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Kratom: A Drug of Concern

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Kratom, an herbal nonprescription medication native to Southeast Asia, has become increasingly prevalent in the United States. It is being used by patients who are seeking alternative pain treatments to opioids and for opioid addiction; however, US Food and Drug Administration (FDA) has not approved kratom for medical use.[1,2] The herbal product, which comes from a tropical tree called *Mitragyna speciosa,* has the ability to produce psychotropic effects similar to opioids at high doses, considered to be between five and 15 grams, and stimulants at low doses, considered to be between one and five grams. Additional effects of taking kratom can include nausea, itching, sweating, dry mouth, constipation, increased heart rate, vomiting, weight loss, hepatotoxicity, hallucinations, and in rare cases, seizures.[1,3] The leaves contain the active components mitragynine and 7-hydroxymitragynine, which interact with mu- and delta-opioid receptors and produce opioid-like effects as well as improve mood and anxiety.[4] The more potent of the two is 7-hydroxymitragynine, while mitragynine is more abundant and about 13 times more potent than morphine.[5] Kratom does have potential for abuse and dependence, which has been seen more and more over the past few years in the US. It is not currently a scheduled substance, but Drug Enforcement Administration (DEA) has labeled kratom as a "drug of concern."[1]

Kratom is available on the internet and at gas stations and smoke shops. It comes in several forms, including capsules, tablets, powder packets, extracts, and gum. The leaves can be directly chewed, smoked, or brewed into tea.[2,4] Alternative names kratom goes by include biak, ketum, kakuam, ithang, thom, and herbal speedball.[4]

Although rare, kratom-related toxicity should be treated as a medical emergency. FDA has identified at least 44 deaths in relation to the use of kratom. The majority of deaths involved contaminated products or coingestants, including illicit drugs, opioids, benzodiazepines, gabapentin, cough syrup, and loperamide. However, one case in particular is suspected to be caused by pure kratom alone.[4] Although the efficacy of results is conflicting in animal studies, it is recommended that naloxone be considered for reversing an acute kratom overdose with a respiratory depression due to its safety profile.[3,5]

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CBD, the Farm Bill, and Alabama

With the enactment of the Agriculture Improvement Act of 2018, commonly known as the farm bill, many questions have been raised for Alabama pharmacists and the Alabama State Board of Pharmacy. The farm bill changes certain federal oversight relating to hemp production, sale, and possession. These changes remove hemp (and therefore, hemp-related products) from the

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National Pharmacy Compliance News

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The applicability of articles in the *National Pharmacy Compliance News* to a particular state or jurisdiction can only be ascertained by examining the law of such state or jurisdiction.

Final Guidance Documents Address FDA Policies Related to DSCSA

To help ensure that prescription drug products are identified and traced properly as they move through the supply chain in compliance with federal law, Food and Drug Administration (FDA) issued two final guidance documents related to the Drug Supply Chain Security Act (DSCSA). Released on September 19, 2018, the following final guidance documents will help ensure there are no disruptions in the supply chain as manufacturers and repackagers include a product identifier on the package or case.

- *Product Identifier Requirements Under the Drug Supply Chain Security Act – Compliance Policy* addresses industry-wide readiness for implementation of the new requirements aimed at enhancing the security of the drug supply chain. As the agency continues to work with stakeholders to ensure proper implementation of the law, this guidance document specifies FDA's one-year delay in enforcing the manufacturers' requirement to include a product identifier on the package or case of products to November 27, 2018.
- *Grandfathering Policy for Packages and Homogenous Cases of Product Without a Product Identifier* outlines the circumstances in which packages and cases of product that were in the supply chain before the November 2018 product identifier requirement are considered grandfathered. The grandfathering policy describes the circumstances under which products already in the supply chain can remain in distribution without being relabeled with a product identifier.

The final guidance documents can be found at *www.fda.gov/newsevents/newsroom/fdainbrief/ucm621095.htm.*

First FDA-Approved Drug Containing Extract From Cannabis Plant to Be Placed in Schedule V

On September 27, 2018, the United States Department of Justice and Drug Enforcement Administration (DEA) announced that Epidiolex® – which contains cannabidiol, a chemical constituent of the cannabis plant, and is the first FDA-approved drug to contain a purified extract from the plant – is being placed in Schedule V of the Controlled Substances Act. FDA approved Epidiolex for the treatment of seizures associated with two rare and severe forms of epilepsy, Lennox-Gastaut syndrome and Dravet syndrome, in patients two years of age and older on June 25, 2018. Additional information is available in the announcement at *www.dea.gov/press-releases/2018/09/27/fda-approved-drug-epidiolex-placed-schedule-v-controlled-substance-act.*

ASHP Guidelines Provide Recommendations for Preventing Patient Harm From Medication Errors

New guidelines from the American Society of Health-System Pharmacists (ASHP) describe opportunities for pharmacists on interprofessional teams to prevent errors across the continuum of care in hospitals and health systems. The "ASHP Guidelines on Preventing Medication Errors in Hospitals" are intended to apply to the acute care setting because of the special collaborative processes established in this setting. However, these guidelines may be applicable to practice settings outside of the acute care setting, especially in health systems.

Further, the ASHP press release notes that the guidelines address numerous areas in the medication-use process where errors may occur, including: patient admission; selection and procurement; storage; ordering, transcribing, and reviewing; preparation; dispensing; administration; monitoring; evaluation; and patient discharge. Published in the October 1, 2018 issue of the *American Journal of Health-System Pharmacy,* the guidelines are available at *www.ajhp.org/content/75/19/1493.* ASHP's October 2, 2018 press release can be found in the News section at *www.ashp.org.*

FDA's Final Guidance Documents Address Compounding and Repackaging of Radiopharmaceuticals

On September 26, 2018, FDA published the final guidance titled *Compounding and Repackaging of Radiopharmaceuticals by Outsourcing Facilities.* In this final guidance for industry, FDA sets forth its policy regarding compounding and repackaging of radiopharmaceuticals for human use by entities that are registered with FDA as outsourcing facilities. This guidance describes how FDA generally intends to apply section 503B of the Federal Food, Drug, and Cosmetic Act (FD&C Act) to radiopharmaceuticals compounded by outsourcing facilities.

In addition, this guidance describes the conditions under which FDA generally does not intend to take action for violations of certain provisions of the FD&C Act when an outsourcing facility repackages radiopharmaceuticals, according to the *Federal Register* notice at *www.gpo.gov/fdsys/pkg/FR-2018-09-26/pdf/2018-20901.pdf.*

At the same time, FDA published the final guidance titled *Compounding and Repackaging of Radiopharmaceuticals by State-Licensed Nuclear Pharmacies, Federal Facilities, and Certain Other Entities.* This guidance sets forth FDA's policy regarding compounding and repackaging of radiopharmaceuticals for human use by state-licensed nuclear pharmacies, federal facilities, and other entities that hold a radioactive materials license for medical use issued by the Nuclear Regulatory Commission or by an Agreement State. Because such radiopharmaceuticals are not eligible for exemptions from provisions of the FD&C Act related to the production of drugs, FDA is issuing this guidance to describe the conditions under which it generally does not intend to take action for violations of certain provisions of the FD&C Act when these entities compound or repackage radiopharmaceuticals. More details are available in the *Federal Register* notice at *www.gpo.gov/fdsys/pkg/FR-2018-09-26/pdf/2018-20902.pdf.*

Pharmacy Toolkit Encourages Conversations With Patients About Prescription Opioids

In collaboration with its pharmacy partners and several state pharmacy associations, Allied Against Opioid Abuse (AAOA) developed a Pharmacy Toolkit to help pharmacists engage and educate patients about the safe use, storage, and disposal of pain medicines. The AAOA Pharmacy Toolkit includes resources to help pharmacists raise awareness among patients about their rights, risks, and responsibilities associated with prescription opioids. These resources include: a pharmacy display, patient handout, patient engagement guide, tips for talking with patients and caregivers, prescriber engagement guide, safe storage and disposal training, and social graphics. To learn more about the Pharmacy Toolkit and to obtain these resources, visit AAOA's website at *https://againstopioidabuse.org.*

Biosimilars Added to FIP's Policy on Pharmacists' Right to Substitute a Medication

To account for the emergence of biological medicines and their biosimilars onto the medical landscape, the International Pharmaceutical Federation (FIP) has added biosimilars to its policy on pharmacists' right to substitute one medicine for another. The revised Statement of Policy titled "Pharmacist's authority in pharmaceutical product selection: therapeutic interchange and substitution" includes the core principles of the original statement and the following:

- generic substitution is recommended as part of the pharmacist's dispensing role;
- pharmacists should be provided with bioavailability data by regulatory authorities and manufacturers; and
- a medicine should only be substituted with a product containing a different active ingredient in agreement with the prescriber.

According to FIP's October 2, 2018 press release, the use of generic names is still encouraged, but the revised statement gives focus to the use of international nonproprietary names. The full Statement of Policy and press release are available at *www.fip.org* in their respective sections.

FDA Offers CE Course on Reducing Hypoglycemic Events in Patients With Type 2 Diabetes

FDA is offering a free, one-hour continuing education (CE) course for health care providers (physicians, pharmacists, nurses, and others) about the reduction of hypoglycemic events in patients with Type 2 diabetes. The course, *Leveraging Health Literacy and Patient Preferences to Reduce Hypoglycemic Events in Patients with Type 2 Diabetes,* will describe the prevalence of hypoglycemic events and identify risk factors leading to an event. Available for credit through October 31, 2020, this course will introduce methods of assessing health literacy and numeracy of patients and caregivers; review effective ways to incorporate patient preferences into care plans; and list action steps to reduce the likelihood of a hypoglycemic event for high-risk patients. To participate in this CE course, visit *http://fdapasediabetes.e-paga.com.*

The FDA Center for Drug Evaluation and Research (CDER) is accredited by the Accreditation Council for Pharmacy Education (ACPE) as a provider of continuing pharmacy education (CPE). This program meets the criteria for one contact hour (0.1 CEU) of CPE credit. The ACPE Universal Activity Number for this knowledge-based activity is 0453-9999-17-449-H01-P. Further, FDA's CDERLearn in the CDER offers a variety of learning opportunities, which can be found at *www.fda.gov/Training/ForHealthProfessionals/ucm545645.htm.*

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federal Controlled Substances Act, which means that hemp is no longer an illegal substance under federal law. The farm bill allows for the sale, production, and possession of cannabidiol (CBD) derived from industrial hemp, with a tetrahydrocannabinol (THC) concentration not more than 0.3% (dry weight). However, the farm bill preserves the authority of FDA to regulate products containing cannabis and cannabis-derived products. In particular, FDA requires any cannabis product that asserts a therapeutic benefit or disease claim to be approved by FDA for its purported use prior to the product being introduced into interstate commerce. This is the consistent standard used by FDA for any product marketed for human or animal use. Deceptive marketing of unproven treatments is a violation of the law.

In addition to FDA requirements, the farm bill requires each state's department of agriculture to coordinate with the state's governor and chief law enforcement officer to develop a plan to license and regulate hemp. This state plan must then be submitted to the Secretary of the US Department of Agriculture (USDA) for approval. Only after that plan is approved by USDA can hemp production commence. This has not yet occurred in Alabama. Many state agencies are working together to develop an understanding of what USDA expects in this plan, but since the government shutdown ended, we have yet to receive answers to our questions.

Given this background, where does all this change put pharmacy? In exactly the same place as before the farm bill passed. The Alabama Uniform Controlled Substances Act (AUCSA) lists any product containing THC to be a Schedule I controlled substance (CS).

Alabama Administrative Code Chapter 420-7-2 Controlled Substances, lays out the Alabama Controlled Substances List, which in section (d)31.7370 defines THC as:

> Meaning tetrahydrocannabinols naturally contained in a plant of the genus cannabis (cannabis plant), as well as synthetic equivalents of the substances contained in the cannabis plant, or in the resinous extractives of such plant, and/or synthetic substances, derivatives, and their isomers with similar chemical structure and pharmacological activity to those substances contained in the plant, such as the following:
>
> - 1 cis or trans tetrahydrocannabinol, and their optical isomers.
> - 6 cis or trans tetrahydrocannabinol, and their optical isomers.
> - 3,4 cis or trans tetrahydrocannabinol, and its optical isomers.
>
> (Since nomenclature of these substances is not internationally standardized, compounds of these structures, regardless of numerical designation of atomic positions covered.)

Until the Alabama Department of Public Health (ADPH) removes hemp and hemp-derived products from the list of Schedule I CS, Alabama pharmacies and pharmacists must abide by the strictest rule. In this situation, the strictest rule is that CBD products containing any THC are a Schedule I CS under Alabama law. If and/or when the AUCSA is amended by ADPH, then pharmacies would have the ability to sell CBD products, if they are in accordance with current restrictions and any other future regulations that may be implemented by the state.

Current restrictions include:

- Products sold that contain less than 0.3% THC by dry weight
- Products sold that are manufactured from hemp produced by a licensed grower

To state the situation as clearly as possible, pharmacies and pharmacists **cannot,** at this time, sell or possess hemp or hemp-related products containing **any** THC until the AUCSA is changed to remove hemp from Schedule I. While the Board understands that there are other entities selling these products, the Board cannot and does not regulate entities that do not possess a permit with the Board, nor does the Board have any authority to change the status of a CS. However, the Board must enforce current (and the most stringent) law. The Board is maintaining communication with all pertinent agencies regarding this situation and will keep the profession updated as to any changes that occur.

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