Commonly Abused Supplements

HOW TO RECEIVE CREDIT

- Read the enclosed course.
- Complete the questions at the end of the course.
- Return your completed Evaluation to NetCE by mail or fax, or complete online at www.NetCE.com. (If you are a physician, behavioral health professional, or Florida nurse, please return the included Answer Sheet/Evaluation.) Your postmark or facsimile date will be used as your completion date.
- Receive your Certificate(s) of Completion by mail, fax, or email.

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Faculty Disclosure
Contributing faculty, Chelsey McIntyre, PharmD, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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The division planners and director have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Audience
This course is designed for healthcare professionals whose patients are taking or are interested in taking dietary supplements.

Accreditations & Approvals
In support of improving patient care, NetCE is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

As a Jointly Accredited Organization, NetCE is approved to offer social work continuing education by the Association of Social Work Boards (ASWB) Approved Continuing Education (ACE) program. Organizations, not individual courses, are approved under this program. Regulatory boards are the final authority on courses accepted for continuing education credit.

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Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 2 MOC points in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit. Completion of this course constitutes permission to share the completion data with ACCME.

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A complete Works Cited list begins on page 12.

Mention of commercial products does not indicate endorsement.

Successful completion of this CME activity, which includes participation in the activity with individual assessments of the participant and feedback to the participant, enables the participant to earn 2 MOC points in the American Board of Pediatrics' (ABP) Maintenance of Certification (MOC) program. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABP MOC credit.

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Through an agreement between the Accreditation Council for Continuing Medical Education and the Royal College of Physicians and Surgeons of Canada, medical practitioners participating in the Royal College MOC Program may record completion of accredited activities registered under the ACCME's "CME in Support of MOC" program in Section 3 of the Royal College's MOC Program.

NetCE designates this continuing education activity for 2 ANCC contact hours.

IPCE CREDIT™

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NetCE designates this continuing education activity for 2.4 hours for Alabama nurses.

AACN Synergy CERP Category A.

Social workers completing this intermediate-to-advanced course receive 2 Clinical continuing education credits.

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Individual State Nursing Approvals

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Individual State Behavioral Health Approvals

In addition to states that accept ASWB, NetCE is approved as a provider of continuing education by the following state boards: Alabama State Board of Social Work Examiners, Provider #0515; Florida Board of Clinical Social Work, Marriage and Family Therapy and Mental Health, Provider #50-2405; Illinois Division of Professional Regulation for Social Workers, License #159.001094; Illinois Division of Professional Regulation for Licensed Professional and Clinical Counselors, License #197.000185; Illinois Division of Professional Regulation for Marriage and Family Therapists, License #168.000190.

Special Approvals

This activity is designed to comply with the requirements of California Assembly Bill 1195, Cultural and Linguistic Competency, and California Assembly Bill 241, Implicit Bias.

About the Sponsor

The purpose of NetCE is to provide challenging curricula to assist healthcare professionals to raise their levels of expertise while fulfilling their continuing education requirements, thereby improving the quality of healthcare.

Our contributing faculty members have taken care to ensure that the information and recommendations are accurate and compatible with the standards generally accepted at the time of publication. The publisher disclaims any liability, loss or damage incurred as a consequence, directly or indirectly, of the use and application of any of the contents. Participants are cautioned about the potential risk of using limited knowledge when integrating new techniques into practice.

Disclosure Statement

It is the policy of NetCE not to accept commercial support. Furthermore, commercial interests are prohibited from distributing or providing access to this activity to learners.

Course Objective

The purpose of this course is to provide healthcare professionals in all practice settings the knowledge necessary to increase their understanding of the commonly abused supplements and their adverse effects.

Learning Objectives

Upon completion of this course, you should be able to:

1. Outline supplements with abuse potential related to weight loss and/or athletic performance.
2. Describe how dietary supplements with laxative effects might be abused.
3. Discuss the potential to misuse specific supplements for recreational or opioid-like experiences.

EVIDENCE-BASED PRACTICE RECOMMENDATION

Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

INTRODUCTION

Use of dietary supplements continues to increase. In addition to their use for the management of medical conditions, dietary supplements are often misused or abused for recreation, body image concerns, athletic performance, and mood enhancement. Poison control center data indicate that abuse and misuse of dietary supplements occurs across the life span, with reports in adolescents to those older than 60 years of age [1].

Abuse refers to the use of a substance to gain a psychotropic effect. Misuse refers to the use of a substance for reasons other than a psychotropic effect. While abuse and misuse of dietary supplements is similar in many ways to other forms of substance abuse, there are a few things that set it apart from that of prescription medications, alcohol, tobacco, and illicit drugs. Many consumers perceive products that are natural to be synonymous with safety, which is certainly not the case. Additionally, availability of supplements reduces barriers to their access and legality concerns [1].

The focus of this course will be on the following commonly abused supplements, how they work, and their associated safety concerns:

- Stimulants (1,3-dimethylamylamine [1,3-DMAA], bitter orange, caffeine, ephedra, octopamine)
- Laxatives (castor oil, senna)
- Gamma hydroxybutyrate (GHB)
- Kratom

Note that these select supplements are commonly abused in North America. Supplements commonly abused in other parts of the world are beyond the scope of this course.

ABUSE POTENTIAL RELATED TO WEIGHT LOSS AND/OR ATHLETIC PERFORMANCE

Stimulants are a class of substances that speed up the body's systems, and for this reason, they are commonly referred to as "uppers." There are numerous U.S. Food and Drug Administration (FDA)-approved stimulants that are safely used under medical supervision for accepted medical uses (e.g., nasal decongestants, treatment of attention deficit hyperactivity disorder [ADHD]). Stimulant supplements are commonly touted for their energy-boosting beneficial effects on athletic performance and for promoting weight loss.

1,3-DIMETHYLAMYLAMINE (1,3-DMAA)

1,3-DMAA, also called methylhexaneamine, is a synthetic stimulant, meaning that it is prepared in a lab. It was originally developed as an ingredient for relieving nasal congestion because of its stimulant and vasoconstrictive activity. It has more recently been marketed in dietary supplements for athletic performance and weight loss [2].

Quality Concerns

Formulations of 1,3-DMAA often list rose geranium oil, geranium oil, or geranium stems as an ingredient on the label. While some manufacturers claim that 1,3-DMAA is a natural compound found in geranium oil, this claim has not been confirmed by laboratory analysis. In 2011, Health Canada determined that there is no credible evidence that 1,3-DMAA is derived from the geranium plant. As a result, there is concern that formulations purportedly containing "rose geranium oil," "geranium oil," and "geranium stems" may actually be adding the synthetic drug to their supplements [2].

Regulatory Concerns

In 2011, Health Canada determined that 1,3-DMAA should be considered a drug and is not allowed to be included in dietary supplements [2]. In 2013, the FDA declared products containing 1,3-DMAA to be illegal and to have potential health risks. 1,3-DMAA has been included on the prohibited lists of the World Anti-Doping Agency (WADA) and the U.S. Department of Defense (DoD) for more than 10 years [2].

Safety

Although 1,3-DMAA has been associated with cardiovascular adverse effects, these concerns have rarely been reported in patients taking 1,3-DMAA alone. Most of the severe adverse effects related to 1,3-DMAA are associated with its use in combination products [2].

Palpitations and tachycardia are the most common adverse effects reported with 1,3-DMAA-containing products. Angina, atrial fibrillation, chest pressure, hypertension, hypotension, and myocardial infarction have also occurred. In case reports of healthy young adults taking 1,3-DMAA-containing combination products prior to exercise, cardiac arrest causing death has occurred [2].

BITTER ORANGE AND OCTOPAMINE

Bitter orange is a small, flowering, fruit-bearing tree whose flowers, leaves, and fruits (including peel) have stimulant effects. Bitter orange has numerous active constituents and pharmacologic effects which vary by plant part and preparation method [3].

The fruit and the peel of bitter orange contain the adrenergic agonists synephrine and octopamine, which are frequently cited on labels as active ingredients. Synephrine and octopamine are chemically similar and occur naturally in the body in small amounts. Structurally, synephrine is similar to epinephrine and octopamine is similar to norepinephrine [3; 4].

Quality Concerns

Many marketed bitter orange products contain greater amounts of synephrine and other natural and synthetic amines than is stated on the label, increasing the risk for serious stimulant-related adverse effects. In a laboratory analysis of marketed bitter orange products, only 22% of the products tested had synephrine content within 20% of the amount stated on labels. The analysis also confirmed the presence of the synthetic amines methylsynephrine and isopropyloctopamine, neither of which are permitted in dietary supplements [3].

Similarly, the amount of octopamine found in products marketed for athletic performance is much greater than the quantity found naturally occurring in some plants (e.g., bitter orange). Natural levels of octopamine in bitter orange are less than 0.03%. A review of 32 products showed that octopamine was present in two products at levels as high as 11% and 12.9%, suggesting that manufacturers are adding synthetic octopamine to supplement products. In an analysis of bitter orange extract, octopamine was identified in all three products tested, although it only appeared on the label of two products. One analyzed product contained only 2.8% of the quantity of octopamine stated on the label [4].

Regulatory Concerns

Since the FDA banned ephedra in 2004, bitter orange has been frequently used in products labeled as "ephedra-free." Synephrine, a constituent of bitter orange, is considered a banned substance by the National Collegiate Athletic Association (NCAA). Similarly, octopamine has been included on the WADA prohibited list [3; 4].

Safety

Most of the severe adverse effects related to bitter orange are associated with its use in combination products. Hypertension and tachycardia are the most common adverse effects reported with bitter orange-containing products, particularly in combination with caffeine and/or other stimulant ingredients. Other adverse effects reported with the use of bitter orange- or synephrine-containing multi-ingredient products, with or without other stimulants, include

blackout, cardiac arrest, collapse, ischemic stroke, myocardial infarction, QT prolongation, tachyarrhythmia, tachycardia, variant angina, ventricular fibrillation, and death [3].

A clinical evaluation of safety outcomes has not been conducted for octopamine, but given its chemical similarity to synephrine, adverse effects similar to those seen with other stimulants can be expected [4].

CAFFEINE

Caffeine might be one of the best-known stimulants. It is a naturally occurring, bitter-tasting methylxanthine compound found in the leaves, seeds, or fruits of more than 60 plants, including coffee (*Coffea arabica*) beans, cacao (*Theobroma cacao*) beans, kola (*Cola acuminata*) nuts, guarana (*Paullinia cupana*) berries, and tea (*Camellia sinensis*) leaves. It is structurally related to theophylline, theobromine, and uric acid and is a nonselective adenosine antagonist [5].

Caffeine is present in a wide variety of beverages [5]:

- One cup of brewed coffee provides 95–200 mg of caffeine.
- An 8-ounce serving of black tea provides 25–110 mg of caffeine.
- An 8-ounce serving of green tea provides 30–50 mg of caffeine.
- A 12-ounce soft drink (e.g. cola) provides 20–80 mg of caffeine.
- A serving of sports or energy drink typically provides 48–300 mg of caffeine.

Caffeine is also available alone or in combination with other ingredients in some prescription and over-the-counter products that are approved for specific medical uses (e.g., to help restore mental alertness and wakefulness when experiencing fatigue or drowsiness). Caffeine tablets contain up to about 200 mg of caffeine [5].

Keep in mind that only the amount of added caffeine must be stated on product labels, and the amount of caffeine from caffeine-containing natural ingredients (e.g., coffee, green tea) is not required to be provided, making it difficult to determine the total amount of caffeine in a given product.

Caffeine has been demonstrated to improve athletic performance. It decreases perceived levels of exertion, enabling athletes to feel less tired and increase their performance. It can also improve anaerobic exercise performance. Within limits, the NCAA allows caffeine consumption. During competition, however, urine concentrations must not exceed 15 mcg/mL. Consumption of 600–800 mg of caffeine would need to be consumed two to three hours prior to performance in most people in order to achieve this urine concentration [5].

Safety

A review by Health Canada and a subsequent large meta-analysis conducted in the United States show that caffeine doses up to 400 mg daily are not associated with significant adverse cardiovascular, bone, behavioral, or reproductive effects in healthy adults. Similarly, the U.S. Dietary Guidelines Advisory Committee states that there is strong and consistent evidence that consumption of caffeine 400 mg daily is not associated with increased risk of major chronic diseases, such as cardiovascular disease or cancer, in healthy adults [5].

Caffeine is generally well tolerated, with regular use and in moderate doses. Common side effects include cause anxiety, diarrhea, diuresis, headache, insomnia, muscular tremors, nausea, and restlessness. But caffeine can become unsafe when used long-term and/or in high doses [5].

Acute use of high doses, typically those exceeding 400 mg daily, have been associated with significant adverse effects, such as tachyarrhythmia and sleep disturbances. Some people may experience serious toxicity even at lower doses, owing to caffeine's effects being impacted by smoking status, age, and prior caffeine use [5].

Some caffeine products for supplement use are highly concentrated or pure formulations. These are most concerning because they have a high risk for being mistakenly used in excessive and potentially dangerous doses. Powdered pure caffeine can contain as much as 3.2 grams of caffeine in a single teaspoon and concentrated liquid caffeine can contain about 2 grams of caffeine in as little as one-half cup [5].

With large amounts of caffeine (more than 10 mg per kg daily), there have been reports of aortic dissection, atrial fibrillation, cardiac arrest, celiac artery trunk dissection, chest pain, coronary artery vasospasm, extrasystoles, hemorrhagic stroke, ischemic stroke, tachycardia, transient ischemic attack, and ventricular tachycardia [5].

The acute oral dose of caffeine resulting in death in adults is estimated to be 10–14 grams (150–200 mg per kg), although fatality has occurred at lower doses. Deaths typically have been attributed to ventricular fibrillation [5]. At least two deaths have been linked to the use of highly concentrated and pure formulations. In 2018, the FDA announced that highly concentrated and pure formulations of caffeine are unlawful when sold directly to consumers in bulk quantities [5].

There have been numerous case reports of seizures with excessive caffeine intake and also when combining caffeine with other stimulants. Life-threatening events are also more common after taking caffeine-containing energy or weight loss products when compared with non-caffeine containing products. Deaths have occurred following consumption of caffeine alone or in combination with other stimulants or alcohol [5].

EPHEDRA

Ephedra, sometimes called *ma huang*, is a stimulant herb usually taken from the stem and branches of *Ephedra sinica*. It contains the principal alkaloid constituents ephedrine, pseudoephedrine, and sometimes small amounts of phenylpropanolamine. It has a long history of use in traditional Chinese medicine. It has traditionally been used for allergy symptoms, arthritis, asthma, bone pain, bronchitis, edema, headache, nephritis, and symptoms of the common cold and influenza. It has also been marketed as "herbal ecstasy," for use as a recreational drug [6].

While most *Ephedra* species contain ephedrine alkaloids, Mormon tea (*Ephedra nevadensis* or *Ephedra viridis*) is a plant in the *Ephedra* genus that is devoid of ephedrine and other alkaloids. Some other plants also contain ephedrine alkaloids, including *Sida cordifolia* and *Pinellia ternate* [6].

Regulatory Concerns

Because of the potential for serious safety concerns associated with its use, ephedra, *Sida cordifolia*, *Pinellia ternata*, or other ephedrine-containing herbs have been banned in the United States since 2004. Despite this ban, ephedra products can still be obtained on the Internet, often in combination products containing caffeine and/or other stimulants (e.g., synephrine, phenylethylamine [PEA], and yohimbine) [6].

Like other stimulants, ephedra is sometimes touted for its performance-enhancing effects, but these effects have not been substantiated in clinical studies. Ephedra appears on the prohibited list of many large sports and other organizations, including the NCAA [6].

Quality Concerns

There is considerable inter- and intra-product variability in labeled ephedra content. This increases concerns about ephedra toxicity.

There is also significant variability in the amounts of constituents found in ephedra supplements. In one study, ephedra supplements were found to contain 1.08–13.54 mg of ephedrine and 0.52–9.46 mg of pseudoephedrine per recommended dose. In other studies, 1 gram of a dry extract of ephedra was found to contain 58.9 mg of total ephedrine alkaloids, comprised of 0.44 mg of norephedrine, 1.09 mg of methylephedrine, 1.01 mg of norpseudoephedrine, 11.21 mg of pseudoephedrine, and 45.15 mg of ephedrine [6].

Norpseudoephedrine, a Schedule IV controlled substance, has been found to be a contaminant in some ephedra products [6].

Safety

Prior to its removal from the U.S. market, ephedra accounted for less than 1% of herbal product sales but was responsible for 64% of herbal adverse reaction reports to poison control centers. In a review of 926 cases of potential ephedra-related adverse effects reported to the FDA, 37 patients had serious or fatal adverse reactions [6].

Ephedra can cause severe life-threatening or disabling adverse effects in some people. It has been linked to significant cardiovascular effects, including cardiac arrhythmias, cardiac arrest, cardiomyopathy, heart failure, and myocardial infarction, as well as seizure, stroke, psychosis, and sudden death. There is some evidence that taking more than 32 mg daily might increase the risk of hemorrhagic stroke, including subarachnoid hemorrhage and intracerebral hemorrhage, by more than threefold [6].

While prolonged use and high doses might increase the risk of serious adverse effects, serious adverse effects have also been reported at low doses (e.g., 20–60 mg of ephedra alkaloids) in the short-term. It is impossible to determine who might be at the greatest risk from ephedra's adverse effects, but people with existing cardiovascular disease and those using combinations of stimulants might be at increased risk [6].

In addition to serious cardiovascular effects, cases of hepatotoxicity (e.g., acute hepatitis, liver failure) from ephedra-containing supplements have been reported after an average of three months of ephedra ingestion. Some cases of hepatotoxicity have resolved with discontinuation of ephedra, but others have required liver transplantation. Immune reactions and contamination have been proposed as potential causes of hepatotoxicity, but the majority of evidence suggests that ephedra-related hepatotoxicity is idiosyncratic in nature [6].

STIMULANT INTERACTION CONCERNS

Interactions with Lab Tests

Some stimulants might cause false-positive test results on urine amphetamine and/or methamphetamine drug screens. This should be considered when interpreting urine drug screen results in patients who deny amphetamine and/or methamphetamine use [5; 6].

Interactions with Drugs and Supplements

Stimulants can have a fair amount of drug interactions. The most notable drug interaction concern is for the combination of a stimulant with other drugs or supplements that are stimulants or have stimulant properties. This combination can increase the risk of adverse effects, particularly cardiovascular adverse effects [2; 3; 4; 5; 6].

LAXATIVES

While laxatives themselves are not addicting, they are commonly misused for weight-loss effects. With the exception of senna, over-the-counter laxatives, which are not exempt from misuse, will not be covered in this course.

SENNA

Senna is the fruit (pod) or leaf of the plant *Senna alexandrina*. Senna contains sennosides, which are high molecular weight dianthrone glycosides [7].

Because sennosides are prodrugs, they are not absorbed in the gastrointestinal (GI) tract and are instead activated by enzymes in the colon. The cathartic properties of the senna leaf are greater than the fruit. Effects usually occur within 6 to 10 hours after oral administration [7].

Senna is an FDA-approved nonprescription stimulant laxative found in many commercially available products that are approved for the short-term treatment of constipation in adults and children 2 years of age or older. These products contain the active ingredient sennosides [7].

Senna is also available in dietary supplements containing variable amounts of the leaf. Senna leaf is sometimes added to weight loss products or "cleansing" teas, but these uses are unproven and may be unsafe [7].

CASTOR OIL

Castor oil is the oil that comes from castor beans (seeds). Unlike the beans, castor oil does not contain the deadly poison ricin [8].

Castor oil is a stimulant laxative that has been used as a laxative in multiple systems of medicine (e.g., Unani, Ayurvedic) in India since 2000 B.C.E. It is hydrolyzed in the duodenum by pancreatic lipase to release ricinoleic acid [8].

While the exact mechanism of ricinoleic acid is unknown, laxative effects appear to result from a combination of fluid secretion and increased peristalsis. The onset of action is usually within two, but sometimes up to six, hours [8].

Castor oil is sometimes flavored (e.g., with cinnamon, peppermint, or other flavorings) to mask its overall slightly bitter and nauseating taste [8].

SAFETY

Stimulant laxatives can cause abdominal pain and discomfort, bloating, cramping, diarrhea, faintness, flatulence, fecal urgency, and nausea. Use of laxatives at high doses and for long periods might be unsafe. Abuse of laxatives can cause fluid and electrolyte, particularly potassium, losses. Theoretically, this can increase the risk for arrhythmias. There is also a risk of malabsorption as a result of intestinal hypermotility [7; 8].

Cases of "cathartic colon" have been described in the literature following chronic use of both senna and castor oil. Cathartic colon refers to radiographically diagnosed anatomic changes to the colon, such as benign narrowing, colonic dilation, and loss of colonic folds. The clinical relevance of such changes is unclear [7; 8].

Chronic use of senna can also cause pseudomelanosis coli (pigmented spots along the intestinal mucosa), but this condition is harmless, reverses with cessation, and has not been shown to be associated with an increased risk of developing colorectal adenoma or carcinoma [7].

Long-term use of laxatives is thought to result in habituation and/or tolerance. Habituation refers to a reduced or even absent laxative response, and tolerance refers to the need for increased doses in order to maintain the desired laxative response. Both habituation and tolerance could theoretically be induced by damage to the colon or by an adaptive mechanism counteracting the laxative's effect on motility and/or secretion [9].

Uncontrolled observational studies in humans and conflicting data from prospective animal studies have raised concerns that chronic stimulant laxative use can actually cause nerve or muscle damage to the colon, but these concerns have been largely disproven by higher quality studies [9]. While tolerance may occur in patients with severely slow colonic transit in whom other types of laxatives are ineffective, development of tolerance seems to be uncommon in the majority of users.

Be sure to ask patients about dietary supplement usage while obtaining their medication history. And be on the lookout for purchasing practices that might suggest inappropriate use.

ABUSE POTENTIAL RELATED TO RECREATIONAL USE

Like prescription drugs, many supplements are abused on the party scene and for varying other recreational reasons. Among these is gamma-hydroxybutyrate (GHB) for its euphoric, amnestic, and calming effects.

GHB

GHB is a short-chain fatty acid made from gamma aminobutyric acid (GABA). GHB is naturally occurring in the brains of mammals in very small amounts. The highest concentrations in the brain are found in the basal ganglia. GHB is also found in other tissues, including the kidneys, liver, heart, skeletal muscle, and brown fat [10].

GHB is an agonist at GABA-B receptors and is also converted to GABA. The central nervous system (CNS) depressant effects of GHB, especially those observed at higher doses, can be attributed to direct agonist activity at GABA-B receptors. GHB has also been reported to raise dynorphin levels through its effects on the endogenous opioid system. Stimulation of GHB receptors also results in a reduction in dopamine release in the basal ganglia and influences dopamine release in the substantia nigra [10].

GHB abuse became popular among teens and young adults at dance clubs and raves in the 1990s, but use persists today. GHB is used as a party drug, for its euphoric and calming effects and for sexual arousal, and in cases of drug-facilitated sexual assault. It is usually sold as a clear, colorless liquid or as a white powder that can be dissolved in liquid [10].

In the United States, GHB is federally classified as a Schedule I controlled substance, making production, sale, and possession outside of medical use illegal. The major source of GHB is through clandestine synthesis by local operators [10].

An FDA-approved prescription form of the sodium salt of GHB, known as sodium oxybate (Xyrem), is labeled for the treatment of cataplexy or excessive daytime sleepiness in patients 7 years of age or older with narcolepsy. Sodium oxybate is a Schedule III controlled substance and seems to be safe when used appropriately under medical supervision [10].

Several chemically related analogs of GHB, including gamma butyrolactone (GBL) and 1,4-butanediol (BD), are rapidly converted to GHB in the body and have similar effects to the parent compound. Popularity of these analogs increased with the regulatory restriction of GHB as a Schedule I controlled substance. These analogs are legally available as industrial solvents, but are also sold illicitly as supplements for bodybuilding, weight loss, reversal of baldness, drug addiction, and other uses. GBL and BD are abused for the same reasons as GHB. Routine toxicologic screens do not detect the presence of these analogs, so abuse can be difficult to identify [16].

Safety

When used orally without medical supervision (i.e., not as a prescription medicine), GHB is not safe for any use. Serious side effects include ataxia, cardiac arrest, coma, respiratory depression, tonic-clonic seizure, variable heart rate, and death. The analogs GBL and BD have also been associated with a large number of reports of such serious adverse reactions [10; 16].

Concomitant use of GHB and its analogs with alcohol and some other co-ingestants can increase the risk of CNS and respiratory depression, as well as other severe adverse effects. Alcohol may also inhibit the clearance of GHB [10].

EVIDENCE-BASED PRACTICE RECOMMENDATION

The UK Department of Health asserts that persons providing services to patients who use GHB should advise these individuals to be aware of the added risks of mixing GHB with other sedative drugs.

(https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/673978/clinical_guidelines_2017.pdf. Last accessed October 27, 2022.)

Level of Evidence: Consensus Statement/Expert Opinion

GHB is commonly used in cases of drug-facilitated sexual assault. Patients can help avoid becoming a victim by never taking a drink from a stranger and never leaving a drink unattended. If poisoning is suspected, call poison control at 1-800-222-1222 [10]. There is no antidote for GHB toxicity, and treatment is limited to supportive care. In patients with severe GHB intoxication, maintaining airway patency with intubation, if necessary, is the most important intervention. Because GHB can cause a rapid loss of consciousness, gastric lavage and induction of emesis are contraindicated. Symptomatic bradycardia can be managed with atropine, and seizures respond effectively to benzodiazepines [11; 12]. Withdrawal symptoms are best managed with anxiolytics [13].

Regular GHB use can also cause dependence requiring inpatient detoxification. Withdrawal from GHB can cause agitation, anxiety, diaphoresis, delirium with auditory and visual hallucinations, hypertension, insomnia, panic, psychoses, rhabdomyolysis, tachycardia, terror, and tremor [10].

ABUSE POTENTIAL RELATED TO OPIOID-LIKE EFFECTS

KRATOM

Similar to an opioid, kratom is mainly used for its opioid-like effects. Kratom, *Mitragyna speciosa*, is a tropical tree that is native to Southeast Asia. The leaves are the part of the plant that has garnered interest, either when chewed as whole leaves, consumed as beverages prepared from the leaves (e.g.,

tea, juice), powdered and packaged into gel caps, or as an extract. The leaves have also been crushed and then smoked, but kratom is mostly abused through oral ingestion [14].

Kratom contains a long list of constituents, including corynantheidine, isopaynantheine, mitraciliatine, paynantheine, speciociliatine, speciogynine, and 9-hydroxycorynantheidine, but the alkaloids mitragynine and 7-hydroxymitraginine are thought to be its main active constituents. Twenty kratom leaves are estimated to contain about 18 mg of mitragynine [14].

Kratom contains the mu-opioid receptor agonist 7-hydroxymitragynine. 7-Hydroxymitragynine is estimated to be approximately 10 times as potent as morphine [14].

Kratom also contains a number of mu-opioid receptor partial agonists, including mitragynine. Mitragynine is estimated to be about 25% as potent as morphine, but it is present in much larger quantities than 7-hydroxymitragynine. Mitragynine makes up about 60% of kratom's alkaloid content and 7-hydroxymytragynine makes up 2% [14].

Kratom has both stimulant- and opioid-like properties, and its effects when taken by mouth are dose-dependent. Higher doses of kratom (e.g., 5–15 grams) are said to produce analgesic opioid-like effects, while lower doses (e.g., 1–5 grams) have stimulating effects [14].

Kratom has been used for its psychoactive properties and opium-like effects. It has been used for centuries in Thailand and Malaysia in socioreligious ceremonies, as an aid to combat fatigue in laborers, as an opioid substitute, and for other medical purposes. Several recent surveys have identified self-treatment of acute or chronic pain as the primary use for kratom. However, there is not enough information to support the use of kratom for any condition, and the risks certainly do not outweigh any potential benefits given its safety profile [14].

In the past, kratom use has not been widespread in the United States, but poison control center data show that interest seems to be growing. Between 2014 and 2019, U.S. poison control centers saw a rapid increase in kratom exposures [1].

In 2016, the Drug Enforcement Administration (DEA) attempted to ban kratom by making its mitragynine and 7-hydroxymitragynine constituents Schedule I substances in the United States under the Controlled Substances Act (CSA). This attempt to schedule these constituents was met with intense backlash from the public, industry, and some members of Congress [14]. While the DEA cited concerns of increases in the incidence of kratom-related seizures and calls to poison control centers related to kratom, the DEA ultimately withdrew its intent to schedule based on this strong opposition.

While the kratom tree and its leaves are illegal or restricted in some countries and states, it is not illegal in the United States. It is readily available for in-person purchase in many states, in addition to Internet sales. The manufacturing, sale, or possession of kratom products are not currently regulated by the FDA or DEA, but the DEA has listed kratom as a drug and chemical of concern [15].

Kratom has been reported to be contaminated with various substances, including heavy metals and phenethylamine (PEA), an amphetamine-like substance. In 2018, the Centers for Disease Control and Prevention (CDC) reported a *Salmonella* outbreak sickening at least 134 people in more than 35 states that was found to be linked to kratom products [14].

Some kratom products have been suspected to be adulterated with respect to the active constituents. In a laboratory analysis, samples of some commercially available kratom products were found to contain 4.5-fold higher concentrations of 7-hydroxymitragynine than are usually present in kratom leaves [14].

Safety

The FDA has warned consumers on multiple occasions that kratom is unsafe. Kratom has been linked to serious adverse effects, including respiratory depression, aggression, hallucinations, delusions, vomiting, seizures, liver damage, severe withdrawal, and death. Short-term use, especially in combination with other substances, has been associated with cases of intrahepatic cholestasis, rhabdomyolysis, seizure, encephalopathy syndrome, and death. Long-term use has been associated with tolerance and withdrawal

symptoms, including aggression, anxiety, muscle aches and spasms, nausea and vomiting, shakiness and tremors, and QT interval prolongation [14].

Interactions with Drugs

Kratom seems to inhibit many enzymes commonly involved in the metabolism of drugs, potentially increasing their levels and effects. It also might have overlapping effects with drugs that have similar mechanisms [14].

Interactions with Conditions

In patients with alcohol use disorder or other psychiatric disorders, epidemiologic research suggests an increased risk of suicide with kratom use. In patients with existing cardiac conditions, kratom use can increase the risk of tachycardia [14].

In animal studies, kratom seems to cross the placenta. In humans, there have been multiple reports of neonatal abstinence syndrome (NAS) in infants born to patients using kratom during pregnancy [14].

Do not assume that potentially harmful use of supplements only occurs in young people. With kratom use on the rise among all demographics, increased use of kratom among older adults is particularly concerning as data have shown severe effects in this population [14].

CONSIDERATIONS FOR NON-ENGLISH-PROFICIENT PATIENTS

For patients who are not proficient in English, it is important that information regarding the benefits and risks associated with the use of dietary supplements be provided in their native language, if possible. When there is an obvious disconnect in the communication process between the practitioner and patient due to the patient's lack of proficiency in the English language, an interpreter is required. Interpreters can be a valuable resource to help bridge the communication and cultural gap between patients and practitioners. Interpreters are more than passive agents who translate and transmit information back and forth from party to party. When they are enlisted and treated as part of the interdisciplinary clinical team, they serve as cultural brokers who ultimately enhance the clinical encounter.

CONCLUSION

Dietary supplement use continues to increase. In 2020, U.S. supplement sales surpassed $10 billion for the first time ever [17]. Unfortunately, with increased use also comes increased abuse and misuse. Recreation, body image concerns, athletic performance, and mood enhancement continue to drive inappropriate use. Knowing the common culprits, how they work, and their potential adverse effects can enhance patient education and the detection of potential supplement abuse.

Implicit Bias in Health Care

The role of implicit biases on healthcare outcomes has become a concern, as there is some evidence that implicit biases contribute to health disparities, professionals' attitudes toward and interactions with patients, quality of care, diagnoses, and treatment decisions. This may produce differences in help-seeking, diagnoses, and ultimately treatments and interventions. Implicit biases may also unwittingly produce professional behaviors, attitudes, and interactions that reduce patients' trust and comfort with their provider, leading to earlier termination of visits and/or reduced adherence and follow-up. Disadvantaged groups are marginalized in the healthcare system and vulnerable on multiple levels; health professionals' implicit biases can further exacerbate these existing disadvantages.

Interventions or strategies designed to reduce implicit bias may be categorized as change-based or control-based. Change-based interventions focus on reducing or changing cognitive associations underlying implicit biases. These interventions might include challenging stereotypes. Conversely, control-based interventions involve reducing the effects of the implicit bias on the individual's behaviors. These strategies include increasing awareness of biased thoughts and responses. The two types of interventions are not mutually exclusive and may be used synergistically.

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