and 10 µM) decreased live cell counts, but not survival rate in undifferentiated HL-60 cells and under granulocytic differentiation. Histamine H4 receptor mRNA was expressed in HL-60 cells, whereas the expression gradually decreased under granulocytic ATRA-differentiation. Thioperamide, a histamine H4 receptor antagonist or DEVD-FMK, a caspase-3 inhibitor protected clozapine-induced decrease of survival rate, but not of live cell counts. 4-Methylhistamine, a histamine H4 receptor agonist as well as clozapine decreased survival rate and live cell counts. **Conclusion:** HL-60 cells under granulocytic differentiation were vulnerable for cytotoxicity of clozapine and would be in vitro assay systems for hematopoietic toxicity. Histamine H4 receptor is involved in development of clozapine-induced hematopoietic toxicity with apoptosis, and may be one of the target for preventing it in process of granulocytic differentiation.

### PM428

**Combination of Clozapine with Long Acting Injectable Antipsychotics in Treatment Resistant Schizophrenia: Preliminary Evidence from Health Care Utilization Indices**

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**Abstract**

**Objectives:** Clozapine is indicated for Treatment Resistant Schizophrenia (TRS) yet only 30-60% of patients will respond to optimum treatment. There have been studies of clozapine augmentation with oral second generation antipsychotics (SGA) with mixed results but no studies considering the combination with long acting injectable (LAI) antipsychotics. This study attempts to establish the efficacy of the combination of clozapine and LAI antipsychotics in TRS.

**Methods:** A mirror-image study design was employed to review health care utilization measures 2 years pre and post combination of clozapine with a LAI (either first generation antipsychotic (FGA) or SGA) in a small sample of patients (N=20) with chronic psychotic disorders followed by the Assertive Community Treatment service in Calgary, Alberta.

**Results:** Paired sample t tests showed a statistically significant reduction in average ED visits in the two post combination with an average 1.8 fewer ED visits (95%CI = [0.58 to 3.02], p=0.024). There was also a statistically significant reduction in number of hospital admissions in the 2 year post combination with a mean reduction of 0.85 admissions (95%CI = [0.36 to 1.34], p=0.008). There was no statistically significant reduction in hospital bed days between pre- and post-combination.

**Conclusions:** The combination of clozapine and a long acting injectable antipsychotic appears to reduce health care utilization in terms of ED visits and number of hospital admissions. Future research will investigate the effects of this combination on psychopathology and health related quality of life outcomes in this patient population.

### PM429

**Comparison of haloperidol and blonanserin on development of dopamine supersensitivity after chronic treatment**

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**Abstract**

**Background:** Long-term treatment with antipsychotic drugs in patients with schizophrenia occasionally causes dopamine supersensitivity psychosis (DSP), which is characterized by acute exacerbation of psychiatric symptoms due to discontinuation of antipsychotics, tolerance to the therapeutic effects of antipsychotics, and presence of tardive dyskinesia. Many studies have shown that DSP is attributed to compensatory upregulation of dopamine D3 receptor (D3R) density as a result of chronic and excessive blockade of D3Rs by antipsychotics (Iyo et al., 2013).

**Objective:** Blonanserin (BNS) is an atypical antipsychotic drug, which has high affinity for D3R, dopamine D3 receptor (D3R), and 5-HT2A receptor and weak or very low affinity for other receptors. The present study investigated whether chronic treatment with BNS causes DSP.

**Method:** Male Wistar rats (6-week-old) were orally administered haloperidol (HPD) and BNS, at doses of 1.1 mg/kg and 0.78 mg/kg, respectively, or vehicle twice daily for 28 days. These doses were equivalent to two times the 50% effective doses of HPD and BNS in a methamphetamine-induced hyperlocomotion test in rats, respectively. Seven days after drug discontinuation, a quinpirole (0.5 mg/kg, sc)-induced hyperlocomotion test or a radioligand binding assay using [H-]raclopride for striatal D3R was conducted. We also investigated the effects of chronic treatments with HPD and BNS on D3R and D3R mRNA levels in five brain regions.

**Results:** Chronic treatment with HPD significantly increased locomotor activity and D3R density (i.e. Bmax) compared with vehicle treatment. In contrast, chronic BNS treatment did not affect both locomotor activity and D3R density. There were no changes in D3R and D3R mRNA levels in chronic HPD- and BNS-treated groups, respectively.

**Conclusion:** The present results suggest that long-term treatment with BNS is less likely to cause DSP compared to treatment with the typical antipsychotic drug, HPD.

### PM430

**Blonanserin reversed phencyclidine-induced novel object recognition deficit and induced cortical dopamine and acetylcholine efflux through dopamine D3 receptor antagonism**

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**Abstract**

**Objective:** Blonanserin (Blon) is an atypical antipsychotic drug (AAPPD) with comparable affinity to D3 and D2 receptors. The purpose of this study was to determine the ability of Blon to enhance cortical neurotransmitters efflux, determine the role of D2 receptor antagonism in that process, and determine the role of D3 receptor blockade to improve the deficit in novel object recognition (NOR) in sub-chronic phencyclidine (PCP)-treated rats, a model of schizophrenia.

**Methods:** Guide cannula with dummy probes were placed to the medial prefrontal cortex (mPFC) and dorsal striatum (dSTR) for microdialysis in mice. Rats received vehicle or PCP for 7 days, followed by a 7-day washout for the NOR study. The D2 receptor antagonist, NGB2904 (NGB) or Blon was administered to rats 30min prior to acquisition. Another group of rats received a combination of sub-effective doses (SED) of NGB and Blon.

**Results:** Blon increased DA, norepinephrine (NE) and ACh efflux in mPFC and dSTR. NGB increased DA and Ach, but not NE efflux,
in mPFC and DA efflux in dSTR. NGB and Blo improved the scPCP-induced NOR deficit. The combination of SED NGB and Blo improved the NOR deficit.

Conclusions: D3 receptor blockade may contribute to the ability of Blo to increase cortical ACh and DA efflux, as well as to restore NOR in scPCP deficit. D3 receptor blockade may be an important component of the efficacy of Blo to enhance neurotransmitter efflux and improve cognitive function.

**PM431** Effects of iloperidon and nemonaprid on depression, anxiety-like behaviour and locomotion: Altered gene expression levels of FGF2, synapsin and NGF in the hippocampus of mice

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**Abstract**

Atypical antipsychotics are known to possess more beneficial effects on emotional dysfunction in schizophrenia compared to classical antipsychotics. Iloperidon and nemonaprid are new atypical antipsychotics drugs used in clinics. This study aimed to investigate the effects of these drugs on depression-, anxiety-like behaviors and locomotion in naive mice, using forced swimming test (FST), elevated plus maze (EPM) and open field tests. Moreover the effects of drugs on expression levels of FGF2, synapsin and NGF in the hippocampus of mice were determined using quantitative real-time polymerase chain reaction. Mice were treated chronically with iloperidon (0.5 and 1 mg/kg) and nemonaprid (0.5 and 1 mg/kg) for 15 days and drugs were also administered intraperitoneally 60 min before the tests.

Our study revealed that: (1) In FST test, iloperidon (0.5 and 1 mg/kg, p<0.01, p<0.001; respectively) significantly decreased immobility time while nemonaprid had no significant effect. (2) In EPM test, iloperidon (0.5 mg/kg; p<0.05) significantly increased % time spent in open arm’s while nemonaprid insignificantly increased this parameter. Nemonaprid (1 mg/kg; p<0.05) significantly increased % open arm entries while iloperidon (0.5 mg/kg) also insignificantly increased this parameter. (3) In open field test, iloperidon (1 mg/kg; p<0.05) significantly increased the total distance moved while nemonaprid (0.5 and 1 mg/kg; p<0.05, p<0.01; respectively) significantly decreased this parameter. Nemonaprid (0.5 and 1 mg/kg; p<0.05, p<0.001; respectively) significantly decreased the speed of the animals. (4) Chronic administration of iloperidon and nemonaprid significantly increased the expression of FGF2, synapsin and NGF and thus may promote neuroplasticity via the up-regulation of neutropic factors.

So both iloperidon and nemonaprid exerted anxiolytic effects while only iloperidon had antidepressant effects; and these drugs had opposite effects on locomotion. Thus iloperidon seems to possess superior effects compared to nemonaprid in schizophrenic patients with mood disorders.

**PM432** Evaluation of the extrapyramidal side effects (EPS) liability of NMDA receptor glycine-binding site agonists

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**Abstract**

Glutamatergic system is implicated in pathogenesis of schizophrenia (Glutamate hypothesis) and stimulants for NMDA receptor glycine-binding sites are expected as novel medications for schizophrenia, especially for negative symptoms and cognitive impairments. However, the actions of NMDA receptor glycine-binding site agonists in modulating antipsychotic-induced EPS remain to be clarified. In this study, we examined the effects of the glycine-site agonists of NMDA receptors, D-cycloserine, D-serine and glycine on haloperidol-induced EPS (i.e., bradykinesia and catalepsy) in rodents. NMDA receptor glycine-binding site agonist, D-cycloserine (3–30 mg/kg, i.p.) significantly improved haloperidol (1 mg/kg, i.p.)-induced bradykinesia in a dose-dependent manner. D-serine (100–1000 mg/kg, i.p.) also reduced haloperidol-induced bradykinesia, but glycine (30–300 mg/kg, i.p.) did not. Attenuation of haloperidol-induced bradykinesia by D-cycloserine was reversed by the NMDA antagonist MK-801 or the NOS inhibitor L-NAME. In addition, microinjection of D-cycloserine (10 μg/μl) into substantia nigra or dorsolateral striatum, both significantly attenuated the EPS induction. The present results indicates that activation of glycine-binding sites of NMDA receptors alleviates the antipsychotic-induced EPS, implying that the glycine-binding site agonists of NMDA receptors, like D-cycloserine, provide benefits not only for the efficacy, but also in terms of EPS induction in the treatment of schizophrenia.

**PM433** Prenatal risperidone exposure impaired cognitive function and enhances prepulse inhibition of acoustic startle reflex in adult male mice

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**Abstract**

Objective: Psychiatric disorders are relatively common among women of childbearing age. However, the use of antipsychotics during pregnancy remains controversial. Previous animal studies indicate that prenatal exposure to antipsychotics may impair the cognitive function of adult offspring. The current study investigated whether prenatal risperidone treatment would produce long-term effects on behavior in adult male offspring.

Methods: All plug-positive female C57BL/6 mice were randomized two groups. Pregnant dams of both groups received a daily intraperitoneal injection of risperidone (2mg/kg body weight) or vehicle from embryonic day 6 to 16. Pups were reared by their biological mothers. Experiment 1 examined the short-term effects of prenatal risperidone on hippocampal synaptic protein expression levels of the male pups on P10. In experiment 2, mice were examined in the spontaneous locomotion, spatial object recognition, elevated plus maze and prepulse inhibition of acoustic startle reflex sequentially on P75.

Results: The data showed no significant difference in the body weight of treated offspring as compared to those of the controls. The postsynaptic protein PSD-95 in the hippocampus of male pups was downregulated by prenatal risperidone exposure. The total distance traveled in the novel environment of the open field test did not reveal any differences between two groups. Male mice offspring exposed to risperidone showed deficits in novel object recognition when compared with control group. Prenatal risperidone treatment has no significant effects on anxiety-related behavior in adult male offspring. However, the offspring of risperidone group showed significantly potentiated PPI.

Conclusion: Prenatal exposure to risperidone during a critical period of brain development leaves a lasting imprint on the...