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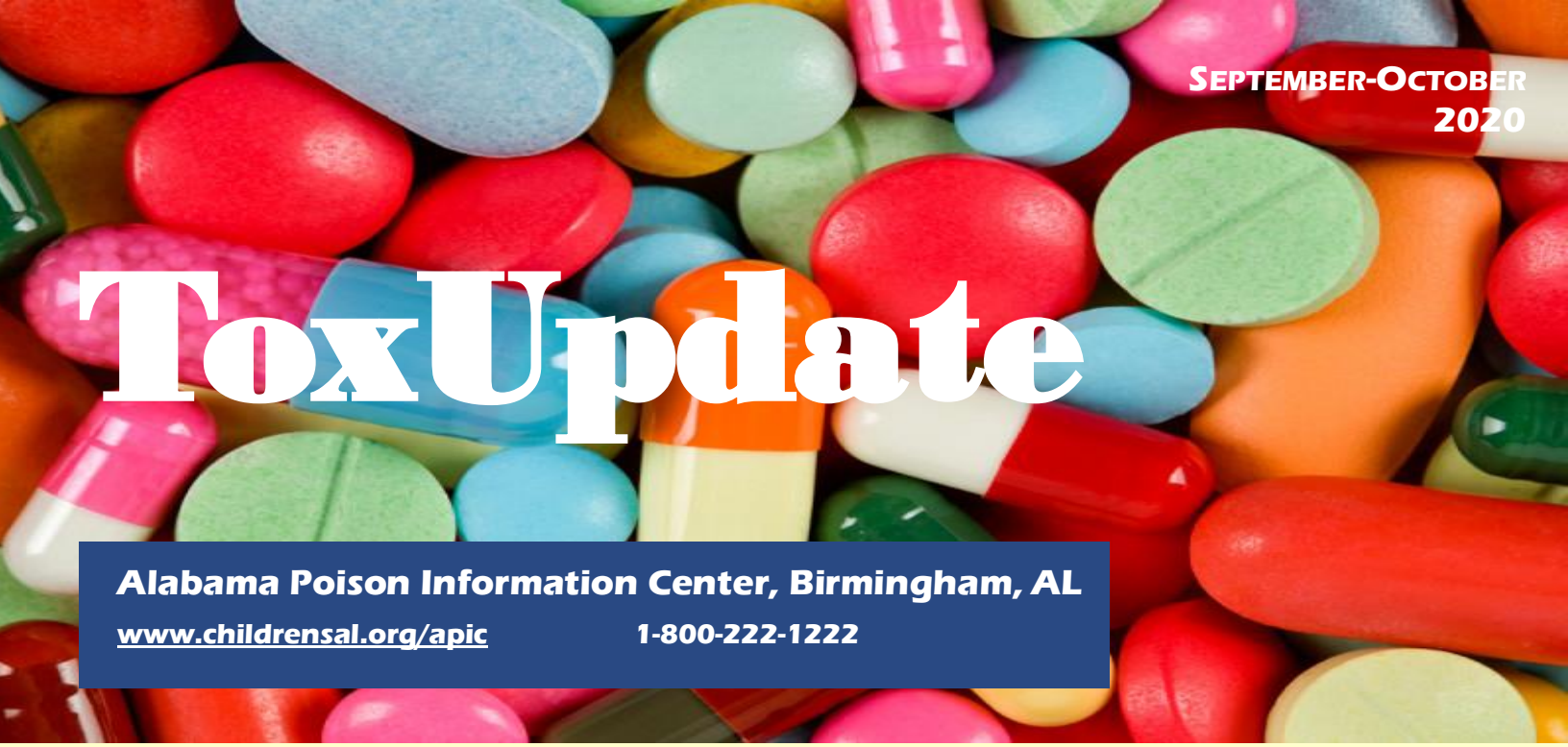

ToxUpdate

Alabama Poison Information Center, Birmingham, AL
www.childrensal.org/apic 1-800-222-1222

Abuse-Deterrent Opioid Formulations

By Olivia Dauphin, Samford University PharmD Candidate

Abuse-deterrent opioid formulations (ADFs) aim to make it more difficult or less rewarding to abuse certain orally prescribed opioids via specific routes. These formulations have been created in response to the high incidence of prescription opioid abuse and addiction. Available ADFs work to alter the physical and chemical properties of the drug formulation to deter abuse or accidental misuse by patients. Targeted routes of abuse typically include chewing, snorting, and injecting. These formulations are evaluated for their resistance to physical and chemical manipulation. Physical alterations work to prevent crushing or grinding by common tools. Chemical alterations work to prevent dissolution by various solvents and/or make it difficult for intranasal and IV abuse.

Currently, there are four opioids with FDA approved ADF labeling available in the United States: OxyContin® (oxycodone), Xtampza ER® (oxycodone), MorphaBond ER® (morphine), and Hysingla ER® (hydrocodone). All available formulations are extended-release. OxyContin became the first FDA approved ADF after it was reformulated in 2010 due to widespread abuse of its original formulation. OxyContin uses high-molecular-weight polyethylene oxide to form a coating that resists damage and form a gel when introduced to liquid solvents. The formation of a gel makes it more difficult to uptake drug through a needle. Xtampza ER is a capsule formulation that can be opened and sprinkled on food. The capsule contains microspheres made of hydrophobic fatty acids and waxes that resist damage and solidify when in contact with solvents. MorphaBond ER relies on several different layers to resist damage and prevent adequate dissolution for IV abuse. Hysingla ER uses technology like OxyContin to create a polyethylene oxide coating to resist damage and IV abuse.

ADFs are potentially beneficial in protecting against intentional abuse and unintentional therapeutic errors by patients. Standard ER formulations run the risk

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Special Interest Articles

Did you know?

According to *The Lancet*, vitamin D supplementation could show promise as a therapeutic agent in treatment of COVID-19. Interest in vitamin D as prevention or treatment of acute respiratory infections dates to the 1930s when cod liver oil was recommended to reduce absences from work in industry.

Vitamin D Therapeutic Uses and Toxicity

"Vitamin D is a fat-soluble vitamin that acts as a steroid hormone so there is potential for it to accumulate in the body and cause toxicity."

By Davis Campbell, Samford University PharmD Candidate

In foods and dietary supplements, vitamin D has two main forms, D2 (ergocalciferol) and D3 (cholecalciferol). It is commonly found in multivitamins but is available by itself over the counter or in combination with calcium. Prescription strength vitamin D is usually given in cases of severe deficiency or for the prevention and treatment of rickets, osteomalacia, osteoporosis and hypoparathyroidism. It promotes calcium absorption and aids in maintaining serum calcium and phosphate levels. Recommended daily allowance for vitamin D for ages 1 to 70 is 15 mcg (600 IU) with that amount increasing to 20 mcg (800 IU) over the age of 70. The intake at which vitamin D becomes toxic is not clear but the Institute of Medicine has defined the tolerable upper intake level to be 100 mcg (4000 IU) daily for healthy adults and children age 9 to 18 years old with daily doses of 50,000 to 150,000 IU described as causing toxicity.

In 2016, there was a change in the units of measure on labels of over the counter vitamins that contained fat soluble vitamins (Vitamin A, D, and E). The changes came from the US Food and Drug Administration (FDA) and were published in the Federal Register on May 27, 2016. It required that the traditional use of International Units (IU) be stated as metric units of measure like micrograms (mcg) or milligrams (mg). It also required manufacturers to list absolute values in mcg or mg in addition to the percent daily value. As the Institute for Safe Medication Practices discourages the use of IU, due to cases of mistaking IU for IV, manufacturers are not restricted from still listing IU in addition to mcg or mg. For vitamin D, 1 IU is the biological equivalent of 0.025 mcg cholecalciferol or ergocalciferol.

Vitamin D is a fat-soluble vitamin that acts as a steroid hormone so there is a potential for it to accumulate in the body and cause toxicity. Especially given the long half-life of the active form (calcitriol or 1,25-dihydroxyvitamin D3) being 15 hours and the precursor (calcidiol or 25-hydroxyvitamin D3) being 15 days. Overdose is rare but severe toxicity can result from chronic ingestion of large amounts through fortified foods and supplementation. Mild to moderate toxicity can present with nausea, vomiting and abdominal cramps in the event of acute ingestion with other symptoms like anorexia, constipation or diarrhea, weakness, fatigue, irritability, drowsiness, headache and dizziness. Symptoms of severe toxicity are due to hypercalcemia secondary to the chronic high dose ingestion of vitamin D. These symptoms may include seizures, confusion, ataxia, psychotic disturbances, coma, or renal failure with a potential for cardiac dysrhythmias to occur. It is possible that vitamin D may act as a vascular toxin due to structural similarity to 25-hydroxycholesterol. The manifestations of toxicity in this respect could be medial degeneration, calcification of the coronary arteries, and smooth muscle cell proliferation as it has been observed in animal studies.

Severe toxicity with vitamin D supplementation may occur for a few reasons. Patients who purchase vitamin D supplements over the counter without the supervision of a doctor may be at risk for taking amounts high above the recommended daily allowance. In cases where prescription strength vitamin D is being prescribed by a physician, it is usually done where there is enough monitoring of serum vitamin D levels by measuring 25-hydroxyvitamin D in the blood. Severe toxicities are possible in these cases where patients are taking more vitamin D than prescribed either from taking their dose more frequently or by supplementing with over the counter products.

Since news of the Covid-19 pandemic, it is possible that people have turned to vitamin supplementation in order to improve their immune function. By taking large doses of multivitamins and vitamin D containing products, the they are putting themselves at risk for vitamin D toxicity. As the coronavirus continues, we may see a rise in the number of toxic exposures. In the event of vitamin D toxicity, monitor calcium and phosphate levels and contact the Alabama Poison Information Center for treatment recommendations. *(References on page 4)*

Xyway™ Helping Sleep Waves?

By Stephen Parker, Samford University PharmD Candidate

Narcolepsy is a condition that affects an estimated 200,000 people in the United States. This number could be higher due to the challenge of diagnosing narcolepsy. The cause of narcolepsy is not currently understood. People with narcolepsy lack the ability to regulate their sleep-wake cycle which results in excessive daytime sleepiness (EDS), cataplexy, and sleep paralysis (not necessarily at the same time). Treatment of narcolepsy includes taking scheduled naps or stimulants (e.g., modafinil or amphetamines). Another measure to help regulate the sleep-wake cycle is to treat with an oxybate salts (CNS depressants).

Xyrem® is sodium oxybate, and it is currently prescribed to treat EDS and cataplexy. Xywav is a newly approved oxybate salt (calcium, magnesium, potassium, and sodium) used to treat narcolepsy similarly to Xyrem with significantly less sodium. Both medications can be used in patients 7 and older, and they have similar dosing schedules: one dose at bedtime with a second dose 2.5-4 hours later. The recommended dose for Xywav is 4.5-9 g in adults (pediatric dosing is available in the package insert). JAZZ Pharmaceuticals, Inc. is not expecting patients that are well controlled on Xyrem to switch to Xywav, but Xywav may be better alternative for patients that have to restrict sodium intake while taking medications for narcolepsy. Xywav is expected to be available by the end of this year and will be monitored by the Xywav and Xyrem REMS program due to its abuse potential. Gamma-hydroxybutyrate (GHB) is the active moiety of Xywav. The effects of Xywav are thought to be mediated through GHB and GABA B receptors. At low dosages, GHB is thought to deliver a euphoric effect, but at higher dosages it can make a person drowsy which is why some people misuse GHB as a "date-rape" drug.

Mild toxicity can present as hallucinations, euphoria, and dizziness. Severe toxicity can lead to respiratory depression, bradycardia, and even coma. Mild toxicity from GHB can begin within 15-30 minutes of ingestion while severe toxicity can occur within 30-40 minutes after overdose. Patients will normally recover within 4 hours post ingestion if basic life support is given (e.g., insuring a patient airway). Complete resolution of symptoms is expected to occur within 8 hours of ingestion. In the event of an accidental overdose or pediatric ingestion, the poison center should be contacted in order to monitor the patient's symptoms. GHB toxicity can be life-threatening. GHB is rapidly cleared and is eliminated in the urine (<5 % unchanged within 6-8 hours), therefore it is important to collect a urine sample as soon as possible.

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of enhanced drug release when crushed or damaged. ADFs protect against unintentional therapeutic errors by preventing dose dumping if a patient tries to crush an ER formulation to make it easier to swallow. This same mechanism may protect children who find and chew on these drugs.

It is important to note that abuse is still possible with ADFs, and more research is needed to determine the effectiveness of ADFs in reducing the prevalence of opioid addiction and abuse.

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The FDA developed an in vitro chewing method intended to predict oral bioavailability of abuse-deterrent opioid products following chewing.

Natural Sources of Vitamin D

Food	Serving Size	Vitamin D [a] (IU)
Salmon		
Fresh wild	3.5 oz.	600-1000
Fresh farmed	3.5 oz.	100-250
Sardines, canned	3.5 oz.	300
Tuna, canned	3.5 oz.	236
Mackerel, canned	3.5 oz.	250
Shitake mushroom		
Fresh	3.5 oz.	100
Canned	3.5 oz.	1600
Egg, hard-boiled	3.5 oz.	20

[a] The activity of 40 IU of vitamin D is equivalent to 1 µg.

Source: Golden NH, Abrams SA; Committee on Nutrition. Optimizing bone health in children and adolescents. Pediatrics. 2014 Oct;134(4):e1229-43. doi: 10.1542/peds.2014-2173. Review. PubMed PMID: 25266429.

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