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P.2.051 Ziprasidone negative symptom efficacy in long-term clinical trials

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Purpose: We reviewed ziprasidone' s efficacy in treating negative symptoms in long-term, double-blind trials and in extension studies of patients switched to ziprasidone from other antipsychotics.

Methods: Changes in PANSS Negative Subscale scores were evaluated in four randomized, double-blind studies of ziprasidone versus placebo (52 weeks), haloperidol (28 weeks), olanzapine (>6 months), and risperidone (52 weeks), using analysis of covariance (ANCOVA). In three open-label extension studies (=215 days) evaluating improvement following switch to ziprasidone from conventional agents, olanzapine, or risperidone, changes in PANSS Negative Subscale scores were analyzed using paired t-tests.

Results: Ziprasidone was superior to placebo (LOCF, $P<0.05$) in improving negative symptoms. Change in PANSS Negative score was not significantly greater than that with haloperidol, but percentage of PANSS Negative responders (=20% decrease) was higher ($P<0.05$). Ziprasidone' s treatment effect was comparable to olanzapine' s (95% CI: −2.3, 2.8) and risperidone' s (95% CI: −3.2, 2.4). In the switch studies, improvement was observed for patients switched from conventional agents ($P<0.01$), olanzapine ($P<0.05$), and risperidone ($P<0.01$).

Conclusions: In long-term treatment of negative symptoms of schizophrenia, ziprasidone showed efficacy superior to placebo' s and comparable to olanzapine' s and risperidone' s and a responder rate higher than haloperidol' s. Significant long-term improvement was also observed in patients switched from other antipsychotics.

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P.2.052 Addition of nicotine to the D_2 antagonist raclopride or the weak D_4 antagonist L-745,870 augments NMDA-induced currents in pyramidal cells from the rat medial prefrontal cortex

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Clinical studies have observed that around 90% of schizophrenic patients smoke, compared to approximately 20% of the general population in the USA, and it has been proposed that these patients are attempting to self-medicate with nicotine to improve symptoms of the disease. The high prevalence of smoking among schizophrenic patients may be reduced by the atypical antipsychotic drug (APD) clozapine, which effectively blocks e.g. 5-HT_{2A} receptors, dopamine (DA)-D_4 receptors and á$_2$-adrenoceptors, but only moderately so D_2 receptors. However, no reduction in nicotine dependence is obtained with typical APDs, i.e. potent D_2 antagonists.

Moreover, atypical APDs, but not typical APDs, as well as chronic nicotine preferentially increase DA release in the medial prefrontal cortex (mPFC), a brain region which plays a key role in working memory and tentatively in the pathogenesis of schizophrenia. Prefrontal DA interacts with D_1 receptors, which in turn may interact with N-methyl-D-aspartate (NMDA) receptors to enhance neuronal excitability in mPFC. Indeed, atypical APDs may, better than typicals, improve cognitive dysfunctioning in schizophrenia, and recently it was shown that atypicals, in contrast to typicals, enhance NMDA-induced currents in pyramidal cells of the mPFC from the rat. We have therefore investigated the effect of nicotine (100 nM) on the NMDA-induced currents in the mPFC of the rat, both when given alone and in combination with a selective D_2 antagonist (raclopride; 1 ìM) or a weak D_4 antagonist (L-745,870; 100 nM).

The intracellular single-electrode voltage-clamp technique was used to record pyramidal cells in layer V and VI of the mPFC in slice preparations from rat brain. All cells were held at −60 mV during the recording and tetratodoxin (to block actions potentials), glycin (to enhance the NMDA-induced responses) and bicuculline (to block the GABA-A responses) were included in the Ringer solution. All drugs, including NMDA, were added to the recording chamber via the perfusion solution. In contrast to atypical APDs, raclopride did not augment NMDA-induced currents in pyramidal cells of the mPFC. Neither did nicotine alone, or L-745,870.

However, the combination of nicotine with raclopride or L-745,870 significantly (one-way ANOVA, followed by post-hoc LSD-test; $p< 0.05$) increased the NMDA-induced currents in pyramidal cells of the rat mPFC, thus producing an effect similar to clozapine. These findings may have bearing on the spontaneous reduction in smoking seen in schizophrenic patients, when switched from D_2 antagonists (e.g. typical APDs) to clozapine.

In preliminary experiments, we have recently observed that the selective á$_2$ antagonist idazoxan (1 ìM), when added to raclopride may provide augmentation of electrically evoked excitatory post-synaptic potentials (EPSPs) in pyramidal cells of the mPFC. Thus, the á$_2$-antagonistic effect of clozapine may subserve a similar role as nicotine in the mPFC when combined with D_2-blockage.

P.2.053 Effect of acute and chronic treatment with the atypical antipsychotics olanzapine and clozapine in 8-radial arm maze in rats

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Introduction: cognitive deficit is an important symptom in schizophrenia. Atypical antipsychotics are known to improve some cognitive functions in both schizophrenics and dementia patients, but their anticholinergic properties do not argue for such improvement. In this sense scopolamine, a non-specific antimuscarinic drug, is used as gold standard of memory impairment in animal studies. Therefore, we investigated the behavioral effect of acute and chronic treatments with olanzapine and clozapine, two atypical antipsychotics with high occupation of muscarinic receptors,

in a working memory paradigm in the rat. Scopolamine was used for comparison.

Methods: male Wistar rats were trained on the 8-radial arm maze to reach an 80% choice accuracy (between 10 to 20 daily sessions). For test the acute effect of drug treatment, olanzapine (1.25, 2.5, 5 and 10 mg/kg ip), clozapine (5, 10, 20 and 40 mg/kg ip) and scopolamine (0.3, 0.6, 1.2 and 2.4 mg/kg ip) were administered 30 min before performance in maze task. Using a computerized video track system, motor activity was also measured during test performance. After the acute test, rats were chronically treated for 14 days with olanzapine (2.5, 5 and 10 mg/kg ip), clozapine (2.5, 5 and 10 mg/kg ip) or scopolamine (0.3 and 0.6 mg/kg ip). During this period training sessions were reduced to alternate days. 24 h after the last dose, rats were again tested in the radial arm maze. The experimental parameters measured were number of correct arm choices, number of errors or reentered arms, number of reinforcers consumed in the maze and time employed to complete de task. Statistical analysis was performed using one-way ANOVA and Dunnett' s test for post hoc comparisons. To determine the association level between the number of correct choices or errors and the activity level, a simple regression analysis was made.

Results: acute olanzapine, clozapine and scopolamine caused a significant decrease in motor activity level while apparently impairing memory. At the range of doses used, olanzapine and clozapine induced a dose-related sedative effect in treated animals in contrast with animals treated with scopolamine. While chronic treatment with olanzapine, clozapine and scopolamine neither impaired memory task nor modified motor activity level. The effects of acute olanzapine (R^2= 0.68) and clozapine (R^2= 0.67) were closely related to decreased motor activity levels, whereas scopolamine was less related (R^2= 0.46). The effects of chronic treatment were not related to any motor activity modifications (R^2= 0.22, 0.16 and 0.12 respectively).

Conclusion: we conclude that chronic treatment with olanzapine, clozapine and scopolamine does not negatively affect working memory performance, and suggest that chronic muscarinic cholinergic antagonism by drugs does not indefectibly cause memory impairment.

This study was partially funded by Eli Lilly (Spain).

P.2.054 Adherence to antipsychotic dosing guidelines in the treatment of hospitalised psychotic patients in Belgium

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Antipsychotic medication is the cornerstone of the treatment of psychotic disorders like schizophrenia. Despite the proven effectiveness of these drugs, compliance is often problematic due to the regular occurrence of unpleasant side effects. Research repeatedly demonstrated that, for both first- and second-generation antipsychotics, the occurrence of these side effects is dose-related. It is therefore often stated that something like an "optimal dose" exists for typical as well as for atypical antipsychotics. The concept "optimal dose" refers to a dosage minimising undesirable side effects while optimising symptomatological effectiveness. The administered dose considered optimal does vary as a function of phase of illness. For instance both sensitivity to side effects and therapeutic effectiveness are higher in first episode patients. The present study aims to record antipsychotic dosing in hospitalised psychotic patients in Belgium. Data on antipsychotic medication are available through the use of PECC (Psychosis Evaluation tool for Common use by Caregivers), a standardised, computerised comprehensive assessment instrument. It registers antipsychotic drug use, while also assessing symptomatology, additional medication and a number of demographic and clinical variables. Currently, 1075 psychotic patients are being followed with PECC. To allow for a valid evaluation of the appropriateness of dosing strategies applied, three patient groups were defined. The definition considers the segmentation by the treating clinician and the patient' s duration of illness: first episode patients, chronic patients and treatment resistant patients. Based on the literature, an adequate dose range for typical as well as atypical antipsychotics was outlined for each patient group. For first episode patients it is advocated to use atypical antipsychotic doses ranging from 2 to 4 mg risperidone equivalents, while doses of typical antipsychotics should lie between 3 to 5 mg haloperidol equivalents. For chronic and treatment resistant patients, similar dosing guidelines were formulated: doses of atypical antipsychotics should lie between 4 to 6 mg risperidone equivalents while for typical antipsychotics doses between 5 to 10 mg haloperidol equivalents are considered optimal. Our results show that for first episode patients the mean doses of atypical (in risperidone equivalents) and typical (in haloperidol equivalents) antipsychotics, equal respectively 4.3mg (STD=2) and 7.5mg (STD=10.5), and are thus slightly above the upper limit of the advocated dose range. Within this patient group, about 40% receives too high a dose. A similar pattern is observed in treatment resistant patients. Although mean doses for both typical (Mean=10.1, STD=10.1) and atypical (Mean=5.9, STD=2.5) antipsychotics virtually coincide with the upper end of the advocated dose range, around 40% of patients again receive a dose that exceeds recommendations. Dosing is more optimal in the chronic patient group, where mean doses of 5.2mg (STD=2.4) and 8.4mg (STD=9.8) are registered. About one quarter of these chronic patients receives too high a dose. Our findings indicate that doses administered in clinical practice are often too high. Since there is no evidence that higher doses are more effective, these treatment practices unnecessarily expose patients to undesirable side effects.

P.2.055 The influence of antipsychotic drug treatment on anticholinergic use and complexity of medication schemes in hospitalised psychotic patients in Belgium

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Although antipsychotic medication is the cornerstone of the treatment of psychotic disorders like schizophrenia, treatment compliance is often a problem. This is due to, amongst others, the unpleasant side effects often associated with antipsychotic drug use and the complexity of the medication schemes prescribed. Since cognitive deficits, and memory problems in particular, are often part of a psychotic patients' symptomatology, complicated medication schemes cause patients to simply forget their medication. Monotherapy could help in limiting these problems. Due to their broader symptomatological effectiveness and more favourable side-effect profile monotherapy of second-generation antipsychotics is preferred to monotherapy of first-generation