Background: Biomarker-guided treatments are needed in psychiatry and previous data suggest redox dysregulation / oxidative stress may be a target in schizophrenia (1,2). A previous add-on trial with the antioxidant N-Acetyl-Cysteine (NAC) led to negative symptoms reductions in chronic patients (3). We aim to study NAC impact on symptoms and neurocognition in early psychosis (EP) and to explore whether glutathione (GSH)/redox markers could represent valid biomarkers to guide treatment.

Methods: In a double-blind, randomized, placebo-controlled trial in 63 EP patients, we assessed the effect of NAC supplementation (2700 mg/day, 6 months) on PANSS, neurocognition (MATRICS Consensus Cognitive Battery [MCCB]), and redox markers (brain GSH [GSH-mPFC], blood cells GSH [GSH-BC] levels, and GSH peroxidase activity [GPx-BC]).

Results: No changes in negative, positive symptoms, or functional outcome were observed with NAC, but significant improvements were found in favor of NAC on the MCCB Processing Speed factor and two of its components: Trail Making and Verbal Fluency. NAC leads to increases in GSH-mPFC by 23% (P < .005) and GSH-BC by 19% (P < .05). In patients with high-baseline GPx-BC (>22.3U/gHb), subgroup explorations revealed an improvement with NAC of positive symptoms when compared to patients with low-baseline GPx (P = .02), with an improvement of positive symptoms in parallel with that of the redox status.

Conclusion: In conclusion, NAC supplementation in a limited sample of EP patients did not improve negative symptoms, which were at modest levels at baseline. However, NAC leads to neurocognition improvement as well as to brain GSH levels increases, pointing to good target engagement. Blood GPx activity, a redox peripheral index associated with brain GSH levels, could help to identify a subgroup of patients who improve their positive symptoms with NAC. Future trials with antioxidant in EP should consider biomarker-guided treatment.

References


SA21. NETWORK ANALYSIS OF THE SANS: ANALYSIS OF 3 RANDOMIZED CLINICAL TRIALS OF PREDOMINANT NEGATIVE SYMPTOMS

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Background: Reasons for the recent mixed success of research into negative symptoms may be informed by conceptualizing negative symptoms as a system that is identifiable from network analysis. Our objectives were to identify (1) negative symptom systems; (2) central negative symptoms within each system; and (2) differences between the systems, based on network analysis of negative symptoms for baseline, end point, and change.

Methods: Patients with chronic schizophrenia and predominant negative symptoms participated in 3 clinical trials that compared placebo and amisulpride to 60 days (n = 487). Network analysis was computed from the Scale for the Assessment of Negative Symptoms (SANS) scores for baseline and end point for severity and estimated change based on mixed models. Central symptoms to each network were identified. The networks were contrasted for connectivity with permutation tests.

Results: Network analysis showed that the baseline and end point symptom severity systems formed symptom groups of Affect, Poor responsiveness, Lack of interest, and Apathy-inattentiveness. The baseline and end point networks did not significantly differ in terms of connectivity, but both significantly (P < .05) differed to the change network. In the change network, the apathy-inattentiveness symptom group split into 3 other groups. The most central symptoms were decreased spontaneous movements at baseline and endpoint, and poverty of speech for estimated change.

Conclusion: We offer preliminary evidence for (1) a replicable negative symptom severity system and (2) symptoms with high centrality (e.g., Decreased Spontaneous Movement) that may be future treatment targets following replication to ensure the current results generalize to other samples.

SA20. POPULATION PHARMACOKINETIC ANALYSIS AND SIMULATIONS OF A 2-MONTH REGIMEN FOR ARIPIPRAZOLE LAUROXIL

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Background: Aripiprazole lauroxil (AL) is a prodrug of aripiprazole, formulated as an extended-release suspension approved for the treatment of schizophrenia by injection every 4 and 6 weeks. Following completion of a Phase 1 study evaluating administration of AL every 8 weeks, a pharmacokinetic (PK) model-based approach was used to evaluate dosing scenarios likely to be encountered in clinical practice for this new dose interval.

Methods: An existing population pharmacokinetic (PopPK) model of AL was updated to include data from 5 clinical studies, including a recently completed Phase 1, open-label study evaluating the PK, safety, and tolerability of AL after administration of 441, 882, or 1064 mg at 4-, 6-, and 8-week intervals to subjects with stable schizophrenia. Data collected from 700 subjects with schizophrenia were included in the analysis. The final PopPK model was subsequently used to assess the exposure of the 8-week regimen relative to already approved AL regimens (441, 662, and 882 mg monthly, and 882 mg every 6 weeks), the impact of missed doses, and reinitiation of treatment with AL 1064 mg every 8 weeks following a delay in dosing.

Results: The final AL PopPK model predicted aripiprazole exposure well with the majority of the observed concentrations contained within the model-predicted 90% prediction interval. Repeated dose simulations showed that 1064 mg every 8 weeks resulted in aripiprazole concentrations that were within the aripiprazole exposure range associated with the efficacious dose range of AL. Additionally, median-simulated steady state concentrations of aripiprazole for the 8-week regimen were comparable to the 882 mg every 6 week and 662 mg monthly regimens (154 ng/mL, 165 ng/mL, and 183 ng/mL, respectively). Aripiprazole concentrations declined slowly when a dose was delayed, declining by <20% for a 14-day delay in the 8-week regimen and readily returned to expected levels when AL dosing was resumed.

Conclusion: Administration of a higher dose of AL (1064 mg) for a longer dose interval (every 2 months) than previously studied results in aripiprazole concentrations that fall within the aripiprazole exposure range of the lowest and highest therapeutic doses of AL, 441 mg monthly and 882 mg monthly. These results show that 1064 mg AL may be suitable for a 2-month dose interval, having the potential to expand the choice of AL treatments. Recommendations for missed doses are based on PK-based modeling and simulation. No clinical studies have been conducted to evaluate these recommendations.