Schizophrenia and Other Psychotic Disorders

EPP434

Efficacy and Safety of Evenamide, a glutamate modulator: Results from a Phase 2/3, international, randomized, double-blind, placebo-controlled add-on trial

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Introduction: Treatment of schizophrenia remains a challenge despite the development of numerous antipsychotics (AP) (Pompili et al CNS NDDT 2017; 16 870-884). The various strategies to address patients' unmet needs, such as AP polypharmacy or switching AP, do not seem to provide adequate benefit. A reason for this may reside in the similarity of mechanisms of action of most APs. However, the monoaminergic systems targeted by these drugs are not always disrupted in schizophrenia, as it is widely accepted that patients who fail to respond to AP have glutamatergic, but not dopaminergic dysfunctions (Moghaddam et al NPP 2012; 37 4-15). Evenamide normalizes excessive glutamate release without affecting its basal levels, and it does not interact with >150 CNS targets. It has been shown to be effective in animal models of psychosis as monotherapy and add-on to AP. Previous trials indicate that evenamide benefits patients with schizophrenia with inadequate response and have shown clinically important benefits lasting up to 1-year in TRS (Anand et al IJNPP 2023; 26 523-528).
Objectives: Study 008A, a phase 2/3 international, randomized, double-blind, placebo-controlled, 4-week trial, assessed the efficacy and safety of evenamide 30 mg *bid* as add-on in patients poorly responding to an SGA.
Methods: Outpatients with a diagnosis of schizophrenia, still symptomatic (PANSS 70-85; CGI-S 4-6) despite treatment with an SGA at a therapeutic dose (confirmed through plasma levels) for an adequate period, were enrolled. Efficacy was assessed on the PANSS, CGI-S, and LOF through the comparison of changes from baseline to Day 29 between evenamide and placebo groups using a MMRM analysis. Moreover, the proportion of patients reaching a clinically important improvement on the PANSS and CGI-C were compared between groups using a logistic regression model (chi-square test). Safety measures comprised: TEAEs, vital signs, labs, ECG/EEG, seizure checklist, physical/neurological/eye examinations, C-SSRS, ESRS-A, CDSS.
Results: 291 patients were randomized in the study in 11 countries (EU, Asia and LATAM), and 280 completed the study. The low attrition rate (<4%), and proportion of patients with TEAEs (~25% in both groups) indicate that evenamide was well tolerated. A statistically significant greater improvement was found on the PANSS total score and on the CGI-S in the evenamide compared to the placebo group. Furthermore, a significantly higher proportion of patients treated with evenamide, compared to those receiving placebo, experienced clinically meaningful benefit measured on the PANSS (≥20% improvement) and CGI-C (at least much improved).
Conclusions: This is the first randomized, placebo-controlled trial to demonstrate the clinical benefit of adding a NCE modulating glutamate in patients with schizophrenia who did not experience adequate response from treatment with a SGA.

Disclosure of Interest: R. Anand Consultant of: AbbVie, Acadia, BiolineRx, Domain, Enkam, Erydel, Forest, Janssen, Hoffman La Roche, Lundbeck, Noema, Ono, Pfizer, UCB, Shire, Sigma-Tau, Takeda, Teva, A. Turolla Employee of: Newron Pharmaceuticals SpA, G. Chinellato Employee of: Newron Pharmaceuticals SpA, R. Giuliani Employee of: Newron Pharmaceuticals SpA, F. Sansi Employee of: Newron Pharmaceuticals SpA, R. Hartman Consultant of: Newron Pharmaceuticals SpA.

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Childhood maltreatment associated with elevated Herpes simplex virus 1 antibody concentrations in severe mental illness

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Introduction: Adverse childhood events have been associated with immune aberrations. Herpes simplex virus 1 (HSV1), a neurotropic pathogen, establishes persistent infection after primary exposure. Elevated HSV1 immunoglobulin (IgG) levels have been found in HSV1-infected patients with severe mental illness (SMI), which likely reflects immune dysregulation.
Objectives: We assessed childhood maltreatment and HSV1 IgG concentrations in adult patients with SMI and healthy controls. We hypothesized that maltreatment would be associated with elevated HSV1 IgG concentrations reflecting a failure in immune competence, and that such a putative association would be stronger in or even restricted to patients.
Methods: We included 448 adult patients with SMI (mean age=31 years, 48% women, 46% HSV1 seropositive), i.e., 259 patients with schizophrenia spectrum and 189 patients with bipolar disorders, and 271 adult healthy controls (mean age=32, 41% women, 46% HSV1 seropositive). We assessed childhood maltreatment with the Childhood Trauma Questionnaire (CTQ), a 28-item retrospective self-report scale. We evaluated circulatory HSV1 IgG concentrations, expressed as continuous and dichotomous measures. In our main analyses, we applied sex- and age-adjusted multiple regressions on HSV1 IgG concentrations.
Results: In patients with SMI ($p=0.002$) but not in healthy controls ($p=0.203$), CTQ total score was associated with HSV1 IgG seropositivity. Among seropositive patients ($p<0.001$) but not healthy controls ($p=0.957$), CTQ total score was associated with increased HSV1 IgG concentrations. Post-hoc analysis among seropositive patients showed that the five subscale scores for physical ($p=0.002$), sexual ($p=0.019$) and emotional abuse ($p=0.002$), and physical

(p=0.012) and emotional neglect (p=0.016) were all associated with increased HSV1 IgG concentrations.
Conclusions: Among patients with SMI, childhood maltreatment is associated with an increased risk of HSV1 infection. Further, among HSV1-infected patients, maltreatment is associated with elevated HSV1 antibody concentrations which may reflect a link between childhood adverse experiences and an immune system dysregulation.

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EPP436

Am I sentenced to life-long use of antipsychotics? A qualitative analysis of Q&A data about stopping antipsychotics from the perspective of users and their relatives

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Introduction: The majority of antipsychotic users at some point want to stop their antipsychotic medication and many do so without consulting their attending physician. So-called non-adherence to antipsychotics has been estimated to be as high as 60% and it has been identified as the most important predictor for relapse, resulting in a four times higher risk of relapse. When asking antipsychotic users, different reasons for wanting to stop are mentioned. These reasons include severe side effects, reduced functioning, experiencing no benefits and long-term physical health concerns. From the perspective of patients, wanting to stop can be considered an understandable and rational reaction given the burdens that antipsychotic use often imposes. Given the current uncertainties surrounding stopping antipsychotics, and given the patients' wish to be involved in treatment decisions and a move away from a paternalistic mental health care model, several shared decision initiatives have been formed to involve patients more in the decisions about stopping or reducing the dose of their antipsychotic. In order to support shared decision-making, insight is needed in which questions antipsychotic users have.
Objectives: The current study aims to gain insight in which questions antipsychotic users and their relatives have, and which factors influence stopping or reducing the dose of antipsychotics, by qualitatively analysing questions posted on an online expert Q&A.
Methods: Data were used from a Dutch existing publicly available anonymous expert Q&A. Questions about stopping or reducing the dose of antipsychotics were analysed using an inductive thematic approach. Questions antipsychotic users and their relatives had about this topic and factors that influences the process were identified.
Results: In total 194 out of 3000 screened questions were about stopping or reducing antipsychotic dose. The most common question was whether it was sensible to stop or reduce the dose. Questions focused on how fast to reduce the dose, what their minimum dose should be and where they could find support. Those that were phasing out their antipsychotic asked when withdrawal symptoms or side effects would subside. Motivations to stop were side effects, difficulties in assuming a normal life and social roles and experiencing no benefits. Barriers were lack of support and return of symptoms. Facilitators were support from others and experiencing a relief from side effects and/or symptoms. Finally, questions were asked about activities that might support discontinuation.
Conclusions: Antipsychotic users continue to be left with many questions about stopping or reducing the dose of antipsychotics. These questions reveal attitudes, preferences and concerns regarding antipsychotic treatment that are important to address when discussing antipsychotic treatment.

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EPP437

Effectiveness of a community-based, multicomponent and case managed treatment for patients with severe schizophrenia

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Introduction: Case management is a model of community intervention in people with severe mental illness.
Objectives: To explore the treatment adherence and effectiveness of patients with severe schizophrenia undergoing treatment in a community-based, case management program (CMP) with an integrated pharmacological and psychosocial approach compared to the standard treatment.
Methods: An observational, longitudinal study was conducted with a ten-year follow-up of patients with severe schizophrenia (CGI-S ≥ 5) treated in mental health units (MHUs) or on a CMP (N = 688). All causes of treatment discontinuation, psychiatric hospital admissions, suicide attempts, and antipsychotic (AP) medications were recorded. Clinical severity was assessed with the CGI-S.
Results: Adherence to the CMP was higher than to the standard treatment ($p < 0.001$). There were fewer hospital admissions and suicide attempts on the CMP than in standard care ($p < 0.001$). Clinical severity decreased more in the CMP than in MHUs ($p < 0.005$). Long-acting injectable (LAI) AP medication was more closely related to these outcomes than oral APs ($p < 0.001$) in both settings, but especially on the CMP.