Aims: To assess the effects of clozapine, olanzapine and haloperidol on cholesterol triglycerides and glucose levels in aggressive schizophrenic patients. To determine whether changes in cholesterol are related to aggression.

Methods: 100 physically aggressive schizophrenics were assigned to a randomized, double-blinded, parallel-group, 12-week treatment. There were 33, 34, and 33 subjects in the clozapine, olanzapine, and haloperidol groups, respectively. Fasting cholesterol, triglycerides and glucose were collected at baseline and at end of study. All aggressive events were recorded.

Results: 95 patients provided blood samples. There were differences among the three medications in weight change (F=7.6, df=2,93; p<.001), with greater weight gain for clozapine and olanzapine than haloperidol. There were significant differences among the 3 groups in changes in cholesterol (F=4.5, df=2,93; p=.01; greater increase for clozapine than for haloperidol, p <.01), triglycerides (F=5.5, df=2,93; p<.01; greater increase in clozapine than haloperidol, p <.01 and olanzapine p=.01) and glucose (F=3.9, df=2,93; p=.02; greater increase for clozapine than for haloperidol, p <.01 and than olanzapine, p=.05). We investigated the relationship to aggression, by dividing patients into high and low cholesterol groups through a median split. Patients in the low cholesterol group were more physically aggressive during the study than those in the high group (F=4.94, df=2,92, p=.03). A significantly higher percentage of the patients in the haloperidol group than in the clozapine group had values below the median.

Conclusions: Clozapine treatment is associated with increases in serum glucose, triglycerides and cholesterol. This increase in cholesterol may explain in part its antiaggressive effect.

P0275

Tardive dystonia in neuroleptic treated bipolar disorder and treated with clozapine - a case report and review of the literature

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Tardive dystonia is an extrapyramidal adverse effect that can arise after prolonged use of dopamine receptor antagonists and is characterized by sustained involuntary muscle contractions frequently causing twisting and repetitive movements or abnormal postures. This occurs most commonly in the head and neck region and can begin as a focal dystonia, which then progresses to a segmental form. The prevalence of tardive dystonia in neuroleptic treated individuals ranges from 0.4% to 4%. Up to half of the patients who develop tardive dystonia tend to do so in the first 5 years of neuroleptic exposure, with onset earlier in males than females. Tardive dystonia tends to be persistent with a low remission rate of 10 percent in 6.6 years. Previous cases of tardive dystonia were mainly reported in patients with schizophrenia spectrum disorders. We report a case of tardive dystonia in a neuroleptic treated bipolar disorder and was treated with clozapine.

Tardive dystonia has been associated with both typical and atypical neuroleptic exposure, such as clozapine, olanzapine, risperidone and ziprasidone. Several authors have suggested the use of clozapine in the treatment of tardive dystonia. The ability of clozapine to treat tardive dystonia may be related to D1 receptor antagonism. There have also been case reports of tardive dystonia treated by olanzapine and quetiapine. Botulinum toxin and dopamine-depleting drugs may also be effective. More recent reports suggested the use of deep brain stimulation of regions such as globus pallidus and subthalamic nucleus in the treatment of tardive dystonia.

P0276

Remission in patients with schizophrenia treated with risperidone long-acting injection: Results from the e-STAR project in Czech Republic and Slovakia

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Objective: Assess illness remission in patients with schizophrenia enrolled in the electronic-Schizophrenia Treatment Adherence Registry (e-STAR) in Czech Republic and Slovakia.

Methods: e-STAR is a secure web-based, ongoing, international, long-term observational study of patients with schizophrenia who initiate RLAI during routine clinical management. Data is collected retrospectively (1 year) and prospectively (2 years). Prospectively patients are evaluated for the following symptoms: delusions, conceptual disorganization, hallucinatory behaviour, mannerisms and posturing, unusual thought content, blunted affect, passive/apathetic social withdrawal, and lack of spontaneity and flow of conversation. Patients in whom all of these symptoms are absent, minimal or mild and within normal boundaries, stable, and do not interfere with thinking, social relations, and behaviour or functioning, were considered to be in cross-sectional remission and if this persisted for at least 6 months, they were considered to be in remission.

Results: 1,068 patients have been enrolled into e-STAR in Czech Republic and Slovakia; 280 patients have been followed for at least 12-months and were included. The majority were male (57.9%) with a diagnosis of schizophrenia or schizoaffective disorder (85.7%, 14.3% respectively) with a mean age of 37±12.1 years and a mean time since diagnosis of 9.2±9 years. The proportion of patients who met the criteria for cross-sectional remission increased from 2.4% at baseline to 37.9% at 12 months. After 12-months, 20.6% of patients met the criteria for illness remission.

Conclusions: Based on 12-month interim results, the proportion of patients who met the criteria for illness remission increased after initiating RLAI.

P0277

Improvements in illness severity and functioning in patients with schizophrenia treated with risperidone long-acting injection in The Netherlands

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Objectives: To assess changes in illness severity (Clinical Global Impression-Severity scale, CGI-S) and functioning (Global Assessment of Functioning, GAF) in patients initiated on risperidone long-acting injection (RLAI) during routine clinical practice and followed up for at least 12 months in the Netherlands.

Methods: e-STAR is an international, prospective, observational study of patients with schizophrenia who have been initiated with RLAI. Data are collected both retrospectively (1 year) and

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prospectively (2 years). Results presented in this report were based on data from patients with at least 12 months of available data in the Netherlands.

Results: There are 190 patients currently enrolled in the Netherlands and 118 patients have at least 12 months of available data. Of the 118 patients, the majority were male (62.7%) with a mean age of 37.7±11.5 years and a mean time since schizophrenia diagnosis of 11.1±21.5 years. The main reasons for switching to RLAI were lack of compliance (42.4%), adverse events (25.4%) and lack of efficacy (24.6%) with previous therapy. At 12 months, 66.9% of patients were still on RLAI treatment. Of the patients who discontinued RLAI, the mean time to discontinuation was 157.8±76.5 days. Mean CGI-S score significantly improved from 4.05±1.14 at baseline to 3.15±1.38 at 12 months ($p<0.001$). Additionally, the mean GAF score significantly improved from 43.8±12.0 at baseline to 55.2±14.7 at 12 months ($p<0.001$).

Conclusion: These interim results showed that treatment with RLAI in patients with schizophrenia was associated with significant improvements in disease severity and functioning.

P0278

Patient and physician satisfaction with risperidone long-acting injection: 18-month interim results from the electronic schizophrenia treatment adherence registry in Belgium

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Objectives: To evaluate patient and physician satisfaction with risperidone long-acting injection (RLAI) in patients with schizophrenia enrolled in the electronic Schizophrenia Treatment Adherence Registry (e-STAR) in Belgium.

Methods: e-STAR is an ongoing, international, prospective, observational study of patients with schizophrenia who start RLAI during their routine clinical management. Treatment satisfaction was assessed by the patient and physician on a 5-point scale from 'very good' to 'very bad'.

Results: 135 patients with mean age 40.9±14 years and duration of illness 9.5±9.2 years initiated treatment with RLAI, followed-up for at least 18 months were included in this analysis. At baseline, only 29.2% of patients expressed ''good'' or ''very good'' satisfaction while 21.1% of them expressed ''bad'' or ''very bad'' with their previous treatment. Similarly at baseline, 38.2% of physicians reported ''good'' or ''very good'' level of satisfaction and 14.6% rated their satisfaction as ''bad'' or ''very bad'' at that time. After initiation of RLAI, both patient and physician satisfaction with treatment improved dramatically. At 18 months, 76.5% of patients were satisfied ('good' or 'very good') with RLAI treatment and only 2.4% felt 'bad' and none reported 'very bad'. Physicians also expressed satisfaction with RLAI with 82.1% of them rated it as 'good' or 'very good'. Only one physician reported satisfaction below 'moderate'.

Conclusions: The low levels of patient and physician satisfaction with treatment prior to RLAI are likely to be a key decision driver to change therapy. After starting treatment with RLAI, both patient and physician satisfaction with the treatment substantially improved.

P0279

RGH-188, a d3/d2 dopamine receptor antagonist/partial agonist atypical antipsychotic candidate

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Objectives: RGH-188 is an orally active, potent dopamine D3/D2 receptor antagonist/partial agonist atypical antipsychotic for the treatment of schizophrenia and bipolar mania.

Results: RGH-188 displayed high affinity to human D3 receptors (Ki: 0.085 nM) and approximately six- and thirty-times less affinity to human D2, and 5-HT1A receptors. In various in vitro and in vivo assays RGH-188 behaved either as an antagonist or as a partial agonist on dopamine D3 and D2 receptors.

RGH-188 displayed potent antipsychotic activity (0.1-0.8 mg/kg) in rodent models such as apomorphine-induced climbing, amphetamine- and phencyclidine-induced hypermotility, conditioned avoidance response. It significantly improved the learning performance of rats (0.02-0.2 mg/kg) impaired by scopolamine in a water-labyrinth learning paradigm. RGH-188 showed no EPS liability as it produced no catalepsy up to 100-fold therapeutic range.

In a nonhuman primate positron emission tomography (PET) study using 11C-raclopride RGH-188 occupied striatal D2/D3 receptors in a dose dependent and saturable manner with an ED50 of 7 μg/kg iv. In healthy male subjects multiple administration of 1 mg RGH-188 resulted in over 70% D2/D3 receptor occupancy and the displacement showed correlation with RGH-188 and metabolites plasma levels.

After single administration to healthy volunteers, Tmax for RGH-188 was 3-4 hours and the terminal disposition half-life was 5-6 days. Over the dose range of 0.5-2.5 mg AUC of the parent drug was approximately dose-proportional. Systemic exposure to the pharmacologically active metabolites, desmethyl- and didesmethyl-RGH-188 was 20-30% and 50-200% of that to the parent, respectively.

P0280

Effect of clozapine and its metabolites on the intracellular calcium concentration in cells of isolated rat islets

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Objective: To study the different effects of clozapine and its metabolites on the intracellular Ca2+ concentration([Ca2+]i) in cells of isolated rat islets.

Methods: Under low or high glucose (3.3 mmol/L or 16.7 mmol/L), the cells of isolated rat islets was treated with 1 mmol/L clozapine, desmethyl-clozapine and clozapine N-oxide respectively, blank control group was also set, [Ca2+]i represented by fluorescence intensity was measured by laser scanning confocal microscope after cells were loaded with calcium sensitive fluorecent indicator Fluo-4/AM.

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