

as well as the current lack of etiological treatments, redox dysregulation is an interesting target. The current study aims at investigating the impact of NAC, a precursor of GSH, the main antioxidant in the brain, on WM integrity in patients in the early psychosis phase. We focused on the fornix bundle that has been shown to be impaired in an animal model of oxidative stress<sup>2</sup> (i.e. impaired GSH synthesis) as well as in early psychosis patients.<sup>3</sup>

**Methods:** WM diffusion properties were estimated using generalized fractional anisotropy (gFA) computed from diffusion spectrum imaging (DSI) brain scans acquired in patients who received either NAC (n=10; mean age=25.3 ± 5.7; males/females 9/1) or placebo (n=10; mean age=24.8 ± 7.9; males/females 5/5) as add-on treatment over 6-months. GSH levels were measured in the medial prefrontal cortex using Magnetic Resonance Spectroscopy (MRS).

**Results:** A non-parametric longitudinal voxel-based analysis limited to the fornix revealed a time x treatment interaction which reached significance in the body of the fornix (corrected p<.04) with NAC patients showing an increase in gFA over 6-month of treatment. Importantly, improvement of gFA (i.e. increase) in the fornix of early psychosis patients (NAC and placebo) correlated with increase in cerebral GSH levels (r=.67; p<.005).

**Discussion:** This study is the first to assess the effect of NAC on WM integrity as assessed by diffusion weighted-imaging in the early phase of psychosis. WM alterations appear early in the illness and become widespread in a more chronic phase of the disease.<sup>4</sup> To the best of our knowledge there is currently no approved medication for schizophrenia that show significant effect on WM integrity. In this study, effects of NAC on WM integrity in the fornix were significant despite the limited sample size. This is a small-scale proof of concept study, which was very demanding for early psychosis patients and needs replication in a larger study. Its potential properties to counteract WM deficits may be even more important in individuals at clinical high risk for psychosis. As NAC add-on treatment is safe with no side effects, this study paves the way for preventive approach at the early stages of psychosis.

#### References:

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### T53. USING ARTIFICIAL INTELLIGENCE PLATFORMS TO ENHANCE STUDY DESIGN IN SCHIZOPHRENIA TRIALS

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**Background:** Remote patient monitoring is critical in ensuring optimal drug exposure. Between 30–50% of CNS trials fail because patients are not following the assigned protocol. It is estimated that non-adherence based on pharmacokinetic (PK) data is as high as 39% in schizophrenia trials. An AI platform that uses software algorithms on smartphones to visually and automatically confirm medication ingestion has been used extensively in schizophrenia trials, phases I-IV. Aggregated data demonstrate the feasibility of using the technology in patients with schizophrenia – where smartphone ownership is estimated to be well above 50% - and the potential value of enhancing study design through predictive data and statistical power.

**Methods:** Aggregated data were collected across seven schizophrenia studies; three trials are completed and four are ongoing. Protocols varied by geography, treatment duration, study design, inclusion/exclusion criteria, dosing regimens, and assessment frequency (US and global; six to 52 weeks' treatment duration, lead-in or washout periods, ages 16–65 years, dosing QD or BID, 1–3 units per dose, inpatient and outpatient). Study subjects used the AI application for each dosing administration. In addition to tracking medication intake, the patient-facing interface also provided automated reminders, alarms, dosing windows, clinic visit scheduling, and protocol-specific dosing instructions. Study teams and sites had access to data, analytics, automated notifications, and intervention dashboards.

**Results:** So far, 43,340 adherence parameters have been collected in studies with target enrollments of 1,312 subjects with schizophrenia. For randomized subjects who received at least 1 dose of the study drug, cumulative average adherence as measured by the AI platform (visual confirmation of ingestion) across all treatment groups, including placebo, is 83.6%. Adherence, as measured by the percentage of PK samples above the lower limit of quantification (LLOQ), is 91.2%. Between 3.9% and 12.5% of subjects triggered fraudulent activity alerts (intentional misuse of the technology). The average number of site interventions per subject per study was 4.7 (33.8% text messages; 34.7% phone calls; 31.5% in-person clinic visits). Adherence data logged on the AI platform were used in most studies as the primary measure of adherence (for at home and in-clinic dosing) and as the basis to evaluate eligibility criteria for randomization following placebo lead-in periods.

**Discussion:** Subjects with schizophrenia (stable, acute, positive and negative symptoms, cognitive impairment) treated with antipsychotics demonstrate high rates of adherence using a smartphone-based AI application. Non-adherence based on PK data ranged from 8.3% to 10.4%; a significant reduction from the 39%-50% non-adherence rates observed in clinical trials and real-world settings. Traditional methods to monitor adherence – pill count and self-report methods – are not reliable enough to be of predictive value in lead-in periods, demonstrate poor concordance with PK data, and do not allow sponsors to resolve issues that may affect adherence in real time. Use of the AI platform in schizophrenia studies demonstrates the potential of the technology to enhance data quality, enable the sponsor to estimate the effect of the investigational drug - when used as directed – and improve the likelihood of detecting a signal.

### T54. TAILOR – TAPERED DISCONTINUATION VERSUS MAINTENANCE THERAPY OF ANTIPSYCHOTIC MEDICATION IN PATIENTS WITH NEWLY DIAGNOSED SCHIZOPHRENIA SPECTRUM DISORDERS IN REMISSION OF PSYCHOTIC SYMPTOMS

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**Background:** Schizophrenia spectrum disorders have major implications for the individuals, their families and society. Antipsychotic medication is the cornerstone in the treatment of psychotic symptoms and is effective in the reduction of psychotic symptoms and of relapse after remission of psychotic symptoms. This is the reason for recommending maintenance treatment with antipsychotic medication in national and international guidelines for the treatment of schizophrenia, one year after remission of psychotic symptoms in first episode psychosis. The aim of the study is to investigate the effect of tapered discontinuation versus maintenance therapy with antipsychotic medication in patients with newly diagnosed schizophrenia or persistent delusional disorder and with

minimum three months remission of psychotic symptoms, and to find minimal effective dose of antipsychotic medication. Negative symptoms, cognitive impairments and the side effects of antipsychotic medication can cause a serious and long-term burden for patients and can reduce their quality of life. The TAILOR study will investigate these important aspects.

**Methods:** The study is a randomized multicenter single blinded clinical trial. The aim is to include 250 patients from the outpatient early intervention program, OPUS, a 2 years manualized psychiatric treatment programme. At baseline patients must have 3 months remission of psychotic symptoms as documented by the SAPS (Schedule for Assessment of Positive Symptoms in Schizophrenia).

The patients will be randomized to either tapered discontinuation or dose reduction of antipsychotic medication or treatment as usual stratified according to substance abuse. The intervention will last for 1 year, and follow up interviews will be made after 1,2 and 5 years.

The patients will receive a user-developed mobile phone application to make daily registrations.

**Results:** The study has been including patients since May 2017.

The first data is expected in 2019.

**Discussion:** The TAILOR trial will contribute to knowledge about the effect of tapering/discontinuation of antipsychotic medication in early phases of schizophrenia spectrum disorders and hopefully the results may guide future clinical treatment regimens of antipsychotic medication.

The trial is a complex medical intervention, and it raises ethical, practical and organizational challenges.

When designing the TAILOR trial ethical questions were raised regarding blinding and the design of the intervention. In the trial only the researchers are blinded, neither clinicians nor patients, because they should be attentive of the high risk of relapse in the discontinuation group. The design gives the clinicians the possibility to adjust the dose of the antipsychotic medication to ensure sufficient treatment. Therefore, the trial only includes assessor blinding and the groups might end up being more similar than intended.

In general, it is of ethical consideration that the trial participants in the tapering/discontinuation group will be subjected to a higher risk of relapse. On the other hand, it seems unethical if research were not to discover the group of patients who can discontinue antipsychotic medication without relapsing.

Practical challenges will be sufficient recruitment or patient motivation and dropout.

## T55. DRIVING ABILITIES IN CLINICALLY STABLE OUTPATIENTS WITH SCHIZOPHRENIA

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**Background:** According to the UN convention of human rights, individual mobility is an important aspect for people suffering from chronic disease. Recent studies have shown that 30% of patients suffering from schizophrenia have a driving license for motorized vehicles, however, studies on driving abilities among this patient group are scarce. Accordingly, the current study investigates the parameters, which are relevant in this regard.

**Methods:** In this naturalistic study, stable patients, diagnosed with schizophrenia according to ICD-10, between 18 and 60 years of age, are recruited on an outpatient basis. They have to be clinically stable without hospitalization for at least 6 months and have to be on the same medication for at least 6 months. Psychopathology and extrapyramidal motor symptoms (EPS) are assessed by means of the Positive and Negative Syndrome Scale (PANSS) and the Modified Simpson-Angus Scale (MSAS), respectively. Driving abilities are investigated by means of a computerized test battery of the Wiener Testsystem, measuring visual perception, reactivity and stress tolerance, concentration, vigilance, and motor coordination.

**Results:** So far, 42 outpatients suffering from schizophrenia, with a mean age of  $42.7 \pm 8.9$  years and a mean duration of illness of  $11.2 \pm 5.5$  years, have been included into the study. 52 % were male and the mean education was  $14.4 \pm 4.0$  years. The mean PANSS total score was  $56.3 \pm 20.3$  (positive symptoms:  $12.9 \pm 5.4$ , negative symptoms:  $13.6 \pm 5.5$ , general symptoms:  $29.7 \pm 13.6$ ). All patients were treated with second generation antipsychotics, and only one had a combination therapy with an additional first generation antipsychotic. We found significant positive correlations between driving abilities and both years of education and EPS, whereas residual symptoms (PANSS) were not associated with driving abilities.

**Discussion:** The relationship between EPS and driving abilities was not surprising, since motor flexibility might be seen as basic requirement in traffic situations. The missing correlation between residual symptomatology and driving abilities, on the other hand, may be explained by very low mean PANSS scores and the small range of scores in our sample. To summarize, these data suggest that in clinically stable outpatients suffering from schizophrenia driving abilities are primarily influenced by EPS rather than by residual symptomatology. Altogether, further studies are needed with a larger sample size.

## T56. AN EXPLORATORY ANALYSIS CONVERTING SCORES BETWEEN THE PANSS AND BNSS

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**Background:** The Brief Negative Symptom Scale is a relatively new instrument designed specifically to measure the negative symptoms in schizophrenia. Recently more clinical trials include the BNSS scale as a secondary or exploratory outcome, typically along with the PANSS. In the current analysis we aimed at establishing the equations that would allow conversion between the BNSS scale total score and the PANSS negative subscale and PANSS negative factors score as well as conversion equations between the expressive deficits and avolition/apathy factors of the scales. (Kirkpatrick, 2011; Strauss, 2012)

**Methods:** Data from 518 schizophrenia clinical trials subjects with both PANSS and BNSS data available were used. Regression analyses predicting the BNSS total score with the PANSS negative subscale score, and the BNSS total score with the PANSS Negative factor (NFS) score were performed on data from all subjects. Regression analyses predicting the BNSS avolition/apathy factor (items 1, 2, 3, 5, 6, 7, and 8) with the PANSS avolition/apathy factor (items N2, N4 and G16) and the BNSS expressive deficits factor (items 4, 9, 10, 11, 12, and 13) with the expressive deficits factor (items N1, N3, N6, G5, G7, and G13) of the PANSS were performed on a sample of 318 subjects with individual BNSS item scores available. In addition to estimating the equations we as well calculated the Pearson's correlations between the scales.

**Results:** The PANSS and BNSS avolition/apathy factors were highly correlated ( $r=0.70$ ) as were the expressive deficit factors ( $r=0.83$ ). The following equations predicting the BNSS total score were obtained from regression analyses performed on 2,560 data points:

$$\text{BNSS\_total} = -11.64 + 2.10 * \text{PANSS\_negative\_subscale}$$

$$\text{BNSS\_total} = -9.26 + 2.11 * \text{PANSS\_NFS}$$

The following equations predicting the BNSS factor scores from the PANSS factor scores were obtained from regression analyses performed on 1,634 data points:

$$\text{BNSS\_avolition/apathy} = -2.40 + 2.38 * \text{PANSS\_avolition/apathy}$$

$$\text{BNSS\_expressive\_deficit\_factor} = -4.21 + 1.27 * \text{PANSS\_expressive\_deficit\_factor}$$

**Discussion:** The BNSS differs from the PANSS negative factor because it addresses all five currently recognized domains of negative symptoms including anhedonia and attempts to differentiate anticipatory from consummatory states. In our analysis we have replicated the strong correlation between the BNSS total score and PANSS negative subscale and newly