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P.2.072 Aripiprazole treatment for acute mania in patients with bipolar I disorder: A placebo-controlled study

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Objective: To compare the efficacy and safety of aripiprazole with placebo for the treatment of acute mania in patients with bipolar I disorder.

Methods: This Phase III, multicentre, double-blind, placebo-controlled study involved 272 patients with bipolar I disorder who were experiencing an acute manic or mixed episode. Patients were randomised to 3 weeks of treatment with either aripiprazole 30 mg/day (with the option to reduce to 15 mg/day for tolerability), or placebo. Key measures of treatment outcome included the Young Mania Rating Scale (Y-MRS) Total score, CGI-BP and the PANSS Hostility subscale scores.

Results: Aripiprazole produced significantly greater improvements from baseline in the Y-MRS score compared with placebo at study endpoint (−12.5 vs −7.2, $p \leqslant 0.01$). Significant differences in Y-MRS score were apparent between the treatment groups by day 4. The proportion of patients responding to treatment (defined as a $\geqslant 50\%$ decrease in Y-MRS score) was significantly higher for aripiprazole than for placebo (53% vs 32%, $p \leqslant 0.01$). Aripiprazole treatment produced significant improvements in CGI-BP Severity of Illness (mania) scale and PANSS Hostility subscale scores compared with placebo (both, $p<0.01$). Discontinuation rates due to adverse events were similar in the aripiprazole and placebo groups, and there were fewer discontinuations due to lack of efficacy among patients receiving aripiprazole than those receiving placebo. There were no significant changes in body weight with aripiprazole compared to placebo.

Conclusion: This is the second study to demonstrate the efficacy and safety of aripiprazole in the treatment of acute mania in patients with bipolar I disorder.

P.2.073 The effect of MK-801 on the phosphorylation of GSK-3 beta in the rat frontal cortex

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Purpose: Previous reports showed that the Ser-9-GSK-3 beta pathways are considered as part of a common signal pathway through which diverse psychomimetics such as D-amphetamine, LSD, and PCP. In this study we tried to elucidate the effect MK-801, another psychomimetics, has on the phosphorylation status of GSK-3 beta and the upstream and downstream signal pathways of GSK-3 beta.

Methods: Male Sprague-Dawley rats were grouped and maintained on a 12 hour light-dark schedule with food and water freely available. MK-801 was injected to the rats intraperitoneally and control animals received the same volume of normal saline. The effect of MK-801 on the phosphorylation of Ser-9-GSK-3 beta, Ser-473-AKT and Ser-133-CREB were examined in the rat cortex by Western blot analysis.

Results: We observed that MK-801 increased the phosphorylation of Ser-9-GSK-3 beta from 15 min after intraperitoneal injection of 1 mg/kg compared to the injection of same volume of vehicle. The increase peaked at 30 min, was maintained until 90 min after the injection. The phosphorylation pattern of GSK-3 beta also changed in dose dependent fashion. When treated with 0, 0.25, 0.5, 1, 2 mg/kg of MK-801, the phosphorylation of GSK-3 beta increased as the drug dosage increased. However, after peaking at 2 mg/kg, the phosphorylation of GSK-3 beta started to decrease when treated with 4 mg/kg and also further decreased when treated with 8 mg/kg of MK-801. To clarify the upstream mechanism of Ser-9-GSK-3 beta phosphorylation, we examined the phosphorylation on Ser-473-AKT, a putative up-stream molecule of Ser-9-GSK. We found that the Ser-473 phosphorylation of AKT changed in concordance with Ser-9-GSK-3 beta phosphorylation with similar temporal and dose-dependent pattern. And Ser-133 phosphorylation of CREB, a putative down-stream molecule of Ser-9-GSK-3 beta, also showed similar temporal and dose-dependent pattern with the phosphorylation of Ser-9-GSK-3 beta and Ser-473-AKT.

Conclusion: We found that MK-801 increased the phosphorylation of Ser-9-GSK-3 beta and Ser-133-CREB similar to other psychomimetics. These findings support the role of these molecules in a common signal pathway of psychomimetic action. We also found that the phosphorylation of Ser-473-AKT changed in concordance with Ser-9-GSK-3 beta phosphorylation with similar temporal and dose-dependent pattern, suggesting AKT as the upstream mechanism in the phosphorylation of Ser-9-GSK-3 beta by MK-801.

P.2.074 Is substance use high among patients with schizophrenia in Turkey?

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Objective: The high rate of substance use disorders and its effects on the course of the psychiatric illness has made the identification and treatment of these individuals a high priority. Alcohol dependence, cigarette smoking and psychostimulant misuse are the three most frequently reported addictions in schizophrenia. Individuals with schizophrenia are at increased risk for comorbid substance use disorders compared to general population. The objective of the present study was to identify the prevalence of substance use and abuse including nicotine, alcohol, prescription and illicit drugs among patients with schizophrenia recruited from a university hospital in Turkey, a developing country, a different culture.

Methods: The study included 49 patients (26 males, 23 females) who met the criteria for DSM-IV diagnosis of schizophrenia who underwent clinical evaluation in either the outpatient or inpatient facilities of Department of Psychiatry, Dokuz Eylul University. The mean age of the patients was 39.3 years (SD=11.9), mean age at onset of illness was 23.5 years (SD=10.1), mean age at first contact with treatment was 24.5 years (SD=8.1) and mean duration of illness was 16.0 years (SD=10.5). Structured Clinical Interview for DSM IV Axis I Disorders (SCID-I)

for schizophrenia and substance use disorders was utilized. The Positive and Negative Syndrome Scale (PANNS), Clinical Global Impression (CGI) Scale, Hamilton Depression Scale were used to evaluate psychiatric symptomatology. The extrapyramidal effects of medication were assessed with the Extrapyramidal Symptom Rating Scale. Fagerström Nicotine Tolerance Questionnaire was used for the severity of nicotine dependence. CAGE (acronym for cut down, annoyed, guilty, eye-opener), and Alcohol Use Disorders Identification Test (AUDIT) were used for screening alcohol related problems. Data analysis was performed using SPSS for Windows (10.0). In order to identify the correlates of substance use, smokers and nonsmokers (former smokers and those who had never smoked), and the alcohol users and non users were compared on demographic and clinical variables. Differences in proportions were measured by using the chi-square test. The significance between groups was tested by Mann-Whitney test.

Results: The prevalence of current cigarette smoking was 69.4%. The prevalence of current alcohol use was 44.9%, with 8.2% of these cases considered to be alcohol abusers. Only one patient (2%) had cannabis abuse. Demographic and clinical characteristics were not found to be significantly associated with cigarette and alcohol use. However, smoking patients had poorer premorbid functioning, earlier onset of illness and greater number of previous hospitalizations compared to nonsmoking patients. While the prevalence of cigarette smoking in patients with schizophrenia was high, the prevalence of alcohol and cannabis use was low compared to other countries.

Conclusion: We conclude that the high level of family support and a low prevalence of alcohol and substance use among general population together with non-availability of illicit substances in our country may account for these findings.

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P.2.075 The histamine H1 receptor gene polymorphic variants and schizophrenia

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Objective: There is growing evidence suggesting involvement of the histaminergic system in the patophysiology of schizophrenia, especially contribution of the H1 receptor to deficit symptoms and perhaps to efficacy of certain atypical antipsychotic drugs. We have therefore selected H1 receptor gene as a candidate and examined four previously described polymorphisms of this gene (−17C/T, Asp349Glu, Phe 358D, Leu449Ser) in the population of the Northern Poland.

Subjects and methods: The study was performed on 204 probands (102 schizophrenic patients and 102 matched healthy controls from the general population). All schizophrenic patients met DSM-IV criteria assessed with the structured interview SCID-I. Clinical symptoms and their intensity were assessed using the Positive and Negative Syndrome Scale (PANSS). Genomic DNA was extracted from leucocytes using a standard phenol-chloroform method and the polymorphisms were analyzed using PCR-SSCP and PCR-RFLP methods. Automated sequencing was performed to confirm the presence of each polymorphism.

Results: There was a trend towards the more frequent incidence of Leu449Ser heterozygotes ($\times^2$=2.01, df=1, p=0.15) and Ser449 allele ($\times^2$=2.01 df=1 p=0.15) among schizophrenic patients than in healthy controls, whereas there were no differences in genotype and allele distribution in case of other analyzed polymorphisms. Moreover, Glu349 allele was not detected at all in both examined groups.

Conclusions: These results suggest no significant association between H1 receptor gene variants and schizophrenia, although there was a weak tendency towards association between Leu449Ser heterozygotes and Ser449 allele and schizophrenia.

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P.2.076 Efficacy of aripiprazole and perphenazine in severe schizophrenia resistant to treatment with atypical antipsychotics

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Objective: A comparison of the efficacy of aripiprazole with that of perphenazine in treatment-resistant patients with continued pronounced symptoms of schizophrenia after a trial of olanzapine or risperidone.

Methods: Patients who were prospectively diagnosed with treatment-resistant schizophrenia (n=300) were randomised to 6 weeks of therapy with aripiprazole (15 or 30 mg/d) or perphenazine (8–64 mg/d). Patients were identified as treatment resistant by examination of their medical history. Confirmation was made by failure of the patient to respond to a 4–6 week trial of olanzapine or risperidone during an open-label treatment phase preceding randomisation. Patients with the most pronounced symptoms (upper tertile by PANSS-Total at randomisation, n=96) were included in this analysis.

Results: Mean PANSS-Total for this group with severe schizophrenia symptoms was 123.7±18.5. At 6 weeks, the mean reduction in the PANSS-Total score was 21.1±3.5 with aripiprazole and 13.5±3.8 with perphenazine, P=NS. The response rate, which was prospectively defined as ⩾30% decrease in PANSS-Total or CGI-I of 1 or 2, was 33% with aripiprazole and 29% with perphenazine.

Conclusions: In treatment-resistant patients with severe schizophrenia who remained highly symptomatic even after treatment with olanzapine or risperidone, therapy with aripiprazole or perphenazine resulted in a marked improvement of symptoms in about one third of the patients. The improvement seen during aripiprazole treatment was greater than with perphenazine, although the difference was statistically non-significant.