

Pharmacologic and clinical assessment of kratom

C. Michael White, Pharm.D., FCP, FCCP, University of Connecticut School of Pharmacy, Storrs, CT, and Department of Pharmacy, Hartford Hospital, Hartford, CT.

Purpose. This article reviews the pharmacology, clinical utility, adverse effects, and abuse potential of kratom.

Summary. The leaves of *M. speciosa* contain the biologically active alkaloids of kratom. Kratom exerts opioid and α -2 receptor agonistic effects as well as antiinflammatory and parasympathetic-impeding effects. There are no published human pharmacologic, pharmacokinetic, or drug interaction studies on kratom or mitragynine, making it virtually impossible to fully understand kratom's therapeutic potential and risks and the populations most likely to benefit or experience harm from its use. Kratom has been used to ameliorate opioid withdrawal symptoms but also induces withdrawal. Human pharmacologic, pharmacokinetic and clinical data are of low quality precluding any firm conclusions regarding safety and efficacy. Respiratory depression has not been commonly reported but kratom does cause a host of adverse effects without clear guidance for how they should be treated. There are numerous assessments where people have been unable to stop using kratom therapy and withdrawal signs and symptoms are problematic. Kratom does not appear in normal drug screens and, when taken with other substances of abuse, may not be recognized. Thirty-six deaths have been attributed to kratom, and the Food and Drug Administration issued a public health warning about the substance in November 2017.

Conclusion. Kratom exerts opioid and α -2 receptor agonistic effects as well as antiinflammatory and parasympathetic-impeding effects. Human pharmacologic, pharmacokinetic, and clinical data are of low quality precluding any firm conclusions regarding safety and efficacy.

Keywords: addiction, herb, kratom, *Mitragyna speciosa*, opioids

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Mitragyna speciosa (kratom) is a member of the Rubiaceae family, the same family that includes coffee and ~6,500 other species of flowering plants.¹ Although reports of its use began in the mid-1800s, this Southeast Asian plant came into the spotlight in the United States in 2016.² In September 2016, the Drug Enforcement Agency (DEA) proposed making kratom a Schedule I drug, leading to a backlash and outcry from the public, researchers, and 51 legislators.^{3,4} DEA agreed to delay its ruling on scheduling kratom, though it remains a DEA “drug of concern” (i.e., not regulated but poses a risk to persons abusing it).^{5,6} It is illegal to possess or use kra-

tom in Alabama, Arkansas, Indiana, Tennessee, Vermont, and Wisconsin.⁵ Kratom is banned in Thailand and Malaysia and controlled in many European Union countries but not in Germany or the United Kingdom.⁷

Kratom is sold over the Internet and in “smoke/head shops,” tea shops and bars, gas stations, and other boutique shops as loose chopped leaves, capsules, compressed tablets, and concentrated extracts under the name kratom, ketum, and *Mitragyna speciosa*.^{8,9} It can be chewed, smoked, or ingested orally.^{8,9} A “4 × 100” cocktail consisting of kratom tea, caffeinated soda, ice cubes, and cough syrup containing codeine, dextromethorphan, and di-

Address correspondence to Dr. White (charles.white@uconn.edu).

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phenhydramine is commonly used in Thailand.¹⁰ Kratom has also been combined with o-desmethylnaltrexone in a product called krypton, and an extract of kratom, called mitragynine, has been substituted for or added to synthetic cannabinoids such as K2 products (products supposed to contain only synthetic cannabinoids).¹¹

American Kratom Association Executive Director Paul Pelosi Jr., son of U.S. Representative Nancy Pelosi, said that based on his understanding of industry sales figures, 4–5 million Americans may be using kratom.³ This is much higher than the figure of several hundred thousand people that has been estimated previously, but the discrepancy may be partially related to the adulteration of other legal or quasi-legal products of abuse with kratom.^{3,11} The National Institute on Drug Abuse does not ask about kratom use in its surveys of 8th, 10th, and 12th graders in the United States, and kratom's main constituents do not appear on standard drug screens.^{9,12} These facts are particularly troubling, since kratom may be available to underage individuals who cannot order alcohol and believe that legality equates with safety. Indonesia is a major source of kratom production, and warehouses in the United States store millions of dollars of product from that country.³ These data suggest that kratom, a drug most clinicians never heard of before 2016, is commonly used in the United States.

Data on the prevalence of kratom use in Europe or other developed countries is not available. However, according to a 2008 national survey in Thailand, 1,078,152 people reported using kratom and up to 70% of the male population use kratom daily in several southern districts.¹⁰

The DEA ruling to label kratom as a Schedule I drug will have major implications for recreational users, people substituting kratom for other drugs of abuse, clinicians caring for kratom users, and researchers. This article reviews kratom's pharmacology, clinical utility, adverse effects, and

KEY POINTS

- Kratom is a naturally derived opioid analgesic with a low risk of respiratory depression and, although under Drug Enforcement Agency review, is currently legal to sell, possess, and use in the United States.
- Human pharmacologic, pharmacokinetic and clinical data are of low quality precluding any firm conclusions regarding safety and efficacy.
- Kratom can cause tolerance and withdrawal symptoms that make abstinence from the substance difficult or impossible without professional help.

abuse potential as well as the warning issued by the Food and Drug Administration (FDA) about kratom in November 2017.

Pharmacology and role in abstinence

The leaves of *M. speciosa* contain the biologically active alkaloids of kratom.^{9,13} Of the compounds isolated from kratom, mitragynine contains 66% of the total alkaloid content, followed by paynantheine (9%), speciogynine (7%), 7-hydroxymitragynine (2%), and speciophylline (1%), with 20 other alkaloids found in trace amounts.^{9,13} Mitragynine is a white amorphous powder that is soluble in alcohol, chloroform, and acetic acid but in an animal study only had an absolute oral bioavailability of 3%.^{2,13}

The average weight of an *M. speciosa* leaf when picked is 1.7 g and 0.43 g when dried. Twenty leaves contain ~17 mg of mitragynine.¹⁴ However, the concentrations of alkaloids may vary among batches, as the time course of alkaloid degradation in the fresh and dried forms is unknown, and the manufacture and storage of the prod-

ucts is unregulated, raising questions about stability and adulteration.¹⁵ In an assessment of several kratom products commercially sold in the Western world, the concentrations of 7-hydroxymitragynine was substantially higher than could be achieved with fresh or dried leaves.¹⁵

In animal studies using noxious or painful stimuli, extracts of kratom prolonged the latency of nociceptive responses. These responses were attenuated by naloxone, supporting the theory of an opioid agonist mechanism of action. Caffeine coadministration enhanced the antinociceptive effects of a kratom alkaloid extract, as did the use of acetaminophen.¹³

Most of the opioidlike activity of kratom has been attributed to mitragynine and 7-hydroxymitragynine, both of which exhibit dose-related antinociceptive effects and stimulate μ - and δ -opioid receptors.⁹ While found in a much lower concentration in kratom leaves, 7-hydroxymitragynine is 46-fold more potent than mitragynine and 13-fold stronger than morphine as an antinociceptive compound.¹³ Importantly, oral kratom doses of 807 and 920 mg/kg did not induce respiratory depression.¹⁶

Mitragynine stimulates postsynaptic α -2 adrenergic receptors.^{9,17} Dexmedetomidine is an α -2 adrenergic agonist used for sedation, and clonidine is an α -2 adrenergic agonist used to manage pain, anxiety, attention deficit disorder, and symptoms of withdrawal (e.g., from opiates, benzodiazepines, alcohol, tobacco). This may be why kratom can attenuate withdrawal symptoms from opioid withdrawal in excess of the potency of its opioid actions and why it might be more dangerous when used with other sedative and hypnotic agents. Both of these α -2 adrenergic agonists accentuate the sedative, hypnotic, and analgesic effects of other drugs.^{9,17}

A final mechanism of kratom analgesia is suppression of inflammation.¹³ Mitragynine inhibits cyclooxygenase-2 mRNA and protein expression in a dose-dependent manner. This might

explain why administration of kratom extract inhibited acute limb edema while long-term kratom use prevented the growth of granuloma tissue in animal studies.¹³

Kratom induces constipation through opioid and nonopioid mechanisms. A methanolic extract of kratom reduced defecation frequency and fecal weight in a castor oil–induced diarrhea model and slowed intestinal transit in rats.¹³ Naloxone preadministration only partially ameliorated these gastrointestinal effects. Intestinal transit time was also suppressed when subcutaneous 7-hydroxymitragynine was administered to mice.¹³ Paynantheine, speciociliatine, and speciogynine impede intestinal smooth muscle function.^{9,13} Speciociliatine inhibits acetylcholine release from presynaptic nerves while paynantheine and speciogynine inhibits muscarinic receptors in ileal smooth muscles.⁹

Kratom has been used to ameliorate opioid withdrawal symptoms but also induces withdrawal. In zebra fish, long-term morphine administration (1.5 mg/L for 2 weeks) resulted in withdrawal symptoms (decreased exploration, erratic swimming, cortisol activation, and prodynorphine transcript production) that was attenuated by the administration of mitragynine 2 mg/L.¹³ In rats, acute mitragynine administration induced locomotor sensitization and anxiolysis and impaired passive avoidance learning, memory consolidation, and retrieval.⁷ After 14 days of intraperitoneal mitragynine 30 mg/kg, severe somatic withdrawal signs (paw tremor, shakes, piloerection, teeth chattering) and anxiety occurred 12–24 hours after withholding a mitragynine dose. The rats exhibited hypersensitivity to small challenge doses of mitragynine (3 mg/kg) for up to 14 days after withholding therapy. Furthermore, rats treated with 28 days of intraperitoneal mitragynine (1, 5, or 10 mg/kg) had significant impairment of learning and memory with all 3 doses on days 1, 3, and 7 of withdrawal. These impairments were in

line with those induced by morphine withdrawal.

In another rat study, mitragynine 1, 10, and 100 mg/kg was given orally for 28 days.¹⁸ No deaths occurred, but elevated liver transaminases occurred and histological liver (hepatocyte hypertrophy and hemorrhage) damage was found in rats given moderate-to-high doses of mitragynine, and medullary damage (vacuolation and necrosis of neuronal cells) occurred with high doses. The day after stopping therapy (day 29), the cumulative withdrawal score was elevated from baseline in a dose-related fashion based on the intensity of previous mitragynine exposure. The same relationship held true 14 days after withholding mitragynine, but the scores were substantially reduced from day 1 withdrawal values.¹⁸

In vitro, a methanolic extract of kratom inhibited cytochrome P-450 (CYP) isoenzymes 2C9, 2D6, 1A2, and 3A4, with the most potent blockade seen with CYP 2D6.^{2,13} Opioids such as codeine, hydrocodone, fentanyl, methadone, oxycodone, and tramadol are CYP substrates.¹⁹ In addition, illicit drugs such as 3,4-methylenedioxymethamphetamine (commonly called MDMA) and several synthetic cannabinoids are CYP substrates, and reports have documented the adulteration of illegal or unregulated products of abuse with opioids, MDMA, and synthetic cannabinoids.^{20,21} Other CYP substrates, including caffeinated soda, codeine, and dextromethorphan, are sometimes used together with kratom in the “4 × 100” preparation as well as the CYP 2D6 inhibitor diphenhydramine.⁹ The pharmacokinetics of mitragynine in rats suggest a time to maximum concentration of 1.2–1.8 hours, an elimination half-life of 3.9–9.4 hours, and a volume of distribution of 37.9–89.5 L/kg.^{9,13}

Published reports

There are no published human pharmacologic or drug interaction studies on kratom or mitragynine,^{2,9,10,13} making it virtually impossible to fully

understand kratom's therapeutic potential and risks and the populations most likely to benefit or experience harm from its use. A search of clinicaltrials.gov using the index terms *kratom* and *mytragyna* found no studies, either completed or underway.²²

Anecdotal reports suggest that kratom produces an unusual combination of stimulant and opioidlike effects.^{9,23} The stimulant effects of 1–5 g of raw leaves are not perceived as being as potent as those of amphetamines, and some people with chronic pain appreciate the stimulant effects as opposed to the depressant effects of normal opioid agonists. When greater amounts (5–15 g of raw leaves) are ingested, analgesia is enhanced and the sedative effects overcome the stimulant effects. The euphoric effects of kratom are perceived as being less pronounced than those arising from traditional opioid agonists.^{9,23}

Discussion threads initiated and propagated on Drugbuyers.com (now Drugs.com), a website with health information for the lay public, surged in 2005 and overwhelmingly involved the use of kratom for opioid addiction.²⁴ In 1836 and 1895, kratom was identified as a treatment for opium addiction and as an opium substitute in Southeast Asia, but a formal assessment of its benefits is lacking.¹³

A case report described the use of kratom in Thailand to treat 2 people addicted to heroin.¹⁰ Methadone was ineffective for 1 patient, and methadone was not routinely available for the other patient. Both patients felt that kratom was a suitable maintenance medication, though 1 patient felt that methadone would have been better.

The best data on the use of kratom to manage drug withdrawal symptoms comes from a survey of 136 kratom users in Malaysia.²⁵ Overall, 90% were using kratom to reduce addiction to other drugs and 84% to ameliorate the effects of withdrawal from opioid addiction. Before turning to kratom, 77% of subjects had used cannabis and 53% had used heroin. When giv-

en urine drug screens, 46%, 10%, 4%, and 1% of kratom users tested positive for concomitant use of cannabis, heroin, amphetamine, and methamphetamine, respectively. Information on the frequency of use of these other drugs of abuse was not collected. On average, 3.2 glasses of kratom were consumed daily, and the average duration of kratom use was 3.5 years. The benefits of continuing kratom were self-reported and included reduced withdrawal symptoms, increased work capacity, and increased energy. Loss of weight, hyperpigmentation of the face, dehydration, and constipation were commonly reported adverse effects. However, 78% of patients reported trying to stop using kratom in the past, though all had failed.²⁵

Adverse effects

Relatively few cases of acute toxicity with kratom have been reported in the Western literature, and many of the cases are confounded by the concomitant consumption of other drugs. It cannot be determined definitively if the paucity of reports is because of superior safety versus other drugs of abuse or because kratom use is not recognized by clinicians and law enforcement.

In an assessment of calls to poison control center in Texas from 1998 to September 2013, 14 kratom-related cases were reported, all of which occurred from 2009 through 2013.²⁶ Eight of the cases involved kratom alone, and the rest involved the concomitant use of other substances (wild dagga, wormwood, alprazolam, synthetic cannabinoid, tryptamine, alcohol, and methamphetamine). Eighty-six percent of patients were treated in a healthcare facility and 14% at home. Overall, 29%, 36%, and 7% had mild, moderate, and major adverse effects, respectively; 28% of people were unable to be assessed for adverse-effect severity. The most common adverse effects included tachycardia, hypertension, agitation, nausea, vomiting, confusion, tremor, and diaphoresis. One subject had elevated creatinine

phosphokinase concentrations. Therapy included i.v. fluids (43%), benzodiazepines (29%) or other sedatives (14%), antiemetics (7%), antihypertensives (7%), and oxygen (7%).²⁷

An assessment of calls to U.S. poison control centers from 2010 through 2015 revealed 660 reports of kratom exposure.⁶ The volume of kratom-related calls increased from 26 in 2010 to 263 calls in 2015, with 75% of calls placed by healthcare providers. Sixty-five percent of calls were for patients exposed solely to kratom, 72% of patients were male, and the median age was 28 years. The major adverse effects included tachycardia (25%), agitation or irritability (24%), drowsiness (19%), nausea (15%), and hypertension (12%). Outcomes were more severe when kratom was combined with other drugs. Twenty-five percent of patients had minimal adverse signs or symptoms, 42% had moderately severe adverse effects, and 7% experienced life-threatening adverse effects or residual disability. No outcome was reported in 26% of cases. One death was reported in a patient taking paroxetine and lamotrigine in addition to kratom.⁶

Nine deaths were reported after the ingestion of krypton, a product containing kratom and O-desmethylnaloxone.² Blood levels of mitragynine (0.02–0.18 µg/g) and O-desmethylnaloxone (0.4–4.3 µg/g) were identified in these cases. Another death reported resulted from the concomitant use of mitragynine and propylhexedrine.² In Texas, a death attributable to kratom was included in a news report in February 2013, but specific details of the case were not given.²⁶ Another death occurred in a middle-aged man who was found dead at home.²⁷ An autopsy revealed no significant pathological findings, and drug screening revealed normal concentrations of zopiclone, citalopram, and lamotrigine. However, serum concentrations of mitragynine (1.06 mg/L) and 7-hydroxymitragynine (0.15 mg/L) were also found during the autopsy,

which led to the conclusion that the cause of death was an accidental overdose of kratom.²⁷ In total, FDA is aware of 36 deaths associated with the use of kratom-containing products and of reports that kratom has been laced with other opioids (e.g., hydrocodone).²⁸

Three reported cases of seizures due to kratom were reported, but 2 cases involved the concomitant ingestion of an additional drug (modafinil or *Datura stramonium*).²⁹ *D. stramonium* (jimsonweed), a plant native to Mexico, is purported to have analgesic, antispasmodic, and hallucinogenic effects. In one case, the patient lost consciousness 30 minutes after drinking kratom and *D. stramonium* tea and began seizing at home and an hour after arrival in the emergency department. Lorazepam and phenytoin were administered, and the patient recovered and was discharged. His urine mitragynine concentration was 167 ng/mL.²⁹

Kratom has been reported to cause hypothyroidism in a single case report and intrahepatic cholestasis in another, with only the latter having basic animal data to support the event.^{2,18}

Addiction to kratom

There are case reports of patients in Europe and the United States becoming physically dependent or addicted to kratom.⁹ In each case, the individual exhibited tolerance to the effects of kratom and showed overt symptoms of withdrawal when kratom was discontinued. Symptoms included irritability, dysphoria, nausea, diarrhea, hypertension, insomnia, rhinorrhea, myalgia, and arthralgia.⁹

Much of the data on the tolerance and withdrawal associated with kratom comes from Southeast Asia. In 1975, 30 kratom-addicted people in Thailand were studied.¹⁴ Ninety percent of users were 30–70 years old (though 73% became addicted at 20–39 years), 97% were male, 87% were married, and 63% were middle class. The people chewed the fresh leaf or ingested the crushed dried

leaf 3–10 times per day and followed this consumption by drinking warm water (40%) or hot coffee (60%). The initial dose was ~3 leaves daily but grew to 10–20 leaves daily in 40% of people and to 21–30 leaves daily in 37% of people. People began chewing the leaves to overcome fatigue and weariness and increased the number of leaves ingested over time to satisfy their addiction. People reported an onset of action of 5–10 minutes with feelings of increased strength, vitality, and happiness. Periodic consumption throughout the day allowed them to work very long hours in the fields or in the sun with less achiness and fatigue. Anorexia, weight loss, insomnia, xerostomia, constipation, ptosis, black small stools, darkening of the skin on the cheeks, frequent micturition, and limited sexual desire were commonly reported. Five people reported developing delusions, hallucinations, and confusion, though 2 of them were using other drugs (amphetamines, heroin, and alcohol). One patient reported having convulsions. Withdrawal symptoms included hostility, tearfulness, rhinorrhea, inability to work, arthralgia and myalgia, and “jerky motions” of the limbs.¹⁴

In 2014, a study was conducted in Malaysia among 293 male kratom users (mean age, 29 years; 58% single; 66% employed).²⁹ Thirty-six percent were former users of other illicit drugs, and half began using kratom at age 11–21 years. The average frequency of use was 3.5 times daily. In Malaysia, kratom is consumed as a fresh squeezed juice; 13% of study participants consumed 0.5–1.5 glasses daily, 42% consumed 2–3 glasses daily, and 44% consumed more than 3 glasses daily. One glass of kratom contained 350 mL of kratom juice given alone or mixed with caffeinated soda, dextromethorphan, or nimetazepam (a benzodiazepine). The mitragynine content per glass averaged 79 mg (range, 75–83 mg). The majority of people used kratom to enhance their ability to work long hours with less pain and fatigue, 31% began use out of curiosity

or peer pressure, and 15% used kratom to wean themselves from illicit drugs and alcohol. Eighty-nine percent of subjects tried to abstain from kratom in the past, but all had relapsed. Physical withdrawal symptoms in those who tried to quit included insomnia, anorexia, nausea, vomiting, diarrhea, myalgia, muscle spasms or tremor, shakiness, lacrimation, rhinorrhea, and hot flashes. About 65% of people experienced mild physical withdrawal symptoms, and 35% had moderate-to-severe symptoms. These withdrawal symptoms lasted for up to 3 days in 64% of subjects but longer than 3 days in 36% of subjects. Psychological symptoms of withdrawal included anxiousness, anhedonia, restlessness, anger, and tension. Seventy-three percent of subjects experienced multiple psychological withdrawal symptoms. Those who consumed more than 3 glasses of juice daily (odds ratio [OR], 7.05; 95% confidence interval [CI], 4.09–12.13) or used kratom 3 or more times daily (OR, 5.19; 95% CI, 3.02–8.92) were 7 and 5 times more likely, respectively, to report severe dependence than those who consumed less kratom.³⁰

In 2015, another study assessed the social functioning of the same 293 Malaysian kratom users.³¹ None of the kratom users endured any medical problems requiring hospitalization directly related to kratom use, and none felt like they needed treatment for their kratom use during the prior 30 days. None of the respondents had used other illicit drugs in the prior 30 days, which was confirmed by urine toxicology screening. Thirteen percent of subjects reported depressive symptoms, 14% reported anxiety, 17% reported trouble concentrating or remembering, 6% reported violent behavior, and fewer than 1% reported hallucinations or attempted suicide in the prior 30 days. While subjects felt they could control their addiction, none were abstinent, and only 18% went more than 3 months before relapsing. The subjects and researchers believed that kratom use was not

as destructive socially and financially as heroin or opium addiction but that kratom was an addictive substance.³¹

The following is FDA's position on kratom²⁸:

It's very troubling to the FDA that patients believe they can use kratom to treat opioid withdrawal symptoms. The FDA is devoted to expanding the development and use of medical therapy to assist in the treatment of opioid use disorder. However, an important part of our commitment to this effort means making sure patients have access to treatments that are proven to be safe and effective. There is no reliable evidence to support the use of kratom as a treatment for opioid use disorder. Patients addicted to opioids are using kratom without dependable instructions for use and more importantly, without consultation with a licensed health care provider about the product's dangers, potential side effects or interactions with other drugs.

Treatment of adverse events and withdrawal

Table 1 summarizes the adverse events and withdrawal symptoms reported with kratom and some potential treatments.^{2,6,9,13,20,21,24–34} While adverse events that coincide with opioids can be theoretically treated with naloxone, there are nonopioid mechanisms for symptoms such as constipation and nausea and vomiting, suggesting that other therapies would be superior or needed adjunctively. Seizures are not commonly associated with opioids but can occur at high doses, and naloxone can reverse those effects.³² However, seizures are also associated with overdoses of stimulants, which are not amenable to naloxone therapy but may be treated with benzodiazepines and other anticonvulsants.^{20,21,29} The benefits of giving naloxone need to be weighed against the withdrawal symptoms the patient will experience. Similarly, the value of add-

Table 1. Pharmacologic Effects of Kratom From Human Trials^{2,6,9,13,20,21,24-34,a}

| Adverse Events | Therapy for Adverse Events | Withdrawal Effects | Therapy for Withdrawal |
|------------------------------|----------------------------------------------|-----------------------------|---------------------------------------|
| Tachycardia and hypertension | Benzodiazepines, negative chronotropic drugs | Agitation and anxiety | Benzodiazepines, α -2 agonists |
| Nausea and constipation | Antiemetics, laxative plus stool softener | Abdominal pain and diarrhea | Nonopioid antidiarrheals |
| Confusion and hallucinations | Benzodiazepines, naloxone | Limb muscle spasms | Benzodiazepines |
| Seizures | Benzodiazepines, naloxone, anticonvulsants | Joint and muscle pain | Nonopioid pain relievers |
| Sedation | Naloxone | ... | ... |

^aTreatments for adverse events and withdrawal are general treatment suggestions and were not studied in any clinical trials of kratom.

ing an α -2 antagonist to ameliorate adverse effects via that mechanism is unknown.^{20,21} An α -2 agonist has been used to treat patients trying to achieve kratom abstinence, a strategy that has been helpful with other opioids as well.¹⁷

In one patient, the use of dihydrocodeine and lofexidine (an α -2 agonist) was used to attenuate the subjective and objective withdrawal phenomena, which have been described as similar to those experienced with other opioids.³³ In another patient, the combination of doxepin and diazepam was used to treat a patient dependent on both alcohol and kratom.³⁴

Conclusion

Kratom exerts opioid and α -2 receptor agonistic effects as well as antiinflammatory and parasympathetic-impeding effects. Human pharmacologic, pharmacokinetic, and clinical data are of low quality precluding any firm conclusions regarding safety and efficacy.

Disclosures

The author has declared no potential conflicts of interest.

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