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ToxUpdate

Alabama Poison Information Center, Birmingham, AL

www.childrensal.org/apic 1-800-222-1222

Lybalvi® Approved May 2021

By Danica Mack, PharmD Candidate 2022, Samford University

Lybalvi (olanzapine and samidorphan) is an oral tablet taken once daily to treat bipolar I disorder or schizophrenia, approved by the U.S. Food and Drug Administration in May of 2021. Like all products containing olanzapine, this combination also carries a black box warning for increased mortality in elderly patients with dementia-related psychosis. This medication is a combination of a second-generation antipsychotic and an opioid antagonist which is included to help mitigate weight gain, a common adverse effect seen with olanzapine therapy. It is available in four dosing combinations: 5 mg, 10 mg, 15 mg, or 20 mg of olanzapine with 10 mg of samidorphan.

Olanzapine works by antagonizing the serotonin 5-HT2A and 5-HT2C, dopamine D1-4, histamine H1, and alpha1-adrenergic receptors. Also, there is moderate antagonism of 5-HT3 and muscarinic M1-5 receptors and weak binding to GABA-A and beta-adrenergic receptors. Samidorphan is a mu-opioid antagonist with partial agonist activity at kappa- and delta-opioid receptors.[4]

Olanzapine can cause anticholinergic effects such as tachycardia and decreased GI motility. Samidorphan is an opioid antagonist and may increase the risk of opioid overdose in patients that resume opioid therapy after discontinuation. Overdose of olanzapine can potentially cause severe toxicity or even fatalities. There was a reported fatal exposure to 450 mg; however, adults have also survived doses of approximately 2 grams with supportive care. The risk of toxicity is greater for children and drug naïve adults. Contact Alabama Poison Information Center at 1-800-222-1222 for concerns of Lybalvi overdose.

1. *Drug approval package: Lybalvi*. accessdata.fda.gov. (n.d.). Retrieved November 18, 2021, from https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/213378Orig1Orig2s000TOC.cfm.
2. LYBALVI® (Olanzapine and samidorphan) | HCP web site. https://www.lybalvi.com. (Accessed November 18, 2021).
3. Lybalvi. POISINDEX® System (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA. Available at: https://www.micromedexsolutions.com/ (Accessed November 18, 2021).
4. Lybalvi. In: UpToDate. Waltham (MA): UpToDate, Inc.; [updated 6/24/21; accessed 11/14/2021]. www.uptodate.com

ALABAMA POISON INFORMATION CENTER

800-222-1222

Special Interest Articles

- Lybalvi®
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Did you know?

A common winter weather hazard is exposure to carbon monoxide (CO) gas. Colorless, odorless, and tasteless, there are no specific warning signs of CO exposure. The American Association of Poison Control Centers (AAPCC) recommends these actions to prevent CO poisoning:

- Never attempt to heat your home using oven, clothes dryer, or automobile
- Generators should only be used outdoors
- Install CO detector on each level of your home
- Have heating system and chimney inspected regularly

Toxins as Treatments

By Rebecca Worsham, PharmD Candidate 2022, Samford University

"Venoms provide an optimistic opportunity for drug discovery because most of the proteins and peptides that make up venoms tend to be selective and precise in their cellular targets, making it less likely for side effects to develop."

Venoms are poisons produced within the exocrine glands of more than 170,000 venomous animals, such as snakes, spiders, scorpions, and snails.[1,2] Venoms are composed of numerous highly complex polypeptides and proteins that act as neurotoxins, hemotoxins, and myotoxins at various exogenous targets, including cellular receptors, enzymes, and ion channels.[1,3] When injected, these toxins result in severe physiological outcomes, including paralysis, coagulopathy, dysglycemia, and hypotension.

In nature, venom serves primarily as an adaptive advantage for predators to attack and kill prey. The toxins within venom disrupt key physiological pathways, subduing prey. As dangerous as venom can be in the animal kingdom, pharmaceutical researchers and developers have identified venom as an attractive avenue for drug discovery. The toxicological mechanisms of venom that help capture prey can be translated into modern-day therapies and the development of new pharmaceutical agents.

In the 1960s, researchers identified the presence of bradykinin-potentiating peptides (BPP) in the venom of the Jararaca pit viper.[2] These peptides were found to cause inhibition of angiotensin-converting enzymes (ACE), which lead to hypotension resulting in death when injected into prey.4 Researchers at Bristol-Myers Squibb were able to utilize the venom from the Jararaca pit viper to develop a molecule that mimicked the hypotensive properties of BPPs.[2] The resulting molecule, known as captopril, was the first ACE-inhibitor and was introduced as a pharmacological treatment for hypertension in 1981.[4]

Since the development of captopril, there have been a total of 6 venom-based medications that have obtained FDA approval.[5] The antiplatelet medication eptifibatide was isolated from the venom of pigmy rattlesnakes and is used to treat patients with unstable angina, non-ST elevation myocardial infarction, and those undergoing percutaneous coronary interventions (PCI).[2] Another antiplatelet drug, tirofiban, was derived from the venom of the saw-scaled viper and has similar indications to eptifibatide.[4] Bivalirudin is an anticoagulant isolated from the hirudin proteins produced by medicinal leeches; it is used for thromboprophylaxis in patients undergoing a PCI.[4] The medication ziconotide is a potent analgesic derived from the toxins in the venom of cone snails.[4] Exenatide, an incretin mimetic of glucagon-like peptide-1 (GLP-1) used to treat type 2 diabetes, was developed from the exendin peptides found in the saliva of a venomous lizard, the Gila monster.[4]

Venoms provide an optimistic opportunity for drug discovery because most of the proteins and peptides that make up venoms tend to be selective and precise in their cellular targets, making it less likely for side effects to develop.[5] Developing medications from these proteins and peptides also comes with significant limitations, such as impaired oral absorption, risk of eliciting immune reactions, and the expensive cost of production.[2] However, ongoing research into the potential uses for toxins from venom continues as there is growing promise that venom-based medications can provide a new generation of treatments for cancer, autoimmune diseases, and pain.[4]

1. Langenegger N. Spider Venom: Components, Modes of Action, and Novel Strategies in Transcriptomic and Proteomic Analyses. *Toxins*. 2019;11(10):611. doi:10.3390/toxins11100611
2. Kupferschmidt K. From Toxins to Treatments. *Science*. 2013;342(6163):1162-1164. doi:10.1126/science.342.6163.1162
3. Watkins JB. Toxic Effects of Plants and Animals. In: *Casarett & Doull's Essentials of Toxicology*. 3rd ed. McGraw Hill; 2015. https://accesspharmacy-mhmedical-com.ezproxy.samford.edu/content.aspx?bookid=1540§ionid=92528244. Accessed August 31, 2021.
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Spravato® for the treatment of treatment-resistant depression and major depressive disorder with suicidal thoughts or actions

By AJ Phillips, PharmD Candidate 2022, Samford University

Spravato is a relatively new nasal spray designed for patients with treatment-resistant depression (TRD) or major depressive disorder with suicidal thoughts or actions (MDSI), taken along with an oral antidepressant. This drug contains esketamine, the *S*-enantiomer of ketamine, making it a Schedule III medication. Esketamine is a non-competitive *N*-methyl-D-aspartate (NMDA) receptor antagonist; both short and long-term trials have shown that it benefits depressed patients.[1]

Spravato is supplied as a nasal administration device that delivers two esketamine 28 mg sprays, and patients require two or three devices for each 56 to 84 mg dose. The medication is initially dosed twice weekly during weeks 1-4, weekly during weeks 5-8, followed by weekly or bi-weekly doses to treat patients with TRD. Patients with MDSI receive eight doses over four weeks. Each administration device is sealed in a single blister package, coming in groupings as large as three, and is only given under the supervision of a healthcare provider.[1]

The adverse effects of esketamine are similar to those of ketamine, primarily dissociation, anxiety, lethargy, GI upset, and feeling dizzy or drunk. Similarly, overdose effects such as sedation and respiratory depression are possible, and some patients could experience seizures.[2]

Because this medication is currently only administered under the supervision of healthcare providers and the product is sealed in individual blisters, it is unlikely an unintentional or intentional overdose could occur. Patients need to be monitored for two hours after administration.[1] Contact the poison center at 1-800-222-1222 for more information about the toxic effects of Spravato.

1. Spravato [package insert]. Lakewood, NJ: Janssen Pharmaceuticals, Inc; 2019. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/211243lbl.pdf
2. Esketamine. In: In Depth Answers [database on the Internet]. Greenwood Village (CO): IBM Corporation; 2017 [cited 2021 Nov 17]. Available from: www.micromedexsolutions.com.