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RPCC Pharmacy Forum

Special Interest Articles:

- Eucrisa
- Non-BZDRAs
- New Opioids



Did you know?

According to the *U.S. Pharmacist*, as many as nine out of ten patients labeled with an opioid allergy do not have a true allergy. Codeine, morphine, and meperidine are the main opioids that cause most allergic-type reactions.

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National Poison Prevention Week

March 19-25, 2017

Poisoning is the #1 cause of injury-related death in the U.S. The third week in March each year is designated as National Poison Prevention Week, a week dedicated to raising awareness about the burden of poisoning in the U.S. and highlighting specific ways to prevent it. Be prepared for poisoning emergencies by programming the Poison Help line in your phone today, 1-800-222-1222!

#NPPW17 #preventpoison

Eucrisa- New Treatment for Atopic Dermatitis

Bailey Lang, PharmD Candidate, 2017

Eucrisa™ is a topical prescription ointment used on the skin to treat mild to moderate eczema in adults and children 2 years of age and older. Eucrisa contains 2% crisaborole, a non-steroidal topical anti-inflammatory phosphodiesterase-4 (PDE-4) inhibitor. By inhibiting PDE-4, an enzyme that regulates inflammatory cytokine production, intracellular concentrations of cyclic adenosine monophosphate (cAMP) are increased and the release of pro-inflammatory cytokines is suppressed.

Eucrisa is the first new treatment for atopic dermatitis in over a decade. Atopic dermatitis affects 18 million adults and children in the United States and it affects 15-20 percent of children in the United States. Eczema usually begins in infancy and Eucrisa is approved for use in children at least 2 years old. The main side effects of Eucrisa are allergic reactions at or near the application site, which can be serious and may include hives, itching, swelling, and redness. The most common side effect of Eucrisa is application site pain, such as burning or stinging.

So far, there are no safety data on the

ingestion of Eucrisa ointment. With a high proportion of use likely being in the pediatric population, it is important to know how to handle an ingestion situation. If a child has ingested Eucrisa ointment, he or she would likely experience adverse reactions similar to the use of oral PDE-4 inhibitors. Oral PDE-4 inhibitors include Otezla (apremilast) and Daliresp (roflumilast).

In an overdose of apremilast, symptomatic and supportive care is the mainstay of therapy. Roflumilast overdose (single doses of 2500 mcg and 5000 mcg were studied) produced an increased incidence of headache, gastrointestinal disorders, dizziness, palpitations, lightheadedness, clamminess, and hypotension. Treatment is symptomatic and supportive care.

Eucrisa is a promising new treatment for patients with eczema. With few adverse effects and unlikely toxicity if accidentally ingested, it has a good safety profile, which is especially important for the large amount of pediatric patients who may use it.

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“Evidence shows a tripling in sleep aid prescriptions from 1998 to 2006 for young adults aged 18–24.”

A Review of FDA- Approved Non-Benzodiazepine Receptor Agonists

Sedative and hypnotic medication sleep aids are used to induce or maintain sleep by suppressing activities in the central nervous system. Over the past two decades, pharmaceutical companies have reported an increased number of prescriptions filled for sleep aids in the United States. Evidence shows a tripling in sleep aid prescriptions from 1998 to 2006 for young adults aged 18–24. Most sleep medicines are on the Beers Criteria of high-risk medicines in the elderly. Although “Z drugs” (zolpidem, zaleplon, eszopiclone) are classified as non-benzodiazepine receptor agonists (non-BZDRAs) due to different chemical structure, the hypothesized mechanism of action is similar to benzodiazepines. The non-BZDRAs interact with GABA-benzodiazepine receptor complexes (GABA(A) alpha-1 subunit), enhancing the function of GABA-mediated chloride channels. Other non-BZDRAs that work outside the GABA-benzodiazepine receptor complex, may be preferred due to lower likelihood of abuse and physical dependence. The following is a review of Non-BZDRAs excluding those that affect the GABA receptors:

Diphenhydramine and Doxylamine- Diphenhydramine (e.g., Sominex) and doxylamine (e.g., Unisom) are first-generation antihistamines that work as competitive antagonists of histamine at the H1 receptor. From an adverse-effect stand-point, these agents can cause confusion, carryover sedation, urinary retention, and multiple other anticholinergic effects. The 2015 Beers criteria update gave a “strong” recommendation to avoid both agents in elderly patients.

Doxepin (Silenor®) - Doxepin is a tricyclic antidepressant with H1-receptor antagonism that produces a sedative effect. While it has been used as an antidepressant for over 50 years, in 2010, the FDA approved it for treatment of insomnia. Doxepin has high selectivity for histamine receptors therefore can be prescribed at a low dose of 3 to 6 mg. Anticholinergic effects are not frequently seen with doses less than or equal to 6 mg. This would be an advantage over diphenhydramine and doxylamine where anticholinergic effects are significantly higher.

Ramelteon (Rozerem®) - Ramelteon is a melatonin receptor agonist with high affinity for melatonin MT1 and MT2 receptors and selectivity over the MT3 receptor. Ramelteon’s affinity for the MT1 and MT2 is significantly more than Melatonin itself. Ramelteon does not appear to have any abuse potential and has a limited ability to cause carryover sedation, rebound insomnia, or withdrawal upon discontinuation. About 3% of patients reported a worsening of insomnia when using ramelteon.

Suvorexant (Belsomra®) - Belsomra is the first orexin receptor antagonist. Neuropeptides orexin A and B promote wakefulness by acting on orexin receptors OX1R and OX2R. Suvorexant is a highly selective antagonist for orexin receptors, thereby exerting pharmacologic activity by blocking OX1R and OX2R receptors that are thought to suppress wake drive. Excessive daytime drowsiness was the most commonly reported adverse event. Suvorexant is contraindicated in patients with narcolepsy due to unique ability to “turn off” wakefulness. Belsomra is a schedule IV controlled substance.

Melatonin- Melatonin (N-acetyl-5-methoxytryptamine) is a natural physiologic neural transducer, an endogenous hormone, produced in the pineal gland from tryptophan and secreted rhythmically, usually at night. Darkness seems to stimulate melatonin secretion, and light inhibits it. Melatonin levels are thought to be lower than normal in some patients with insomnia. Melatonin may reduce the time to fall asleep by 10 minutes. Melatonin does not usually cause a “hangover” effect.

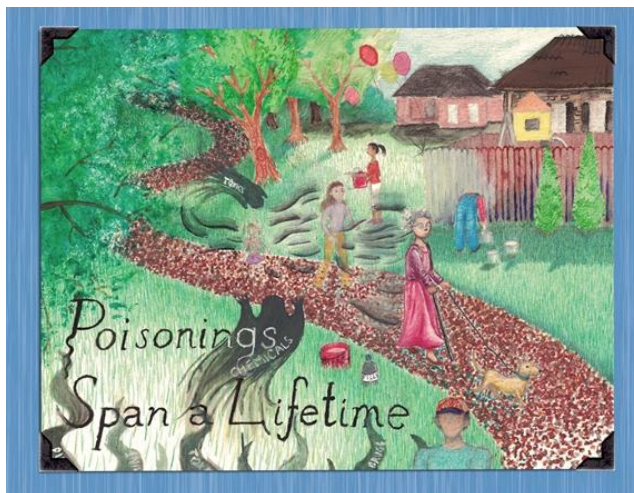
Valerian- Valerian is a perennial flowering plant, whose active parts are the root and rhizome (stem found underground). It is theorized that valerian's sedative effects are caused by a combination of depression of specific centers of the CNS and by direct relaxation of smooth muscle. The components responsible for these effects are the valepotriates, the essential oil components and unidentified water-soluble components. Valerian seems to have benzodiazepine-like effects. To avoid potential benzodiazepine-like withdrawal symptoms following long-term use of valerian, patients should taper doses slowly after extended use. The maximum duration of therapy is 2 weeks.

Non-Benzodiazepine Receptor Agonists for Insomnia

Drug	Standard Dose	Special Dosing Considerations	Toxicology
Diphenhydramine	50 mg once daily	Peak effect seen in ~2 hours	Anticholinergic effects, ↑HR and BP, seizures, agitation, delirium, QRS widening
Doxylamine	25 mg once daily	Peak effect seen in 2-4 hours	Similar to diphenhydramine
Doxepin (Silenor)	3 mg once daily Max: 6 mg daily	Do not take within 3 hours of a meal	CNS depression, seizures, tachycardia, QRS prolongation, hypotension
Ramelteon (Rozerem)	8 mg once daily	Do not take shortly after a high-fat meal	Significant toxicity not anticipated; dizziness, CNS depression, hallucinations, nausea, headache
Suvorexant (Belsomra)	10-20 mg once daily	Do not take with food	Women twice as likely to experience adverse effects, dizziness, headache, abnormal dreams, diarrhea, hallucinations
Melatonin	0.3 to 5 mg once daily	Immediate-release for trouble falling to sleep; Sustained-release for trouble staying asleep	Children: Ingestion of 3-80 mg have resulted in minimal effects.
Valerian	400-900 mg up to 2 hours before bedtime	Drug interactions due to inhibition of CYP3A4 in liver	Dizziness, chest pain, mydriasis, tremors; withdrawal after long-term use may result in cardiac disturbances and delirium

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FDA Approval of Three Abuse-Deterrent Opioids

Jonathan Thaxton, PharmD Candidate, 2017

Prescription opioids have become widely abused in past years. Both immediate release and extended release forms have been manipulated by abusers to deliver spontaneous highs that sometimes have life-threatening consequences.

The introduction of abuse-deterrents in an extended release medication has reduced the number of abuse cases and toxic exposures from opioid medications. One study found that the number of cases of abuse and toxic exposures decreased following the introduction of an extended release oxycodone. Subsequently, the abuse and toxic exposures of medications without abuse-deterrent systems increased. This study supports the idea that abuse-deterrent systems could help prevent toxic exposures and abuse outside the environment of the product's clinical trials.

Recently, the FDA approved three new release mechanisms for older medications to stem the epidemic of opioid abuse. Troxyca ER® was approved August 2016. Vantrela ER® and Arymo ER® were both approved January 2017. All three medications took existing opioid medications and adapted them to new abuse-deterrent formulations. These formulations hope to push back against attempts to break, crush, or alter the stability of the medications.

Troxyca is extended release oxycodone with naltrexone from Pfizer pharmaceuticals. Vantrela ER is an extended release version of the popular hydrocodone in an abuse-deterrent vehicle produced by Teva pharmaceuticals. Finally, Arymo ER is an extended release morphine sulfate produced by Egalet Corporation.

Many mechanisms have been proposed to prevent abuse of opioid drugs. Troxyca ER uses sequestered naltrexone. Should a tablet of Troxyca ER be crushed or chewed, the sequestered naltrexone would be released and competitively displace opioids while blocking opioid receptors. Naltrexone is almost completely absorbed when taken orally; however, a strong first pass effect leads to a bioavailability of 5 to 40%. It is twice as strong and lasts longer than naloxone. Naltrexone's concentrations would peak in one hour after ingestion and its duration of effect would last anywhere from 24 to 72 hours for 50 to 150 mg, respectively.

Vantrela ER and Arymo ER, however, utilize polymer shells surrounding the drug that inhibit the ability to dissolve or crush the medication. Specifically, Egalet Corporation has developed a novel type of injection molding that creates their abuse deterrent tablets known as Guardian technology. The Guardian technology involves the injection molding of non-degradable polymer tubes that allow drug to be dispersed from the open ends. This follows similar "ghost" tablets used in the past, but with proprietary injection molding techniques.

These new technologies may not only help prevent abuse, but may prevent toxicity in accidental overdose. Children who chew on the polymer tablets would have a lower probability of getting a full dose. Likewise, chewing a Troxyca ER tablet would release the antidote to the opioid. Furthermore, tablets that encase the active drug in polymer should prove advantageous in improving the success of whole bowel irrigation. The introduction of new technologies that hinder drug manipulation shed new hope on a growing problem of opioid abuse and could prove advantageous in preventing toxicity in

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