Background: Optimal pharmacological efficacy is crucial in first-episode and early-episode schizophrenia and bipolar I disorder. Olanzapine (OLZ) is a highly efficacious antipsychotic indicated for the treatment of schizophrenia and bipolar I disorder. However, the clinical utility of OLZ may be limited by a propensity to cause significant weight gain and increased metabolic side effects, especially for patients early in the course of their illness. ALKS 3831 is composed of a flexible dose of olanzapine (OLZ) and a fixed dose of 10 mg of samidorphan (SAM), formulated as a bilayer tablet. ALKS 3831 has been shown in Phase 1 and Phase 2 studies to result in significantly less weight gain than OLZ while delivering equivalent antipsychotic efficacy. This Phase 3, 12-week study, is designed to evaluate the effect of ALKS 3831 on body weight in young adults early in the course of diagnosis of a serious mental illness, including a schizophreniform, schizophrenia, or bipolar I disorder diagnosis.
Methods: This is an international (Austria, Germany, Ireland, Israel, Italy, Poland, Spain, UK, and USA) two-arm, double-blind, active-comparator–controlled, multicentre study (planned N=250) that started enrollment in 2017. Key inclusion criteria are a primary diagnosis of schizophreniform disorder, schizophrenia, or bipolar I disorder; a body-mass index (BMI) of ≥18.0 and ≤27.0 kg/m2; and meeting specific criteria for duration of illness and prior antipsychotic exposure. Patients with a bipolar I diagnosis must be in the manic phase. In the US sites, men and women must be aged ≥16 to <40 years at screening, and in Europe, aged ≥18 to <40 years. Exclusion criteria include diagnosis of additional psychiatric conditions and use of prohibited drugs.
Results: Patients will be randomised 1:1 to receive either OLZ or ALKS 3831 treatment for 12 weeks. ALKS 3831 (OLZ + SAM) and matched OLZ + placebo (OLZ + PBO) will be provided as bilayer tablets to be taken by mouth once daily and doses will include ALKS 3831 (OLZ/SAM) 5/10 mg, 10/10 mg, 15/10 mg, 20/10 mg, or (OLZ/PBO) 5 mg, 10 mg, 15 mg, or 20 mg. The primary endpoint will be percent change in body weight from baseline to Week 12. Secondary and exploratory endpoints will include the proportion of patients who gain ≥7% and ≥10% of baseline body weight, metabolic parameters (change in fasting lipids and glucose), body composition measured through bioimpedance, clinical global impression, and safety, pharmacokinetic, and pharmacodynamic parameters. Patients will be offered a supportive clinical care programme during the 12-week treatment period, and also receive a daily medication-adherence monitoring and reminder system (via smartphones).
Discussion: Patients who complete the study will have the option to participate in an open-label 2-year extension of ALKS 3831 (based on clinician and patient decision).
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S227. A PROPOSED ALTERNATIVE BETWEEN DISCONTINUATION AND MAINTENANCE OF ANTIPSYCHOTICS: A GUIDED DOSE REDUCTION TRIAL FOR PATIENTS WITH REMITTED PSYCHOSIS

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Background: Early intervention at the beginning of schizophrenia and related psychotic disorders can get better treatment response. Once symptoms subsided, the majority of patients wish to discontinue medications, yet currently the mainstream opinions still recommend maintenance antipsychotic therapy because non-adherence to medication is the most significant risk factor to predict a relapse. However, recent longitudinal studies assessing patients in community for a longer term found that discontinuation of antipsychotics might not necessarily be parallel to poorer functioning. Also there are studies suggesting a lower percentage of dopamine occupancy by antipsychotic is acceptable in stable patients with psychosis. To elucidate such discrepancies, a hypothetical compromised approach "guided dose reduction, but not aiming at discontinuation" was proposed and an observational clinical trial was initiated since July 2017.
Methods: Outpatients with schizophrenia-related psychotic disorders under remitted states will be recruited and randomized into guided dose reduction group (GDR, target n = 80) and maintenance treatment group (MTG1, target n = 40), and those who eligible to dose reduction yet willing to continue medication will serve as a naturalistic observation group (MTG2, target n = 40). Patients in the GDR will reduce no more than 25% of their current dose of antipsychotics and closely monitored every 4 weeks for at least 24 weeks before next dose reduction adjustment. Patients of both MTGs receive treatment as usual. All patients will be followed up for at least 2 years. The main outcomes of interests are differences in relapse rates, personal social performance, quality of life, drug-related adverse reactions, medication satisfaction, and neurocognitive functioning between groups. Patient's actual medication status will be monitored by keeping a log and therapeutic drug monitoring on selective antipsychotics. Patient's demographics and clinical variables will be taken to test whether these variables are related to outcomes during follow-up.
Results: Currently 26 patients have participated in this study, including 10 males and 16 females, with a Mean (SD) age 31.8(7) years old. Eleven of them were in GDR group, 10 in MTG1, and 5 in MTG2. Their baseline PANSS scores were 36.9(5.7), 37.4(7.9), 49.2(7.4), CGI-S scores were 1.7(0.6), 1.5(0.7), 2(0), and Personal Social Performance (PSP) scores were 82.2(7.9), 83.9(6.8), 77.8(2.3) in GDR, MTG1, and MTG2, respectively. So far one patient in the GDR group has resumed her original dose due to suspected early signs of relapse and no further worsening of symptoms noticed, while one patient of the MTG1 withdrew consent due to feeling unnecessary to receive comprehensive follow-up assessments. Most of patients endorsed no significant difference between ordinary dose and reduced dose at present time.
Discussion: During the first 4 months of this trial, we have not seen any unexpected happening yet. We will continue case recruitment and follow-up to test if the metaphor derived from Cantor's Set and Sierpinski Triangle can serve a valid model for our dose reduction trial and see if such a slow-paced guided dose reduction approach a feasible solution for the debates between medication discontinuation and maintenance.

S228. TOWARD EARLY DETECTION OF TREATMENT RESISTANT SCHIZOPHRENIA: PREDICTIVE INFORMATION ON NON-RESPONSE TO ANTIPSYCHOTICS BY EVALUATION OF A FEW CLINICAL FACTORS: A STUDY BY ROC CURVE ANALYSIS AND CONFIRMATORY MULTIVARIATE ANALYSIS

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Background: Treatment Resistant Schizophrenia (TRS) is associated to poor prognosis and highly disabling course. Early detection of the condition is crucial to rapidly provide targeted interventions. The aim of this study was to evaluate whether it may be possible to distinguish TRS from Antipsychotic Responder Schizophrenia (ARS) patients on the basis of a limited number of measurable clinical factors.
Methods: 60 out of 182 eligible patients were included. A multistep diagnostic procedure to separate TRS from ARS was then used. Clinical parameters were recorded. Rating scales were administered, including: the Neurological Evaluation Scale (NES); the Positive and Negative Syndrome Scale (PANSS); the Heinrichs' Quality of Life Scale (QLS); the UCSD

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 ($\chi(3)=27.25$, p<.0005, Nagelkerke R2=.48); PANSS Negative subscale score among psychopathology variables ($\chi(1)=7.75$, p=.005, Nagelkerke R2=.16); QLS score among quality of life variables ($\chi(1)=7.91$, p=.005, Nagelkerke R2=.16); SLOF Area2 among social functioning variables ($\chi(1)=18.05$, p<.0005, Nagelkerke R2=.34).
The descriptive discriminant analysis function was significant for clinical variables, $\chi(6)=23.84$, 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 $\chi(6)=17.67$, 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 LAIs. 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. Plasma paliperidone levels measured at Visit 2 were highly correlated with levels from Visit 1 (n=18; r = .89, p <.001). Plasma prolactin levels were correlated with levels of plasma paliperidone (n=21, r=0.56, p < .01). Lower scores on the CSFQ – Sexual Desire factor were associated with higher levels of paliperidone (n=19, r =-.61, p<.01) and prolactin (n=19, r=-.56, p <.01). Higher paliperidone levels were associated with more negative scores on the Drug Attitude Inventory (n=19, r=-0.49, p < .05). Plasma paliperidone levels were not associated with scores on the SWN (n=21, r=-.-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 ANTIPSYCHOTIC 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.