T48. ANTIPSYCHOTIC EFFICACY OF EVENAMIDE (NW-3509) IS DUE TO MODULATION OF GLUTAMATERGIC DYSREGULATION

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Background: Over 70% of schizophrenic patients discontinue treatment with first (F)- or second-generation antipsychotics (SGA) due to dissatisfaction with their therapeutic effects; median time to discontinuation ranges from 3–7 months (1). Switching to another antipsychotic, except clozapine, did not yield better results (2). These results indicate it is essential to modulate mechanisms other than dopaminergic (DA)/serotoninergic (5-HT) systems to improve symptoms of schizophrenia (SCZ). Increasingly, NMDA receptor (NMDAr) hypofunction (3) and hippocampal hyperactivity (4) are implicated in the dysregulation of mesolimbic DA and glutamate (Glu) neurons, leading to increasing synaptic activity of Glu in the PFC (5). Augmenting the effects of current antipsychotics with Glu release inhibitors may improve symptoms of psychosis in patients with SCZ.
Evenamide does not interact with monoaminergic (DA, 5-HT, NA, H) pathways affected by current antipsychotics, or with >130 different targets involved in CNS activity, except for sodium channels, leading to modulation of Glu release. Evenamide shows efficacy in animal models of SCZ as monotherapy and as an add-on to FGA or SGA, irrespective of whether impairment was spontaneous, or induced by amphetamine, NMDAr antagonists or stress.
Methods: In a pilot, proof of mechanism, randomized, double-blind, placebo-controlled, parallel group, 4-week trial, evenamide (n=50; 15–25 mg bid) or placebo (n=39) was added to patients with SCZ worsening on their current antipsychotic doses of risperidone (RIS; ≥2 mg/day) or aripiprazole (ARI; ≥10 mg/day), in 2 sites in the US (n=61) and 3 in India (n=28).
Results: 89 patients with SCZ (mean baseline PANSS total: 62.9 ± 7.4; CGI-S: 3.5 ± 0.5), experiencing break-through psychotic symptoms on previously effective and stable doses of RIS (mean dose: 4.2 ± 2.0 mg/day; n=70) or ARI (mean dose: 19.7 ± 7.0 mg/day; n=19) were randomized (1.3:1 ratio) to treatment with evenamide or placebo. Analyses demonstrated the addition of evenamide to RIS or ARI was associated with statistically significant efficacy, based on the PANSS Positive Symptoms sub-scale (mean change, responders), and CGI-C responder rates. The study treatments were very well tolerated; 2 patients on evenamide discontinued treatment due to AEs (atrial fibrillation and seizure). The most common AEs (evenamide vs placebo [%]), were somnolence (16 vs 12.8%), insomnia (10 vs 6%) and headache (6 vs 0%).
Discussion: Addition of evenamide in patients worsening on SGAs modulating DA/5-HT significantly improved positive symptoms and CGI. No AEs such as EPS, endocrine, or sexual side effects, or weight gain were noted. These data indicate that evenamide's Glu antagonism, demonstrated in preclinical experiments, is of value in patients worsening on current antipsychotics. Evenamide, as monotherapy or add-on, has reversed ketamine- and PCP-induced worsening of PPI. The results in the pilot clinical trial demonstrated an absence of side effects common with DA/5-HT blockers, and a rapid onset of action mediated by evenamide targeting altered Glu transmission in patients in whom SGA treatment had lost its efficacy.
Efficacy of evenamide as add-on to antipsychotics would revolutionize development of novel antipsychotics targeting aberrant firing and Glu transmission in SCZ. Potentially pivotal studies with evenamide are in planning to demonstrate that the addition of evenamide, a Glu release inhibitor, augments antipsychotic efficacy in patients worsening on current antipsychotics, and in patients with treatment-resistant SCZ not responding/worsening on clozapine.

T49. THE NEURAPRO STUDY: ADHERENCE TO STUDY MEDICATION

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Background: Adherence to a medication is generally defined as the extent to which patients take medications as prescribed by their health care providers. Poor adherence to study medication is not uncommon posing a major challenge to treatment trails. However, poor adherence may not be randomly distributed but rather be associated with demographic or illness factors. The aim of the present study was to identify factors associated with adherence to study medication in young people at ultrahigh risk of psychosis who participated in the NEURAPRO study.
Methods: Secondary analysis of data collected in a multi-centre, double-blind, placebo-controlled, randomized clinical trial to prevent or delay the onset of psychosis in participants at ultrahigh risk of psychosis testing omega-3 polyunsaturated fatty acids (omega-3 PUFAs) vs. placebo, in combination with cognitive behavioural case management (NEURAPRO) were included in this analysis. Measures included the Brief Psychiatric Rating Scale (BPRS), the Scale for the Assessment of Negative Symptoms (SANS), the Montgomery Asberg Depression Rating Scale (MADRS), the Young Mania Rating Scale (YMRS), the Social and Occupational Functioning Assessment Scale (SOFAS), and the Global Functioning: Social and Role scales. Adherence to the study medication was assessed monthly for each participant based on capsule count. The mean adherence rating over the 6-month intervention period was then computed and categorized as either adherent (≤25% of capsules returned) or non-adherent (>25% of capsules returned). Transition to psychosis was defined on the basis of operationalized criteria and assessed with the Comprehensive Assessment of the At-Risk Mental State. Levels of ω-3 PUFAs in fish oil, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (amongst other fatty acids) were measured as percentage of total fatty acids in erythrocytes at baseline and at month 6 (end-of-intervention).
Results: Of 304 randomised participants, 57.9% (N = 176) were non-adherent (>25% of capsules returned) and 128 (42.1%) were adherent (≤25% capsules returned) to the study medication.
No sex differences were observed for adherence rates. At baseline the omega-3 index (EPA+DHA) was significantly lower in the non-adherent group (P = 0.018). The non-adherent group had significant lower scores on the SOFAS (P = 0.001) and the Global Functioning: Social and Role Scale at baseline assessment (P < 0.001 and P = 0.020, respectively) compared to the adherent group. No statistically significant differences were observed on symptom measures at baseline (BPRS, SANS, MADRS, YMRS). The cumulative transition to psychosis rate at month 12 was significantly higher in the non-adherent group compared to the adherent group (14.8% vs. 4.7%; Log rank test: P < 0.001).