

ToxUpdate

Regional Poison Control Center, Birmingham, AL

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Hormonal Emergency Contraception: Uses and Clinical Effects in Toxicology

By Jill Meyer, Samford University PharmD Candidate

According to the Centers for Disease Control and Prevention, roughly 50% of pregnancies in the United States are unplanned. Unplanned pregnancies largely affect women ages 19 and younger, with more than 4 out of 5 pregnancies in this age group being unplanned. Although research surrounding the use of emergency contraception dates back to the 1960s, the first product labeled for emergency contraceptive use was not FDA approved until 1998. Today, over-the-counter, prescription, hormonal, and non-hormonal options of emergency contraception are available.

Over-the-counter products contain levonorgestrel as the active ingredient. Examples of these products are Aftera[®], Next Choice One Dose[™], Take Action[®], Plan B One-Step[®], and My Way[®]. All of these products may be purchased by anyone of any age or gender. Levonorgestrel is a progestin that prevents conception by inhibiting ovulation, altering the endometrium, and by thickening the cervical mucus to decrease sperm mobility. These products are supplied as one tablet containing 1.5 mg of levonorgestrel. They are FDA approved to be taken within 72 hours of unprotected sex, although effectiveness is maintained if taken up to 120 hours after unprotected sex.

Combined hormonal birth control pills contain both estrogen and progestin, and taking combined oral contraceptive pills is a way in which women can obtain prescription hormonal emergency contraception. If using this method, women will need to take multiple pills in two separate doses to obtain 0.1 mg of ethinyl estradiol and 0.5 mg of levonorgestrel with each dose. The first dose should be taken within 72 hours after unprotected sex, and the second dose is to be taken 12 hours after the first.

Although no significant toxic effects are known to occur after an acute overdose of hormonal contraceptives, there is a risk for some serious adverse events in therapeutic use. These include abdominal pain, dysmenorrhea, pulmonary embolism, venous thrombosis, pulmonary embolus, cerebral thrombosis, headache, and breast tenderness.

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Special Interest Articles

- Emergency Contraception
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Did you know?

In an article on liver injury from herbal and dietary supplements (HDS) published in *Hepatology*, January 2017 issue, HDS-induced liver injury now accounts for 20% of cases of hepatotoxicity in the United States. Anabolic steroids, green tea extract, and multi-ingredient nutritional supplements are the agents most implicated.

Zulresso™: The First and Only Drug Indicated for Postpartum Depression

“Onset of PPD may vary from 4 weeks postpartum to up to 12 months postpartum. Until recently, there have been no medications that are specifically indicated for PPD.”



By Regan David, Samford University PharmD Candidate

Postpartum Depression (PPD) has been classified as one of the most common complications of childbirth and has affected women globally for many years. As a very serious condition of pregnancy, one in nine women can experience PPD. Without proper screening, however, nearly half of cases will go undiagnosed. Onset of PPD may vary from 4 weeks postpartum to up to 12 months postpartum. Until recently, there have been no medications that are specifically indicated for PPD.

On March 19, 2019, the FDA approved Zulresso™ (brexanolone) as the first and only drug indicated to treat PPD in women. Brexanolone will be available June 2019. This drug treats PPD by acting as an allosteric modulator of synaptic and extra synaptic GABA_A receptors, which will vary the degree of receptor activity. Zulresso is available as an IV infusion that is administered for 60 hours (2.5 days) in a healthcare facility with proper monitoring capabilities.

The drug was given breakthrough therapy designation status by the FDA and approval was based on results from three clinical trials. These trials tested safety and efficacy of the drug in women aged 18-45 years old that were ≤ 6 months postpartum and with onset of symptoms in the third trimester and no later than the first 4 weeks of delivery. Reductions in symptoms were seen in 24 hours and maintained the drug's effect through 30 days. The drug achieved the primary endpoint of a significant mean reduction in the Hamilton Rating Scale for Depression (HAM-D) at 60 hours compared to baseline. Common side effects reported were sleepiness, dry mouth, flushing, and loss of consciousness. Also, during one of the studies performed, one patient experienced a side effect of infusion site extravasation.

Due to the high-risk adverse effects experienced during infusion of Zulresso (sleepiness and loss of consciousness), the medication can only be administered through the Risk Evaluation and Mitigation Strategy (REMS) Program. In order to abide by the REMS program guidelines, the healthcare facility dispensing Zulresso must be able to monitor patients continuously during the infusion, have continuous pulse oximetry, have a fall precaution protocol, IV programmable pumps with alarms, assess the patient's health status for signs and symptoms every 2 hours during treatment and assess again after treatment prior to discharge. Prior to infusion, Zulresso must be diluted, as it is a hypertonic medication. During the infusion, patients must not be left alone with their child (ren) due to the potential for excessive sedation and sudden loss of consciousness. The use of opioids, antidepressants, or other CNS depressants should be avoided while using Zulresso due to the risk of increased sedation. Although there is little clinical trial evidence or experience in regards to overdose and toxicity, there were two cases of accidental overdoses that resulted from infusion pump malfunctions. These cases resulted in loss of consciousness. Although this medication shows promising results for treating PPD, risks and benefits should be weighed before beginning this therapy due to its alarming side effects.

References

1. FDA News Release. Food and Drug Administration Web site. <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm633919.htm>. Accessed March 28, 2019.
2. Investors & Media. Sage Therapeutics Website. <https://investor.sagerx.com/news-releases/news-release-details/sage-therapeutics-announces-fda-approval-zulressotm-brexanolone>. Accessed March 27, 2019.
3. Xyrem. Micromedex® 2.0, (electronic version). Truven Health analytics, Greenwood Village, Colorado, USA. <http://www.micromedexsolutions.com>. (Accessed February 26, 2019).
4. Zulresso. In: Micromedex 2.0. Greenwood Village (CO): Thompson Reuters. [updated 03/21/2019; accessed 03/27/2019]. https://www-micromedexsolutionscom.ezproxy.samford.edu/micromedex2/librarian/CS/BF055F/ND_PR/evidenceexpert/ND_P/evidenceexpert/DUPLICATIONSHIELD_SYNC/15AE97/ND_PG/evidenceexpert/ND_B/evidenceexpert/ND_AppProduct/evidenceexpert/ND_T/evidenceexpert/PFAActionId/evidenceexpert.IntermediateToDocumentLink?docId=932640&contentSetId=100&title=Brexanolone&servicesTitle=Brexanolone
5. Zulresso [package insert]. Cambridge, MA: Sage Therapeutics, Inc; 2019.
6. Metzler-Brody S, Colquhoun H, Riesenberger R, et al. Brexanolone injection in post-partum depression: two multicenter, double-blinded, randomised, placebo-controlled, phase 3 trials. *The Lancet*. 2018;392(10152): 1058-1070.

Students Visit Warrior Seniors

Regional Poison Control Center PharmD students presented a Medication Safety talk at the Warrior, AL Senior Center on April 10, 2019. Pictured (L-R) - Micaila Hill, Regan David, and Jill Meyer.



Emergency Contraception (continued)

The combined oral contraceptives have a significantly higher rate of nausea and vomiting versus the levonorgestrel-only products. The dose should be repeated if vomiting occurs within two hours of ingesting either the levonorgestrel-only or the combined oral contraceptive products.

The Poison Control Center receives calls regarding children (less than 6 years of age) who have ingested their mother's oral contraceptives. No long term effects have occurred in girls or boys who unintentionally ingest these hormonal pills as the medicine is quickly absorbed and quickly eliminated from the body. Additionally, no occurrences of vaginal bleeding have been reported in girls in this age group after exposure to ethinyl estradiol (Lynch et al. 2009). Short-term side effects that can occur in children include diarrhea, irritability, and stomach upset. These symptoms go away on their own without intervention. Special considerations may need to be made if the oral contraceptive is also formulated with iron and the poison center should be contacted.

References

1. Bryant B. Professional resource, emergency contraception: FAQs. Pharmacist's Letter/Prescriber's Letter. November 2016. [Electronic version]. <https://pharmacist.therapeuticresearch.com/Content/Segments/PRL/2016/Nov/Emergency-Contraception-FAQs-10371> (Accessed March 28, 2019).
2. Emergency contraception. Practice Bulletin No. 152. American College of Obstetricians and Gynecologists. <https://www.acog.org/Clinical-Guidance-and-Publications/Practice-Bulletins/Committee-on-Practice-Bulletins-Gynecology/Emergency-Contraception?IsMobileSet=false> September 2015. (Accessed March 28, 2019).
3. Emergency contraception over the counter. Princeton University. <https://ec.princeton.edu/questions/qa-otc-access.html>. February 22, 2019. (Accessed March 28, 2019).
4. Lynch AM, McKay B & Murray L (2009) Assessment of short-term outcomes following unintentional ingestions of "oral contraceptive pills" by toddlers, *Clinical Toxicology*, 47:2, 174-177, DOI: 10.1080/15563650802438076.
5. Soloway RAG. Birth control pills and toddlers. Poison Control. <https://www.poison.org/articles/2012-jun/birth-control-pills-and-toddlers>. (Accessed April 15, 2019).
6. Unintended pregnancy prevention. Centers for Disease Control and Prevention. <https://www.cdc.gov/reproductivehealth/unintendedpregnancy/index.htm>. January 22, 2015. (Accessed March 28, 2019).

Nasal Spray Spravato™ Approved for Treatment-Resistant Depression

By Micaila Hill, Auburn University PharmD Candidate

In February 2019, Spravato™ (esketamine hydrochloride) became the first novel antidepressant approved by the FDA in 30 years. Unlike most antidepressants, which exert antidepressive effects through serotonin, norepinephrine, and/or dopamine modulation, esketamine is a non-selective, non-competitive NMDA receptor antagonist. The specific role of NMDA in the pathophysiology of depression is unknown.

Spravato is approved for adult patients with treatment-resistant depression (TRD) and should be used in conjunction with an oral antidepressant. Major depressive disorder (MDD) is considered treatment-resistant if symptoms do not respond to at least two antidepressant trials of sufficient dose and duration. About one-third of patients with MDD do not respond to conventional antidepressants and are estimated to have TRD. The recommendation to approve Spravato for this indication was based on safety and efficacy data from five phase 3 clinical trials, which showed clinically significant, rapid and sustained improvement of depressive symptoms in patients treated with Spravato in combination with a newly initiated oral antidepressant. Compared to conventional antidepressants alone, which may take weeks to titrate and reduce symptom burden, Spravato can be titrated as early as the second administration and provides measurable symptom relief within 24 hours of the first administration.

Spravato is available as a 28mg intranasal device and delivers two sprays, one per nostril. Treatment sessions are conducted under direct supervision of a healthcare provider and consist of nasal administration followed by a post-administration observation period. Sessions are conducted twice weekly for the first four weeks, once weekly for the next four weeks, and then once weekly or biweekly thereafter. Providers should start with administration of 56mg for the first session and titrate to 84mg for subsequent sessions based on response. Depending on the dose required, patients may receive two or three devices per session and should allow 5 minutes between each device. Full administration instructions are available in the package insert.

Spravato has a black box warning for abuse and misuse, sedation, dissociation, and suicidal thoughts and behavior. Esketamine is the S-enantiomer of ketamine, a general anesthetic and commonly abused recreational drug. Due to abuse potential, Spravato is only available through a Risk Evaluation and Mitigation Strategy (REMS) program and, like ketamine, is labeled as a Schedule III controlled substance. Because of the risk of sedation and dissociation, patients should be monitored for at least two hours following each administration and assessed prior to leaving the facility to ensure clinical stability. Many antidepressants are associated with increased risk of suicidality in pediatric patients and young adults, and patients on any antidepressant should be closely monitored for suicidal thoughts and behaviors. The efficacy and safety of Spravato has not been evaluated for patients less than 18 years of age or in women who are pregnant or breastfeeding. Other CNS depressants, psychostimulants, or MAOIs should be used with extreme caution.

In addition to sedation and dissociation, the most common adverse reactions associated with Spravato include increased blood pressure and nausea and vomiting. Providers should assess blood pressure before and after administration and use caution if blood pressure is elevated at baseline. Due to risk of increased blood pressure, Spravato is contraindicated in patients with aneurysmal vascular disease, arteriovenous malformations, or history of intracranial hemorrhage. Patients should be advised to avoid food within 2 hours of administration and liquids within 30 minutes of administration to reduce the risk for nausea and vomiting. No long-term adverse effects have been noted, but safety has not been evaluated past one year of use.

References

1. FDA Advisory Committee Recommends Approval of SPRAVATO™ (esketamine) Nasal Spray CIII for Adults with Treatment-Resistant Depression [press release]. Titusville, NJ: Janssen Pharmaceuticals. February 12, 2019. <https://www.jnj.com/fda-advisory-committee-recommends-approval-of-spravatotm-esketamine-nasal-spray-ciii-for-adults-with-treatment-resistant-depression>. (Accessed March 29, 2019).
2. SPRAVATO™ [package insert]. Janssen Pharmaceuticals, Inc., Titusville, NJ. February 2019. <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=d81a6a79-a74a-44b7-822c-0dfa3036eae4>. (Accessed March 29, 2019).
3. Ketamine Micromedex® 2.0 (electronic version). Truven Health Analytics, Greenwood Village, Colorado, USA. <http://www.micromedexsolutions.com>. (Accessed March 31, 2019)