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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(extrasynaptic) inhibitory currents. Furthermore, in vitro evidence suggests that whereas benzodiazepines are associated with $GABA_AR$ downregulation, zuranolone upregulates the surface expression of $GABA_AR$.

In conclusion, by upregulating $GABA_AR$ expression and increasing phasic and tonic inhibitory GABAergic signaling, zuranolone may rapidly restore and maintain excitatory-inhibitory balance in brain networks, thus allowing the brain to potentially respond appropriately to internal and external stimuli.

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Practical Pharmacotherapy for Opioid Use Disorder in the Age of Fentanyl

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Abstract

Opioid use disorder (OUD) is a serious public health threat. Pharmacotherapy, commonly known as medications for opioid use disorder (MOUD), is established as the cornerstone of OUD treatment. MOUDs reduce likelihood of relapse, promote recovery, and save lives. However, many clinicians are still reluctant to use these medications, in part due to inadequate training and experience. In light of the ongoing opioid overdose epidemic, it has become ever more important for clinicians to confidently and thoughtfully deploy these medications to help patients struggling with OUD. To aid busy clinicians, we have put together a review of the extant literature on three FDA-approved pharmacotherapy options—methadone, buprenorphine, and extended-release naltrexone—with a heavy focus on practical clinical application. We discuss how to effectively engage patients with OUD and initiate them on MOUDs—especially when their primary misused drug is fentanyl. We also review novel strategies, such as buprenorphine microinduction, as well as suggested best practice to effectively transition between MOUDs. Finally, we synthesize our review and recommendations in an algorithmic flowchart to provide visually compelling information.

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Can COVID-19 Cause Acute Psychosis in Pediatric Patients? A Case Report

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Abstract

Objectives. To demonstrate that COVID-19-associated acute psychosis, though rare, can happen in the pediatric patient population. Patients with new-onset psychosis should be tested for COVID-19 infection, and other organic causes of psychosis should also be considered (e.g., delirium, medication-induced psychosis, and catatonia).

Method. Patient X, a 14-year-old female with no known past psychiatric history, presented to the local emergency room following odd behavior for 3 days and having tested positive for COVID-19 2 weeks prior. The patient's mother reported odd behaviors, including the patient claiming her fish was calling her name and her name was being repeated on TV. She had been moving slowly with occasional staring. The patient's mother reported episodes in which the patient was repeating phrases over and over and where she would require redirection to a task. When the patient planned to have a bath, her mother noted that she was naked in her room while looking for something and then needed redirection to go take a bath. She did not have any episodes of agitation. A thorough psychiatric evaluation indicated she was experiencing visual hallucinations. Her vitals were within normal ranges, except for a mildly elevated heart rate. The patient was admitted for further testing, assessment, and management. She was started on chlorpromazine 10 mg daily as needed for psychosis.

Result. A complete blood count with differential (CBC), complete metabolic panel (CMP), and thyroid function results were all within the normal range. Urine drug screening was negative. EKG, CSF analysis, chest X-ray, and brain MRI showed no significant abnormalities. Mild background slowing was noted on EEG, with no interictal/epileptiform discharges or any delta brushes. Therefore, a tentative diagnosis of COVID-19-associated psychosis was made. Treated with chlorpromazine 10 mg daily, the patient gradually improved with no hallucinations or bizarre behavior. She was discharged after 5 days and was not prescribed any medication at discharge. Nine days after discharge, the patient was seen by a pediatric neurologist. She did not report any hallucinations or delusions, but her mother reported that the patient moved slowly and had difficulty identifying common objects. An autoimmune panel, physical exam, and repeat EEG were all unremarkable. The neurologist concluded that her psychosis was most likely post-viral sequelae. The patient continued to improve and returned to school over the span of 2 months.

Conclusion. Acute psychosis after COVID-19 infection is a new and emerging diagnosis with no consensus on management strategies for pediatric or adult patient populations. This case highlights the need for clinicians to be vigilant of subtle, fluid psychotic symptoms, in addition to patients' general mental well-being. We do not have research regarding the long-term consequences of acute psychosis episodes. Further studies are needed to investigate the neuropsychiatric etiology of post-COVID-19 psychosis and the optimum treatment for this group of patients.

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