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Reduce the olanzapine-induced body weight gain with histamine H1 receptor agonist betahistine in rats

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Abstract

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Keywords

rats, h1, reduce, receptor, agonist, betahistine, olanzapine, induced, body, weight, gain, histamine

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Methods: a) Reported cases of NIC and related literature regarding its relationship to NMS were reviewed. (b) 18 NIC episodes, out of 127 episodes of acute catatonia prospectively identified, were analyzed, noting their clinical presentations, laboratory findings, and responses to treatments. The progression of symptoms in each NIC episode was reviewed. All catatonia episodes received benzodiazepines. The responses to benzodiazepines of NIC episodes were compared to that for catatonia episodes associated with mania and schizophrenia.

Results: (a) NIC has been associated with dystonia, parkinsonism, and rarely choreoathetotic movements. Case reports described the successful use of various medications – anticholinergics, amantadine, benzodiazepines – in its treatment. The dystonic and parkinsonian forms of NIC showed different clinical courses and treatment responses. Confusion surrounds the relationship of NIC to NMS. It has been suggested that NIC is a variant of NMS. (b) The NIC episodes presented predominantly in the stuporous form associated with parkinsonism. Delirium, autonomic abnormality, and elevated serum creatine phosphokinase were all common. NMS was diagnosed in 3 episodes (17%). The 3 catatonia groups did not differ significantly in their responses to benzodiazepines; 78% (14/18) of NIC, 75% (12/16) manic catatonia, and 67% (34/51) schizophrenic catatonia showed full responses. A spectrum of presentation across episodes was noted with “simple” NIC without delirium, autonomic disturbances or fever at one end and NMS or “malignant” NIC at the other end. Symptoms in individual episodes showed a similar continuum progression.

Conclusion: Findings of this study support that NIC and NMS are disorders on the same spectrum and NIC be regarded as a variant of NMS.

Policy of full disclosure: None.

P-04.050 Bone density in chronic schizophrenia and schizoaffective disorder with long-term antipsychotic treatment

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Objective: Patients with schizophrenia and Schizoaffective disorder is associated with high rates of low bone mineral density but the etiology of which remains obscure. Previous studies explained by the prolactin-raising properties of antipsychotic medication. This study investigate the association between prolactin level and low bone mineral density and to get comprehension into etiology of low bone mineral density.

Methods: In a cross-sectional study, 45 schizophrenic or schizoaffective patients were the participants in the study and 20 of them were treated with risperidone, 15 with olanzapine and 10 with clozapine. All patients had been monotherapy for at least 1 years. The authors used dual X-ray absorptiometry to determine bone mineral density. A blood sample was taken to measure prolactin and sex hormone axis measures.

Results: There was no significant statistical difference between patients treated with risperidone, olanzapine and clozapine in BMD z scores. Bone mineral density showed highly negative correlation with Positive and Negative Syndrome Scale's negative subscale. Correlations between the levels of prolactin were not significance.

Conclusion: These results suggest that the high rates of low bone mineral density may not result from hyperprolactinemia as a consequence of prolactin raising antipsychotics. But these finding support to more attention about activities, calcium intake, sunlight exposure on patients with schizophrenia and schizoaffective disorder.

Policy of full disclosure: None.

P-04.051 Reduce the olanzapine-induced body weight gain with histamine H1 receptor agonist betahistine in rats

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Objective: Atypical antipsychotic drug olanzapine is effective at treating the multiple domains of schizophrenia through its binding profiles to various neurotransmitter receptors, including serotonergic,

muscarinic and dopamine D2 receptors. Olanzapine is also a potent histamine H1 receptor antagonist, and the high H1 receptor affinity is a predictor for the development of antipsychotic-induced weight gain/obesity. Betahistine acts as a modulator of the histaminergic system and has both H1-agonistic and H3-antagonistic activity in the brain. This study aimed to investigate whether betahistine could be used to treat olanzapine-induced weight gain in a rat model.

Methods: Female Sprague Dawley Rats (n=8/group) were administered with olanzapine (3 mg/kg/day), betahistine (8 mg/kg/day), olanzapine plus betahistine, or vehicle (control) orally 3 times/day for 2-weeks. Body weight and food were recorded.

Results: Compared to the control group, sole olanzapine treatment significantly increased body weight and food intake (p<0.05); but sole betahistine treatment did not affect the body weight and food intake. Combined treatment of these two drugs showed that betahistine tended to relieve body weight gain caused by olanzapine (p=0.067).

Conclusion: The preliminary results suggested that betahistine may be used to reduce the olanzapine-induced weight gain. Further analysis of H1 receptors binding in the animals treated with single or combined olanzapine-betahistine treatments will reveal the neuropharmacological mechanisms underlying these treatments. This study may unravel the central interaction sites of H1 receptor for prevention of weight gain in schizophrenia. This has implications for supporting clinical trials for the improvement of olanzapine induced side-effects obesity.

Policy of full disclosure: None.

P-04.052 Central nervous system effects of the interaction between single doses of risperidone and repeated daily doses of the 5-HT6 antagonist SB742457 in healthy male volunteers

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Objective: 5-HT6 receptor antagonists may play a role in conditions associated with cognitive decline, such as Alzheimer's disease or possibly schizophrenia. The 5HT6 antagonist SB742457 could become a treatment for these disorders. Since atypical antipsychotics are used to treat schizophrenia, the interactions between the 5HT6 antagonist SB742457 and risperidone were investigated, considering possible co-medication.

Methods: This was a randomized, double-blind, two-way crossover interaction study of multiple doses of SB742457 50 mg with single dose risperidone 2 mg in 18 healthy subjects, using the NeuroCart central nervous system battery to measure pharmacodynamics.

Results: Combination treatment was well tolerated, and produced a small increase of risperidone C_{max} (ratio 1.19; 90% CI 1.04, 1.35) but did not affect SB742457 pharmacokinetics. Risperidone decreased (difference; 95% CI) saccadic peak velocity (-70.7 deg/sec; -91.3, -50.1), tapping (-5.2 taps/10 sec; -7.8, -2.6), tracking (-4.8%; -7.1, -2.5), alertness (11.8 mm; 2.7, 20.8) and body sway (ratio 1.24; 1.07, 1.44); and increased EEG theta power (ratio 1.17; 1.03, 1.33) and prolactin (4.36 h*ng/mL; 3.65, 5.19). The combination increased EEG alpha (ratio 1.25; 1.11-1.40) and beta power (1.14; 1.03-1.27). SB742457 alone had no significant effects.

Conclusion: SB742457 and risperidone have limited and clinically irrelevant pharmacokinetic interactions. Most risperidone effects are consistent with previous data. EEG alpha and beta increases are incompatible with enhanced risperidone activity, but could signify mild stimulating effects of the combination. Potential cognitive effects of SB742457 remain to be established.

Policy of full disclosure: This study was sponsored by GlaxoSmithKline.