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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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P-04. Antipsychotics

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 these in-
terests, in 15 major languages. DAI has been primarily used in phar-
maceutical 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 cornerstone of assessing acc-
cceptability and effectiveness of antipsychotic drugs. Clinical trials, facilitated research into clinical and biological aspects of patients’ preferences to psychotropic drugs, and pioneered the study of sub-
jective 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 (SCZ) 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 SCZ may involve brain prefrontal hypodopaminergic. Others have shown that adjunt GAL to the atypical APD risperidone increased brain prefrontal dopamine release and reversed social interaction impairment in mice. Also, nAChRs, blockage, but not cholinergic muscarinic receptor (mAChRs) 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 meca-
mylamine (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 nAChRs modulating properties of GAL are likely to contribute to pro-cognitive activity in SCZ, any contribution to antipsychotic activity by GAL seems medi-
at ed 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 combina-
tion 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 schizo-
phrenia and were being treated with a second generation anti-
psychotic (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 queti-
apine 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 symp-
toms (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 plas-
ma 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 symp-
toms of hypoglycemia or low plasma glucose during OGTT. Taking 20 mg a day she exhibited irritability after meals and marked hy-
oglycemia during testing.

Conclusion: Because hypoglycemia generates symptoms of adre-
nergic 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 mechan-
isms. 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 regula-
tion 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 anti-
psychotic affinity to M3R can be used to predict its weight gain liabil-
ity. Therefore, we examined the relationship between CB1R and M3R binding density in the hypothalamus and DVC following olan-
zapine 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]-SR141716A) and M3R (using [3H]-D-
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
agonist. 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 dimensions (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 control 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 73.6 ± 13.2 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 0.7597 at study end. It is interesting to note that the cognitive subscale score had a highest correlation (0.928) with PSP after paliperidone ER treatment. Excitement subscale scores correlated well with disturbing and aggressive behaviors (0.693) before treatment, and 0.705 after treatment. Negative symptoms and cognitive subscale scores also correlated with socially useful activities, personal and social relationships, 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 blasenar

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Objective: Blasenar 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 blasenar.

Methods: An open, randomised, crossover study was conducted. Ten healthy male volunteers took a single 2-kg oral dose of blasenar 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 blasenar.

Results: Blasenar 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, 1.18 (1.0, 1.36) and 1.08 (0.96, 1.22), 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 (1.76, 7.48), respectively; and for dosing 4 h after meal intake, 2.38 (1.11, 5.08) and 2.53 (1.21, 5.35), respectively.

Conclusion: Food 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 blasenar were therefore significantly affected by dosing between 30 min before and 4 h after meal intake.

Policy of full disclosure: None.