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Olanzapine decreases cannabinoid CB1 receptors in the hypothalamus and brainstem, possibly through muscarinic M3 receptor antagonism

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Abstract

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DAI, and appraise its role in antipsychotic drug trials and clinical psychopharmacology research.

Methods: A comprehensive computer aided search of all the major databases was carried out to identify the original research articles, conference proceedings, registered clinical trials and research dissertations published between 1983 and 2009, and used DAI as a part of study protocol. The list of articles fulfilling the selection criteria was independently reviewed, to identify various themes and variations in its scope of application.

Results: The search revealed 241 original articles that confirmed the sound psychometric properties of DAI and its use across all continents, in 15 major languages. DAI has been primarily used in pharmaceutical industry-led as well as investigator initiated clinical trials of antipsychotic drugs; and also in evaluating interventions aimed at enhancing treatment adherence. DAI has been used in developing other clinical rating scales, and also in exploring therapeutic concepts such as treatment adherence, patients' preferences, insight, functional outcomes and quality of life.

Conclusion: DAI remained the corner stone of assessing acceptability and effectiveness of antipsychotic drugs in clinical trials, facilitated research into clinical and biological aspects of patients' preferences to psychotropic drugs, and pioneered the study of subjective tolerability as a credible scientific discipline.

Policy of full disclosure: None.

P-04.093 Effects of adjunct galantamine to antipsychotics in animal models of antipsychotic activity and extrapyramidal side effect liability: Cholinergic muscarinic receptor mediation

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Objective: Cognitive and psychotic symptom improvement in schizophrenia (SCH) by adjunct treatment with the acetylcholine esterase inhibitor/cholinergic nicotinic receptor (nAChR) allosteric modulator galantamine (GAL) to antipsychotics (APDs) has been reported. Cognitive symptoms in SCH may involve brain prefrontal hypodopaminergia. Others have shown that adjunct GAL to the atypical APD risperidone increased brain prefrontal dopamine release and reversed social interaction impairment in mice. Also, nAChR blockage, but not cholinergic muscarinic receptor (mAChR) blockage, prevented these effects. The role of nAChRs in potential antipsychotic effects of GAL is, however, not clear. Therefore, we here investigated the effects of adjunct GAL (1.25 mg/kg) to the typical APD haloperidol (0.05 mg/kg), or risperidone (0.2 mg/kg), in an animal model of antipsychotic activity with high predictive validity in rats.

Methods: The conditioned avoidance response (CAR) test was used for assessment of antipsychotic activity. Complementary safety assessment for extrapyramidal side effect (EPS) liability was performed using the catalepsy test. Statistical evaluation was performed by means of non-parametric statistics.

Results: Adjunct GAL significantly enhanced antipsychotic-like effects by the low doses of haloperidol or risperidone ($p < 0.05$), but showed a safe EPS liability profile only together with risperidone. Pretreatment with scopolamine (mAChR blockage), but not mecamylamine (nAChR blockage), completely reversed the enhancing effects of adjunct GAL to haloperidol treatment ($p < 0.05$) in the CAR test.

Conclusion: The data suggest that, while nAChR modulating properties of GAL are likely to contribute to pro-cognitive activity in SCH, any contribution to antipsychotic activity by GAL seems mediated primarily via mAChRs, presumably via enhanced endogenous cholinergic mAChR stimulation. This dual property of GAL may offer a unique therapeutic profile for SCH treatment, particularly in combination with atypical APDs.

Policy of full disclosure: None.

P-04.094 Hypoglycemia associated with second generation antipsychotic agents

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Objective: Prolonged hypoglycemia is fatal and it can cause seizures, permanent neurologic damage, or death. We report three cases of hypoglycemia in non-diabetic non-obese inpatients who had schizophrenia and were being treated with a second generation antipsychotic (SGA). The clinical findings of hypoglycemia emerged typically 2–3 hours after meals in all patients after increasing the dose of SGAs. Hypoglycemia was verified with the oral glucose tolerance test in all cases.

Results: Case 1 – A 27 year old woman who took 400 mg of quetiapine a day complained of dizziness, tremor, and palpitations. These symptoms worsened with a 600 mg daily dose of quetiapine. At this point, her blood glucose three hours after lunch was low. Her symptoms (tremor, irritability) resolved after oral sugar intake. Case 2 – A 53 year old man received an oral glucose tolerance test (OGTT) on two successive risperidone doses at 6 mg a day and 8 mg a day. His plasma glucose was markedly low two hours after the test with 8 mg daily risperidone. Although he complained of tremor and palpitations after meals while taking 8 mg of risperidone a day, these symptoms were absent with 6 mg a day. Case 3 – A 32 year old woman received an OGTT while taking two successive doses of olanzapine – 10 mg a day and 20 mg a day. With 10 mg a day she did not have clinical symptoms of hypoglycemia or low plasma glucose during OGTT. Taking 20 mg a day she exhibited irritability after meals and marked hypoglycemia during testing.

Conclusion: Because hypoglycemia generates symptoms of adrenergic stimulation, such as irritability and anxiety, recognition of the possible link between SGAs and hypoglycemia can prevent missed cases in the future and improve differential diagnosis of exacerbation of schizophrenia.

Policy of full disclosure: None.

P-04.095 Olanzapine decreases cannabinoid CB1 receptors in the hypothalamus and brainstem, possibly through muscarinic M3 receptor antagonism

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Objective: Olanzapine can cause weight gain by unknown mechanisms. The endocannabinoid system is implicated in energy regulation through the CB1 receptor (CB1R). We previously reported olanzapine decreases CB1R binding density in the dorsal vagal complex (DVC), which is involved in the regulation of food intake, however effects in the hypothalamus are unknown. The pathway for olanzapine's regulation of CB1R is unclear as olanzapine has no affinity to CB1R, but is a muscarinic M3 receptor (M3R) antagonist. Presynaptic muscarinic M3 receptors (M3R) can regulate endocannabinoid release and antipsychotic affinity to M3R can be used to predict its weight gain liability. Therefore, we examined the relationship between CB1R and M3R binding density in the hypothalamus and DVC following olanzapine treatment.

Methods: Rats were treated with olanzapine (0.75, 1.5, 3.0 or 6.0 mg/kg/day, orally 3x/day, n=6/group) or vehicle (control) for 14-days. CB1R (using [3H]SR-141716A) and M3R (using [3H]4-DAMP, pirenzipine and AF-DX116) binding densities were examined in the arcuate nucleus (Arc), ventromedial hypothalamus (VMH) and DVC. Correlations between binding, weight gain and food intake were analysed.

Results: Olanzapine significantly decreased CB1R and increased M3R binding density in the Arc, VMH and DVC. CB1R negatively correlated to weight gain in the VMH and DVC, whilst M3R in the Arc and DVC positively correlated to weight gain and food intake. CB1R negatively correlated to M3R in the Arc, VMH and DVC.

Conclusion: Use of CB1R-specific ligand confirms our previous report of an olanzapine-induced decrease in CB1R in the DVC, with findings extending to the hypothalamus. Increased M3R binding may be a compensatory up-regulation in response to olanzapine's

antagonism. Olanzapine may influence CB1R through the M3R to stimulate hyperphagia and weight gain.

Policy of full disclosure: None.

P-04.096 Correlation between PANSS and personal and social performance (PSP) improvements in patients with schizophrenia by paliperidone ER treatment

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Objective: By exploring the correlation between five psychopathology domains (negative, positive, excitement, cognitive, and depression/anxiety) measured by PANSS and the four functional domains measured by PSP (Personal and Social Performance) in patients treated with paliperidone ER, this study was trying to establish the possible links between symptom controls and functional improvement.

Methods: This was a 12-week multi-center, open-label, prospective study, conducted in Taiwan from 2008–9. Totally 426 subjects with schizophrenia who had agreed to receive paliperidone ER treatment, and stayed through the first 4 week switching/titration period were enrolled into this study.

Results: In this study, 350 of the 426 subjects completed the 12 weeks follow up. PANSS score was improved from 89.8±29.6 at baseline to 72.7±26.3 at 12th week, while PSP improved from 47.0±16.3 at baseline to 56.6±14.3 at 12th week. The Canonical correlation between PANSS and PSP was 0.7456 at baseline and 0.7579 at study end. It is interesting to note that the cognitive subscale score had a highest correlation (0.9128) with PSP after paliperidone ER treatment. Excitement subscale scores correlated well with disturbing and aggressive behaviors (0.6939 before treatment, and 0.7015 after treatment). Negative symptoms and cognitive subscale scores also correlated with socially useful activities, personal and social reationships, self-care scores of the PSP.

Conclusion: This study demonstrated the effectiveness of paliperidone ER treatment and the correlations found suggest that certain symptom domains might have more impact on patient functioning. Improvement in these symptom domains is important for function recovery for patients with schizophrenia.

Policy of full disclosure: None.

P-04.097 Time effects of food intake on the pharmacokinetics of the novel potent dopamine D2 and serotonin 5-HT2 antagonist blonanserin

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Objective: Blonanserin is a novel potent dopamine D2 and serotonin 5-HT2 antagonist for the treatment of schizophrenia. The aim of this study was to evaluate the time effects of food intake on the pharmacokinetics of blonanserin.

Methods: An open, randomised, crossover study was conducted. Ten healthy male volunteers took a single 2-mg oral dose of blonanserin under the following conditions: fasting, 30 min before eating a standard meal, or 30 min, 2 h or 4 h after eating the meal. Serial blood samples were taken up to 24 h after oral administration of blonanserin.

Results: Blonanserin was rapidly absorbed under all conditions, and there was no difference in the values of tmax between the fasting and the four fed states. The ratios (90% confidence intervals) of the geometric means compared to the fasting condition for Cmax and AUClast were as follows: for dosing 30 min before meal intake, 4.30 (2.01, 9.18) and 4.86 (2.31, 10.19), respectively; for dosing 30 min after meal intake, 3.39 (1.59, 7.25) and 3.01 (1.44, 6.32), respectively; for dosing 2 h after meal intake, 3.72 (1.74, 7.95) and 3.56 (1.70, 7.48), respectively; and for dosing 4 h after meal intake, 2.38 (1.11, 5.08) and 2.55 (1.21, 5.35), respectively.

Conclusion: Food intake increased the Cmax and the AUClast by more than 100% for all time intervals investigated in this study. The extent of absorption and overall bioavailability of blonanserin were therefore significantly affected by dosing between 30 min before and 4 h after meal intake.

Policy of full disclosure: None.

P-04.098 Improved treatment outcomes following a switch from risperidone to olanzapine in a 1-year naturalistic study of schizophrenia patients in Japan

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Objective: This study assessed the clinical and functional outcomes following a switch from risperidone to olanzapine in a 1-year naturalistic study of schizophrenia patients in Japan.

Methods: We used data from a large 1-year prospective, multicenter, observational non-interventional study of individuals who were initiated on olanzapine for the treatment of schizophrenia in Japan. Current analysis focused on patients who were switched at study entry from risperidone to olanzapine (n=258). Changes from baseline to endpoint on clinical and functional measures were assessed with validated measures. Repeated measures analysis was employed for longitudinal measures.

Results: At study entry, 45% were inpatients and 55% outpatient. Participants were in their early 40s' with mean illness duration of 14 years. About half were male. Most were switched from risperidone to olanzapine due to poor medication efficacy (67.8%) and fewer were switched due to medication intolerability (29.1%). Most patients (67.8%) completed the 1-year study. During the follow up period, patients experienced clinically meaningful and statistically significant ($p<0.05$) improvements in overall symptom levels, on positive, negative, depressive and cognitive symptoms, on quality of life and on paid work rates. Most patients (59.2%) demonstrated treatment response to olanzapine and 43.4% experienced symptom remission. Mean weight gain was 2.19 kg, with one- third of patients experiencing clinically meaningful weight gain (at least 7% of baseline weight). Most patients (76.0%) maintained their initial BMI category.

Conclusion: In this 1-year naturalistic study of patients with schizophrenia in Japan, inpatients and outpatients who were switched from risperidone to olanzapine experienced clinically meaningful and statistically significant improvements in their clinical and functional outcomes, which were accompanied by a clinically meaningful weight gain for one-third of the patients. Current findings highlight the favorable benefit to risk profile of switching to olanzapine therapy following treatment failure on risperidone among schizophrenia patients in Japan.

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P-04.099 Long-term outcomes after switching from typical antipsychotics to olanzapine among schizophrenia patients in Japan

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Objective: To assess the long-term clinical, functional and safety-related outcomes following a switch from typical antipsychotics to olanzapine in the treatment of schizophrenia patients in Japan.

Methods: Using data from a large 1-year prospective, multi-center, observational non-interventional study of olanzapine for the treatment of schizophrenia in Japan, patients who were switched from any oral typical antipsychotic to olanzapine were identified. Changes from baseline to endpoint in clinical and functional measures and in body weight were evaluated. Mixed model with repeated measures, controlled for baseline demographics, were applied.

Results: Of 262 patients who switched from typical antipsychotics to olanzapine, 41% were outpatients and 59% inpatient. Most of these patients (71.0%) were switched due to poor medication efficacy and 25.6% due to medication intolerability. Participants, on average, were chronically ill, in their late 40's, with a 20-year history of schizophrenia. About half (51.9%) were male. Most patients (71.4%) completed the 1-year study. Clinically meaningful and statistically significant ($p<0.01$) improvements from baseline to the final study visit were observed in patients' illness severity and quality of life, with improvements in overall symptom severity level and in positive, negative, depressive and cognitive symptoms. Most patients (58.3%) demonstrated a treatment response to olanzapine and 47.4% achieved