Performance-Based Skills Assessment (UPSA); the Personal and Social Performance (PSP) scale and Specific Level of Functioning (SLOF). We used the Receiver Operating Characteristic (ROC) curves analysis to distinguish between TRS and ARS. Confirmatory logistic regression and discriminant analysis were additionally used.

**Results:** Among clinical and demographic parameters, AUCs were significant for previous hospitalizations (AUC=.71; p=.004; SE=.068); antipsychotic dose (AUC=.73; p=.002; SE=.66); duration of illness (AUC=.67; p=.02; SE=.71) and NES score (AUC=.77; p=.0005; SE=.062). Moreover, significant AUCs were found for PANSS Negative subscale score (AUC=.68; p=.013; SE=.068); PANSS total score (AUC=.64; p=.05; SE=.071); QLS score (AUC=.73; p=.003; SE=.067); PSP score (AUC=.69; p=.012; SE=.68); all SLOF areas (AUC ranging from .76 to .68, p=.05), with the exclusion of Area4. A trend toward significance was found for Problem Solving (AUC=.63; p=.08). Among the whole significant variables, the highest specificity for diagnosis was found for NES score and previous hospitalizations (75% and 78.1%, respectively); the highest sensitivity for NES score (71.4%). Accordingly, Odds Ratio of being categorized as TRS were larger for NES score >21.5 (7.5), QLS score >57 (5.49), previous hospitalizations >1.45 and SLOF Area5 <43.5 (4.76 both).

Multivariate analysis supported results of ROC curve analysis. Stepwise logistic regression showed that the following variables were significant predictors of TRS/ARS status: previous hospitalizations, NES score, and antipsychotic dose among clinical variables (χ²=37.25, p<.0005, Nagelkerke R²=.48); PANSS Negative subscale score among psychopathology variables (χ²=7.75, p=.005, Nagelkerke R²=.16); QLS score among quality of life variables (χ²=7.91, p=.005, Nagelkerke R²=.16); SLOF Area2 among social functioning variables (χ²=18.05, p=.0005, Nagelkerke R²=.34). The descriptive discriminant analysis function was significant for clinical variables, (χ²=23.84, p=.001). The most relevant discriminator variables in this group were NES score, antipsychotic doses, and previous hospitalizations. Discriminant function was also significant for SLOF variables χ²=17.67, p=.007, with Area1 and Area3 scores ensuring the highest discriminative power. Discriminant function was only weakly significant for psychopathology and for quality of life variables (PANSS Negative subscale score and QLS score showed the highest discriminative power, respectively).

**Discussion:** Therefore, the evaluation of a few clinical factors may give solid and predictive information about patient potential to be responsive or non-responsive to antipsychotics. A patient exhibiting a combination of 2 or more lifetime hospitalizations; high NSS; high negative symptoms; low quality of life and psychosocial functioning has low possibility (less than approximately 20%, according to our data) to be responsive to antipsychotic agents.

S229. CAN LONG-ACTING INJECTABLE PALIPERIDONE DOSING BE OPTIMIZED WITH PLASMA LEVEL MEASUREMENTS?

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**Background:** Most people with schizophrenia respond robustly to antipsychotic medication but are at very high risk of relapse if these medications are stopped. Long-term maintenance treatment with antipsychotic medication can dramatically reduce the risk of relapse. With long-acting injectable antipsychotic medication (LAI), adherence is documented which may account for superior efficacy in relapse prevention reported in some studies. It is known that plasma antipsychotic levels vary greatly across individuals with standard doses of LAsI. Establishing the lowest effective plasma levels for relapse prevention may also help in minimizing side effects that may contribute to problems with adherence. This study was carried out to describe the plasma paliperidone levels associated with clinical stability in patients receiving the LAI, paliperidone palmitate. We predicted that higher paliperidone plasma levels would be associated with lower subjective well-being and greater levels of sexual dysfunction.

**Methods:** Patients with clinical diagnoses of schizophrenia and schizoaffective disorder attending specialized schizophrenia outpatient clinics at St. Joseph’s Healthcare Hamilton were invited to participate if they were receiving maintenance treatment with paliperidone palmitate. The study involved two visits, 3 to 4 weeks apart, on days that subjects were scheduled to receive consecutive injections of paliperidone palmitate. Plasma paliperidone levels and prolactin levels were drawn prior to the injection at Visit 1 and a second paliperidone levels was drawn at Visit 2. At Visit 1, a series of rating scales were also completed including the Subjective Well-being under Neuroleptic scale – Short version (SWN), the Changes in Sexual Functioning Questionnaire (CSFQ) and the Drug Attitude Inventory (DAI).

**Results:** Twenty-one subjects (11F/10M) provided informed consent for this study and had plasma paliperidone levels measured. Patients had been receiving LAI paliperidone for a mean of 18 months (SD = 11.4). Mean paliperidone levels at Visit 1 (n=21) and Visit 2 (n=18) were 34.9 ng/ml (SD = 20.0 ng/ml; range = 5.1–73.9 ng/ml) and 35.1 ng/ml (SD = 17.2 ng/ml; range = 9.0–67.5 ng/ml), respectively. Paliperidone plasma levels measured at Visit 2 were highly correlated with levels from Visit 1 (n=21; r= .89, p <.001). Plasma prolactin levels were correlated with levels of plasma paliperidone (r= 0.56, p <.01). Lower scores on the CSFQ – Sexual Desire factor were associated with higher levels of paliperidone (r= 0.61, p<.01) and prolactin (r= 0.56, p <.01). Higher paliperidone levels were associated with more negative scores on the Drug Attitude Inventory (r= 0.49, p <.05). Plasma paliperidone levels were not associated with scores on the SWN (n=21, r=-.41, p<.02).

**Discussion:** In patients receiving maintenance treatment with paliperidone palmitate, plasma paliperidone levels varied approximately 15-fold. Higher paliperidone levels were associated with more negative attitudes towards medication and more severe deficits in sexual desire but not with subjective well-being. Many stable patients had plasma level close to the 20ng/ml level which in PET studies leads to 65% dopamine D2 receptor occupancy, a level reported to be associated with antipsychotic response. Our findings raise the possibility that maintaining patients at levels just above the 20ng/ml level may be sufficient for relapse prevention but may spare the adverse effects such as sexual dysfunction associated with higher plasma levels. These results suggest that measuring plasma levels in patients receiving paliperidone as a LAI may be of value in identifying the minimum effective dose for prevention of relapse and side effects.

S230. LONG-TERM ANTPSYCHOTIC MEDICATION IN SCHIZOPHRENIA: BENEFITS, RISKS AND FOLLOW-UP: DATA FROM FINNISH COHORT STUDIES AND SYSTEMATIC REVIEW

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**Background:** Millions of people use antipsychotic medications. Thousands of clinicians (often non-psychiatrists) prescribe and monitor them every day. Existing research reports mostly favorable risk-benefit ratio during the first years of schizophrenia, but their risk-benefit ratio and maintenance efficacy in long-term is not clear.

Our aim was to:
1. analyze long-term antipsychotic use and its determinants in Finnish cohort samples, and
2. review the studies on benefits, risks, and follow-up and monitoring practices of long-term antipsychotic treatments.

**Methods:** 1. We used the data of population-based Northern Finland Birth Cohort 1966 (NFBC1966), and also Finnish therapeutic community data.
2. We performed a systematic literature search on long-term treatment effects, risks and monitoring of antipsychotic medication in schizophrenia.

**Results:** 1. In NFBC1966 in midlife, higher lifetime doses of antipsychotics were associated with alterations in brain morphometry, poorer neurocognition, and poorer clinical outcomes. Clinical follow-up was inadequate even in half of the schizophrenia cases. In therapeutic community cohort, maximal development of psychosocial care reduced the mean dose of antipsychotics in acute psychosis ward from 370 mg/day as chlorpromazine equivalents into 160 mg/day. 2. In the literature review, three main cornerstones in the high quality longitudinal use of antipsychotic medication were: a) high, evidence-based pharmacological quality, b) optimal adjuvant psychosocial therapies, c) sophisticated long-term prescription, monitoring and follow-up practices to minimize nonadherence and psychiatric and somatic failures.

In sum, antipsychotics are effective for acute and mid-term psychosis in prevention of relapses and excess mortality. Long term antipsychotic use especially in high doses may include major iatrogenic harms, as also poorly monitored withholding or discontinuing. When aiming for an optimal benefit-risk ratio and for balancing symptomatic, functional and somatic outcomes, the goal is to aim for lower ranges of effective dosing, as well as choosing an appropriate antipsychotic agent that causes minimal side effects, and to combine adjuvant psychosocial interventions in the treatment. The often recommended personalized smallest effective dose is not so simple but still a realistic strategy in current relapse prevention practices, where doses often are too large for safety reasons.

**Discussion:** Cohort-based register studies are useful in examining long-term medication effects although they contain a risk of residual confounding due to their observational design. However, randomized controlled trials in long, over 3–7 years of follow-up, are unrealistic. The systematic literature review demonstrates major open or conflicting questions in risk-benefit ratio related to long-term outcomes. Non-adherence and attrition are key problems in sustained antipsychotic medication. Standardized prescription and monitoring practices (not so much studied) might improve medication adherence and also outcomes. Current clinical guidelines advise us based on studies from first years of schizophrenia. There are only few and weak patient-level predictors of successful tapering and discontinuation of antipsychotic medication. In the future, clinical follow-up of medication can be improved by structured follow-up and planned continuity. Life span view of antipsychotic medication stresses careful documentation of doses, responses and harms, longitudinal planning and realization of medication as part of the whole treatment program, as well as individualized and tailored selection, dosing (dose as low as possible or minimal effective dose) and follow-up by a well-trained team.

**S231. THE ROLE OF DOPAMINERGIC AND GLUTAMATERGIC NEUROTRANSMISSION IN DELUSIONAL IDEATION AND SENSORY INFORMATION PROCESSING OF PATIENTS WITH SCHIZOPHRENIA IN COMPARISON TO HEALTHY HUMAN PARTICIPANTS**

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**Background:** The primary aim of this study was to generate neurobiological evidence regarding the impact of dopaminergic and glutamatergic neurotransmission on reasoning biases related to delusional ideation in patients with schizophrenia associated with impaired processing of sensory information. The proposed respective roles of these neurotransmitter systems have been encapsulated in the so-called dopamine- and glutamate-hypotheses of schizophrenia. From a behavioural perspective both reduced glutamate and enhanced dopamine levels are currently discussed as critical contributing factors to generate aberrant beliefs (glutamate) during information sampling and to generate confidence or expected precision (dopamine) during action selection. Hence, by modulating levels of glutamate and dopamine in the brain we hypothesized to induce reported impairments of patients with schizophrenia related to delusional ideation.

**Methods:** The study consisted of three aligned experiments: In the first two experiments a prospective interventional drug study was conducted with n=192 participants employing a randomized, placebo-controlled, double-blinded design on two parallel testing-groups, receiving either dopaminergic or glutamatergic neuromodulators: Experiment I: either 2.5mg haloperidol (D1/D2-receptor antagonist; HAL), 2.5mg bromocriptine (D2-receptor agonist; BRO), or placebo (PLC-1). Experiment II: either 120mg Dextromethorphan (NMDA-receptor antagonist, DXM), 250mg D-Cycloserine (NMDA-receptor agonist, CYC), or placebo (PLC-2). In the third experiment n=45 patients with schizophrenia (SZ) and n=45 healthy control participants (HC) matched for gender, age and IQ were investigated. All experiments employed a computerized (Matlab, Cogent) version of the Beadstask (Huq, Garety et al. 1988). In total participants processes 60 Beadstask trials subdivided into three levels of difficulty: (I) easy trials with a bias of 80–90% for one predominant bead color in a sequence, (II) difficult trials (60–70% bias), and (III) ambiguous trials (no bias, 50% likelihood). Additionally, the task consisted of three parts that were presented in a fixed order: an easy draws-to-decision condition, an easy probability estimates condition, and a difficult draws-to-decision condition.

**Results:** In accordance with foregoing studies, SZ patients showed significantly less draws to decision compared to HC (all p≤0.030). Explorative analysis across experimental conditions further revealed no significant differences for participants receiving DXM (NMDA-receptor antagonist) compared SZ patients (all p≥0.090), but obtained less draws to decision in the DXM group than all other groups. Whereas following HAL intervention the number of draws increased significantly compared to any other experimental group (all p≥0.048). Analyzing the probability estimates condition we quantified changes of probability estimates on an individual subject level whenever there was a change of bead color in a sequence (so called disconfirmatory evidence score, DES). In case of easy and difficult trial types we observed significantly higher DES scores in participants with SZ compared to HC (p≤0.003) and again obtained no differences between SZ and DXM (p=0.037).

**Discussion:** Our findings are supportive for a hypothesized relationship between neurotransmitter state alterations of glutamate and dopamine in patients with schizophrenia and the delusional ideation. Future analysis will focus on developing a computational behavioral model of cognitive processing of the Beadstask, implementing our neurobiological findings in order to further disentangle the neurobiological underpinnings of delusional ideation in patients with schizophrenia.

**S232. ALPHA7 NICOTINIC RECEPTOR AGONISTS REVERSE THE HYPERDOPAMINERGIC STATE IN THE MAM MODEL OF SCHIZOPHRENIA**

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**Background:** Most investigations into the pharmacology of schizophrenia have revolved around dopaminergic and glutamatergic neurotransmission; however, one neurotransmitter that has not received adequate attention is the cholinergic system. Indeed, several post-mortem, genetic and epimediologic studies link specifically the alpha7 nicotinic receptor (nAChR) to schizophrenia, and the potential use of alpha7 modulators as a treatment strategy is an active field of research. Nevertheless, studies to date have been limited to normal animals rather than on a validated neurodevelopmental model of schizophrenia. Moreover, knowledge about the differential impact of orthosteric and allosteric modulators in vivo is lacking. Thus, we investigated the effects of alpha7 nAChR modulation on dopamine...