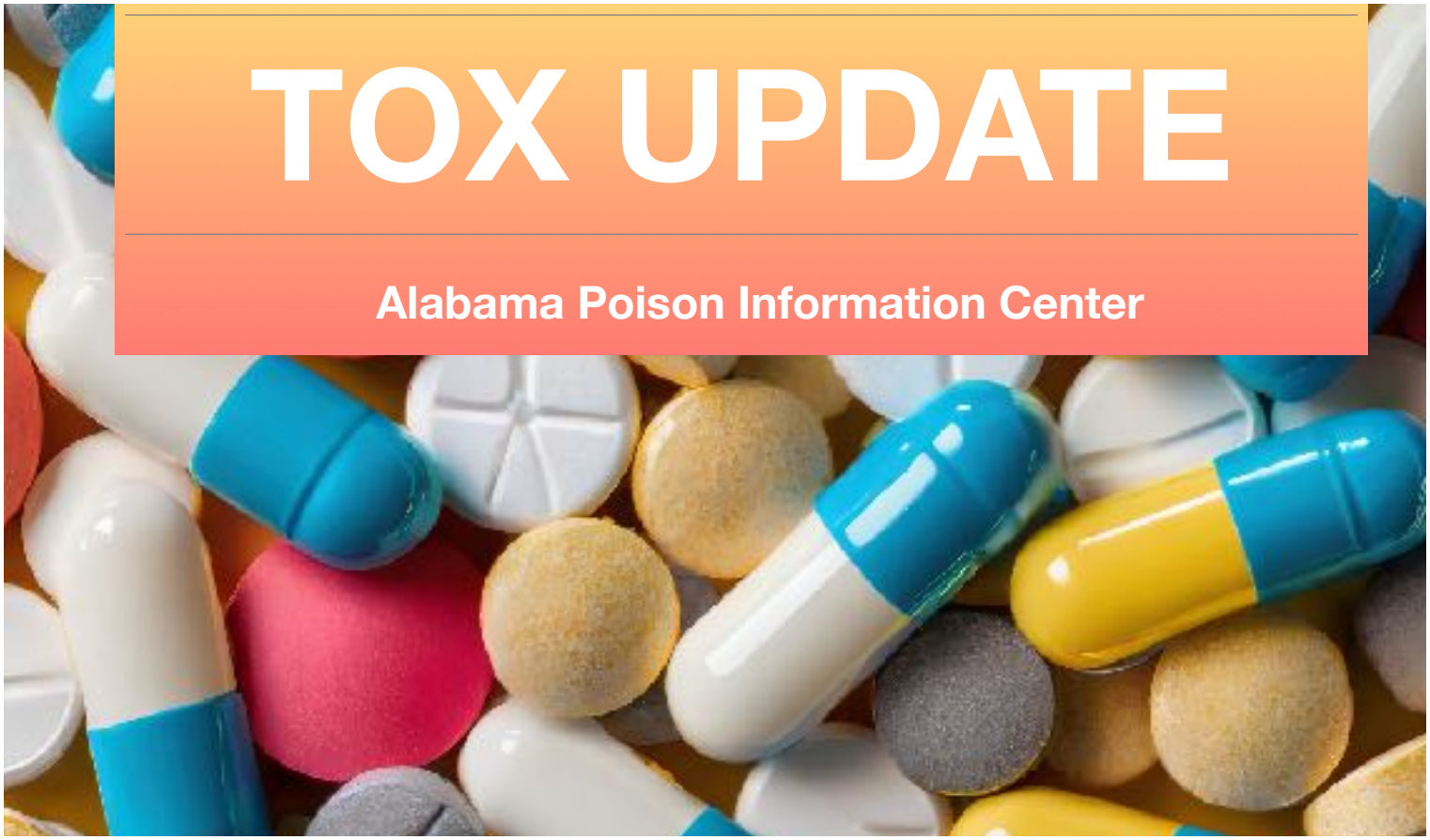
TOX UPDATE

Alabama Poison Information Center



Letter from the Alabama Poison Information Center

ALABAMA POISON INFORMATION CENTER
800-222-1222

As the summer sun fades and the autumn leaves begin to fall, it's not just the scenery that changes. The types of poison exposures we see also shift. While we bid farewell to the sunscreen-related calls of summer, we welcome a new wave of exposures associated with the changing seasons.

One of the most common concerns this fall is the rise in cough and cold medicine exposures. As people reach for over-the-counter remedies to combat the sniffles and sneezes, it's important to remember the potential dangers of accidental overdose, especially in children.

And let's not forget the scary new formulation of acetaminophen gummies. These brightly colored treats can be mistaken for candy, leading to tragic consequences. We'll delve deeper into this alarming issue, and other topics, in this month's newsletter.

In this issue:

- New acetaminophen gummy formulation
- Ashwagandha
- New formulation of colchicine tablets
- Newly approved drug for opioid overdose

ToxUpdate is brought to you by APIC and edited by Rachael Fogel PharmD

The Risk of Sweet Relief: New Acetaminophen Gummy Formulation

By Katelyn Swearengin, PharmD Candidate 2025
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Challenges and controversies surrounding acetaminophen use are recurring as a new dosage form becomes available, requiring reassessment of current knowledge. DrKids® new product, Children's Pain and Fever Bite, a gummy containing acetaminophen, has reached shelves nationwide. Marketed for ages 2-11, the orange-vanilla-flavored gummy contains 80mg of acetaminophen per piece.[1] Although this formulation was created for convenience and exact dosing, it poses a major risk to children who may obtain them unsupervised. In October 2023, the Food and Drug Administration weighed the risks and benefits of medication that tastes like candy. A statement was released stating that a clear definition of candy-like drug products does not exist, and little research on consumer comprehension of these products has been completed.[2] The risk of misuse and accidental overdose exponentially increases when medication tastes and looks like candy, leading to an increase in child overdose visits to the emergency room.[3]



An acute ingestion of 200 mg/kg of acetaminophen in children is enough to cause hepatotoxicity.[4] Metabolism of acetaminophen by cytochrome P450 mixed function oxidase enzymes results in the formation of the toxic metabolite N-acetyl-p-benzoquinone imine (NAPQI).[4] NAPQI is neutralized by glutathione; however, in overdose, natrual glutathione stores are depleted leading to reaction with hepatic macromolecules and subsequent injury.[4] The time in which clinical effects appear depends on acetaminophen ingestion time. Early after ingestion, clinical effects are mild, including nausea, vomiting, and abdominal pain.[4] After 24-48 hours, liver transaminases start to climb, along with evidence of liver necrosis. Diagnosis is established based on acetaminophen levels, which are most accurate when drawn at least 4 hours from the time of an acute ingestion. In acute ingestions, this level is then plotted using the Rumack Matthew nomogram to evaluate toxicity and guide treatment.

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N-acetylcysteine (NAC) therapy is initiated if the serum level falls above the treatment line on the nomogram or if serum levels are unavailable. For the most therapeutic effect, NAC should be initiated within 8-10 hours of ingestion before the toxic metabolite accumulates.[4] The duration of treatment is usually 21 hours. If evidence of liver injury develops, seen as elevated liver function tests (LFTs) or prothrombin time (PT)/international normalized ratio (INR), NAC should be continued until improvement is seen.[4] If initial serum levels fall below the treatment line on the nomogram, the patient is at a low risk of toxicity, and NAC treatment is usually not necessary.[4]

Preventing acetaminophen overdose is crucial by counseling and educating parents on maximum doses, administration, and keeping products out of reach of children.[5] Health professionals play an essential role in raising awareness and warning parents that medications that look and taste like candy pose a significant risk to children who cannot tell the difference. With appropriate education and awareness, parents can deliver medication to their children safely and efficiently.

Ashwagandha (Withania somnífera)

By Kenneth Machado Figueroa, PharmD Candidate 2025
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Ashwagandha, an herb that has gained popularity in recent years, is a key component of Ayurvedic medicine, one of the oldest medicinal practices. It is classified as a Rasayana herb, a term that signifies its ability to promote the health of all tissues and rejuvenate the body. It is also recognized as an "adaptogen," a plant that aids the body in responding to anxiety, stress, and overall well-being. The uses of ashwagandha are diverse, including improving athletic performance, reducing stress and anxiety symptoms, boosting testosterone, reducing blood sugar levels, reducing inflammation, improving memory, and enhancing sleep quality.

Although the plant's roots are the main medicinal component, leaves, flowers, seeds, and fruits are also used. Extracts of the different parts of *Withania somnífera* have been reported to contain different chemical constituents such as alkaloids, steroidal lactones, saponins, withanolides, withaferins, and iron. No specific active ingredient is known to be responsible for its activity. The principal bioactive compounds are withanolides (triterpene lactones). *Withania somnífera* has multiple reactive sites that are implicated as potential therapeutic targets.

Ashwagandha possesses different mechanisms of action. It contains steroidal lactones that have adaptogenic and immunomodulatory properties. Decreased glycosaminoglycan content may be responsible for an anti-inflammatory effect. There is evidence that GABA-ergic mechanisms contribute to anticonvulsant effects. There have also been reports of antibiotic effects. Withaferin A is considered a mitotic poison as well as a radiosensitizer.

This product is supplied as tablets, powder, capsules, gummies, tinctures, paste, and in combination with other herbs. Dosing information is limited. Different dosages used in clinical studies include 300 mg twice daily for 8 to 12 weeks, 240 mg once daily for 60 days, and 500 mg twice daily for 12 weeks of standardized ashwagandha extract.

While ashwagandha is generally well-tolerated, it's important to be aware of potential side effects. These can include CNS and respiratory depression, decreased body temperature, gastrointestinal upset, and kidney and liver abnormalities. In large doses, the intestinal mucosa can be directly irritated, leading to symptoms such as nausea, vomiting, diarrhea, and abdominal pain. It's worth noting that this product is contraindicated in pregnancy and for individuals with hypersensitivity to ashwagandha. Interaction reports are limited, but some studies have shown the potentiation of phenobarbital-induced sleep in animals, and interactions have been observed with some digoxin immunoassays, possibly due to chemical similarities.

Ashwagandha, at reasonable doses, has modest acute toxicity. Liver damage is a possibility, depending on the dose used. Oxidative stress and apoptosis of liver cells is caused by mitochondrial damage and reactive oxygen species. Treatment for toxicity should include symptomatic and supportive care, supporting respiratory, liver, and cardiovascular function.

Lodoco® in Cardiovascular Disease

By Loc Duy Le, PharmD Candidate 2025
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The FDA has approved Lodoco® (colchicine) as the first anti-inflammatory drug specifically for reducing the risk of cardiovascular events in patients with cardiovascular disease. Lodoco® is designed to lower the risk of myocardial infarction, stroke, coronary revascularization, and cardiovascular death in adults with established atherosclerotic disease or multiple cardiovascular risk factors. This approval marks a significant development as Lodoco® targets the inflammatory pathways that contribute to atherosclerotic cardiovascular disease, complementing traditional treatments that focus on lowering cholesterol levels.

Lodoco® is formulated as a once-daily oral tablet at a low dose of 0.5 mg, which can be used alone or in combination with standard lipid-lowering medications. The drug works by inhibiting microtubule assembly, which reduces inflammation and plaque formation in the arteries. The approval was based on a clinical trial involving 5,522 patients with chronic coronary disease. Lodoco® significantly reduced the risk of major cardiovascular events by 31% (hazard ratio, 0.69 [95% CI, 0.57-0.83] $P < 0.001$) compared to a placebo.

However, there are safety considerations. Common side effects include gastrointestinal issues such as diarrhea, vomiting, and abdominal cramping, as well as muscle pain and potential blood-related problems. Also, treatment with colchicine is contraindicated in patients with renal failure or severe hepatic impairment and with concurrent use of strong CYP3A4 or P-GP inhibitors.

A specific toxic dose has not been established. However, ingestions of 0.5 – 0.8 mg/kg can develop serious adverse reactions such as myelosuppression, and ingestion of more than 0.8 mg/kg can result in death. The IV formulation of colchicine is no longer available in the US due to severe toxicity.

This new formulation of colchicine offers promising therapeutic benefits. However, it's crucial to handle and store this medication with utmost care. To prevent accidental ingestion, especially by children, Lodoco® should be kept in a secure location, out of reach and sight. Patients should also adhere strictly to the prescribed dosage and administration instructions to minimize the risk of adverse effects. By following these guidelines, we can ensure the safe and effective use of Lodoco®.

OPVEE®

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Synthetic opioid exposure and overdose have risen in recent years. According to the CDC, overdoses from synthetic opioids have been the primary driver of overdose deaths in the US.[1] From January 2020 to January 2021, overdose deaths involving synthetic opioids, including illicitly manufactured fentanyl, rose 55.6%.[1] Provisional data from 2022 reports that synthetic opioids caused about 90% of all opioid overdose deaths.[2] Illicit fentanyl is being distributed across the country and sold on the illegal drug market.[1] Drug trafficking organizations typically distribute fentanyl by the kilogram, which alone could kill half a million people.[1] Fentanyl overdoses are especially dangerous because only a tiny amount of the drug, such as 2mg, can be fatal. Fentanyl is being mixed with other illicit drugs to increase their potencies, and with illicitly manufactured fentanyl, there is no exact dosing per tablet. The DEA has found counterfeit pills ranging from 0.02 to 5.1 mg of fentanyl per tablet, with 42% of pills tested for fentanyl containing at least 2mg.[1] Fentanyl and other synthetic opioids are fast,

Nalmefene is a 6-methylene analog of naltrexone. Pharmacodynamic studies have shown that nalmefene injection has a longer duration of action than naloxone injection at fully reversing doses.[3] In the pharmacodynamic study, OPVEE® reversed respiratory depression by an average of 98.9% at 5 minutes.[2] Complete recovery of the respiratory drive was seen at 5-15 minutes.[3] In the pharmacokinetic studies, the half-life of OPVEE® was 11.4 hours, and bioavailability was 80.6% relative to the intramuscular administration of nalmefene.[3] Nalmefene is metabolized by the liver primarily by glucuronide conjugation. No dosing adjustments are required for hepatic or renal impairment.[3]

OPVEE® (nalmefene 2.7mg) is indicated for emergency treatment of known/suspected overdose of natural or synthetic opioids in patients over the age of 12 years with respiratory and/or central nervous system depression.[2] OPVEE® is for immediate administration in emergencies and is not a substitute for seeking medical care. If the patient does not respond or responds and then relapses into respiratory depression, readminister OPVEE® using a new nasal spray every 2 to 5 minutes.[2] OPVEE® is for intranasal use only and comes ready to use.[2] This device is like naloxone, a single dose that does not need to be primed and can precipitate severe opioid withdrawal. OPVEE® has limited efficacy with partial opioid agonists or mixed opioid agonists/antagonists. The most common adverse reactions are nasal discomfort, headache, nausea, dizziness, hot flash, vomiting, anxiety, fatigue, nasal congestion, throat irritation, rhinalgia, decreased appetite, dysgeusia, erythema, and hyperhidrosis.

While promising pharmacokinetic and pharmacodynamic data exists to support nalmafene's effects, minimal human data or outcomes-based data in our current opioid landscape is currently available. Naloxone remains an effective reversal agent that is readily available over the counter in Alabama and should continue to remain a first line agent until further data is available.

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