Improvement in Anxiety Symptoms in Depressed Patients Treated With AXS-05 (DEXTROMETHORPHAN-BUPROPION): Results From the Evolve Open-Label, Long-Term Study

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Abstract

Background. Innovative therapies to treat individuals with MDD, especially those with comorbid anxiety, are urgently needed.

AXS-05 (dextromethorphan HBr 45 mg-bupropion HCl 105 mg) is a novel, oral, investigational NMDA receptor antagonist with multimodal activity. The dextromethorphan component of AXS-05 is an NMDA receptor antagonist and a sigma-1 receptor agonist. The bupropion component of AXS-05 serves primarily to increase the bioavailability of dextromethorphan.

Objective. To evaluate the effects of AXS-05 on anxiety in MDD.

Methods. EVOLVE was an open-label study, in which patients were treated with AXS-05 twice daily for up to 15 months. Subjects had either rolled in after a prior AXS-05 study or were directly enrolled and had a DSM-5 diagnosis of MDD, a MADRS score of ≥25, and had been treated with ≥ 1 antidepressant in the current major depressive episode. A total of 186 patients were enrolled. Efficacy endpoints included MADRS and HAM-A. Here we present the results for the directly enrolled patients (n =146).

Results. Mean baseline HAM-A scores were 15.6. Reductions from baseline to Weeks 1, 2, and 6 were 3.4±5.34 ($p< 0.001$), 5.5±5.81 ($p< 0.001$), and 8.6±5.75 ($p< 0.001$), respectively. Improvements on the HAM-A were durable through Month 12 (-10.2±6.33; $p< 0.001$). Remission (HAM-A ≤7) rates on the HAM-A at Weeks 1, 2, and 6 were 19.9%, 36.0%, and 58.1%, respectively. Remission at Month 12 was 78.3%.

Long-term treatment with AXS-05 was generally well tolerated. The most commonly reported adverse events were COVID-19 infection (8.9%), nausea (8.9%), headache (7.5%), dry mouth (6.2%), insomnia (5.5%), and dizziness (5.5%).

Conclusions. These data support the use of AXS-05 in patients with comorbid depression and anxiety.

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Zuranolone, a Positive Allosteric Modulator of the $GABA_A$ Receptor: Hypothesized Mechanism of Action in Major Depressive Disorder

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Abstract

Major depressive disorder (MDD) is a heterogeneous condition characterized by depressed mood and/or loss of interest/pleasure in activities, among other symptoms. Most currently available treatments for depression were developed on the hypothesis that depressive symptoms arise from a depletion of monoamines within the central nervous system (CNS). However, clinical understanding has advanced to identify brain network dysregulation as the primary driver of depression, with monoamines playing a lesser role. Prolonged inability to regulate brain networks may lead to the core symptoms and clinical presentation of MDD. Depression has been linked to impaired neuronal activity in brain networks (e.g., central executive network [CEN], default mode network [DMN], and salience network [SN]). It is hypothesized that improvement in depressive symptoms may result from restoring balance in brain networks governing mood.

γ-aminobutyric acid (GABA) is critical for maintaining and restoring excitatory-inhibitory balance in the brain and regulating brain networks. Approximately one-third of neurons in the CNS are GABAergic, regulating network activity throughout the brain, including regions involved in mood, sleep, and cognition. GABA activates $GABA_A$ receptors ($GABA_AR$), inhibiting neuronal activity through phasic (via synaptic $GABA_AR$) and tonic (via extrasynaptic $GABA_AR$) currents. Tonic GABA currents may play a particularly important role in regulating network activity, since they produce a large net inhibitory effect and are also involved in controlling the excitability of inhibitory interneurons, the key regulators of rhythmic brain network activity.

Zuranolone is an investigational oral $GABA_AR$ positive allosteric modulator and neuroactive steroid. In clinical trials, treatment with zuranolone has shown significant improvement over placebo in depressive symptoms in adults with MDD or postpartum depression, with a generally well-tolerated and consistent safety profile.

The hypothesized mechanism of zuranolone differs from monoamine-based antidepressants and from benzodiazepines. Unlike benzodiazepines, which bind to the α/γ subunit interface in synaptic $GABA_AR$ and enhance phasic inhibitory currents, zuranolone binds to the α/β subunit interface present in nearly all $GABA_AR$, leading to enhanced phasic (synaptic) and tonic

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