and PLV dependent EEG band frequencies and clinical and drug variables. Taken together, investigating the functional connectivity with COH and PLV could give the information about p-CZP and p-NCZP before the laboratory reports, the degree of psychopathology in patients with schizophrenia under CZP, and the differentiations of surface symptoms whether derived from pathophysiology of schizophrenia or from clozapine effects.

T225. OPERATIONAL DEFINITIONS FOR ANTIPSYCHOTIC RESPONSE IN DELUSIONAL DISORDER: A SYSTEMATIC AND CRITICAL REVIEW

Alexandre González-Rodríguez*[,1], Francesc Estrada[1], José Antonio Monreal[2], Diego Palao[2], Javier Labad[2]
[1]*Parc Taulí University Hospital;* [2]*Parc Taulí University Hospital, CIBERSAM, Autonomous University of Barcelona (UAB)*