Psychoactive supplements: What to tell patients

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Educating patients about the risks associated with supplement use can help inform their decisions

Mr. D, age 41, presents to the emergency department (ED) with altered mental status and suspected intoxication. His medical history includes alcohol use disorder and spinal injury. Upon initial examination, he is confused, disorganized, and agitated. He receives IM lorazepam 4 mg to manage his agitation. His laboratory workup includes a negative screening for blood alcohol, slightly elevated creatine kinase, and urine toxicology positive for barbiturates and opioids. During reevaluation by the consulting psychiatrist the following morning, Mr. D is alert, oriented, and calm with an organized thought process. He does not appear to be in withdrawal from any substances and tells the psychiatrist that he takes butalbital/acetaminophen/caffeine/codeine as needed for migraines. Mr. D says that 3 days before he came to the ED, he also began taking a supplement called phenibut that he purchased online for "well-being and sleep."

Natural substances have been used throughout history as medicinal agents, sacred substances in religious rituals, and for recreational purposes.[1] Supplement use in the United States is prevalent, with 57.6% of adults age ≥20 reporting supplement use in the past 30 days.[2] Between 2000 and 2017, US poison control centers recorded a 74.1% increase in calls involving exposure to natural psychoactive substances, mostly driven by cases involving marijuana in adults and adolescents.[3] Like synthetic drugs, herbal supplements may have psychoactive properties, including sedative, stimulant, psychedelic, euphoric, or anticholinergic effects. The variety and unregulated nature of supplements makes managing patients who use supplements particularly challenging.

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Practice Points

- Psychoactive supplements may have sedative, stimulant, psychedelic, euphoric, or anticholinergic effects, and **may be addictive.**
- **Routinely ask patients about their use of dietary supplements or over-the-counter products** because they may be unlikely to voluntarily share this information.
- **Educate patients that despite being widely available, supplements are not always safe or effective** because they are not subject to the same FDA regulations for safety and efficacy as prescription medications.

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Why patients use supplements

People may use supplements to treat or prevent vitamin deficiencies (eg, vitamin D, iron, calcium). Other reasons may include for promoting wellness in various disease states, for weight loss, for recreational use or misuse, or for overall well-being. In the mental health realm, patients report using supplements to treat depression, anxiety, insomnia, memory, or for vague indications such as "mood support."[4,5]

Patients may view supplements as appealing alternatives to prescription medications because they are widely accessible, may be purchased over-the-counter, are inexpensive, and represent a "natural" treatment option.[6] For these reasons, they may also falsely perceive supplements as categorically safe.[1] People with psychiatric diagnoses may choose such alternative treatments due to a history of adverse effects or treatment failure with traditional psychiatric medications, mistrust of the health care or pharmaceutical industry, or based on the recommendations of others.[7]

Regulation, safety, and efficacy of dietary supplements

In the US, dietary supplements are regulated more like food products than medications. Under the Dietary Supplement Health and Education Act of 1994, the FDA regulates the quality, safety, and labeling of supplements using Current Good Manufacturing Practice regulations.[8] The Federal Trade Commission monitors advertisements and marketing. Despite some regulations, dietary supplements may be adulterated or contaminated, contain unknown or toxic ingredients, have inconsistent potencies, or be sold at toxic doses.[9] Importantly, supplements are not required to be evaluated for clinical efficacy. As a result, it is not known if most supplements are effective in treating the conditions for which they are promoted, mainly due to a lack of financial incentive for manufacturers to conduct large, high-quality trials.[5]

Further complicating matters is the inconsistent labeling of supplements or similar products that are easily obtainable via the internet. These products might be marketed as nutritional supplements or nootropics, which often are referred to as "cognitive enhancers" or "smart drugs." New psychoactive substances (NPS) are drugs of misuse or abuse developed to imitate illicit drugs or controlled drug substances.[10] They are sometimes referred to as "herbal highs" or "legal highs."[11] Supplements may also be labeled as performance- or image-enhancing agents and may include medications marketed to promote weight loss. This includes herbal substances (***Table***,[12-19] ***page 38***) and medications associated with neuropsychiatric adverse effects that may be easily accessible online without a prescription.[12,20]

The growing popularity of the internet and social media plays an important role in the availability of supplements and non-regulated substances and may contribute to misleading claims of efficacy and safety. While many herbal supplements are available in pharmacies or supplement stores, NPS are usually sold through anonymous, low-risk means either via traditional online vendors or the deep web (parts of the internet that are not indexed via search engines). Strategies to circumvent regulation and legislative control include labeling NPS as research chemicals, fertilizers, incense, bath salts, or other identifiers and marketing them as "not for human consumption."[21] Manufacturers frequently change the chemical structures of NPS, which allows these products to exist within a legal gray area due to the lag time between when a new compound hits the market and when it is categorized as a regulated substance.[10]

Another category of "supplements" includes medications that are not FDA-approved but are approved for therapeutic use in other countries and readily available in the US via online sources. Such medications include phenibut, a glutamic acid derivative that functions as a gamma-aminobutyric

Clinical Point

Patients may choose to use supplements due to a history of adverse effects or treatment failures with prescription medications

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Clinical Point

Remind patients that supplements are not required to be evaluated for their safety or effectiveness

Table

Psychoactive supplements

Supplement/ substance	Mechanism of action	Common uses	Select neuropsychiatric adverse reactions
Anticholinergic plants (eg, jimson weed)	Antagonism of the central/peripheral muscarinic acetylcholine receptors	Hallucinogenic effects	Somnolence, agitation, confusion, delirium, psychosis, hallucinations, seizures, hyperthermia, coma
Ginseng (*Panax ginseng*)	Modulates noradrenergic, dopaminergic, serotonergic, cholinergic, and endorphin systems	Weight loss	Euphoria, nervousness, insomnia, depression, worsening of pre-existing psychiatric symptoms
Guarana (*Paullinia cupana*)	Stimulant and psychoactive properties; contains high caffeine content	Weight loss, ingredient in energy drinks	Caffeine intoxication, mania, insomnia, somnolence, asthenia, anxiety, impaired concentration
Hallucinogenic mushrooms (eg, psilocybin)	5HT2A receptor antagonist activity	Hallucinogenic effects	Confusion, vertigo, drowsiness, euphoria, anxiety, hallucinations with vivid colors/shapes, muscular weakness, increased deep tension reflexes, ataxia, paresthesia, seizure
Kava (*Piper methysticum*)	Active ingredient kavalactones; may work by targeted actions on GABA pathways	Insomnia, anxiety; may be consumed socially as a beverage	Dizziness, drowsiness, extrapyramidal symptoms, dose-dependent impaired motor coordination and alertness, apathy (at high doses)
Khat (*Catha edulis*)	Cathinone (major psychoactive component) is structurally similar to ephedrine and amphetamines	Stimulant effects, depression, fatigue	Euphoria, hyperactivity, aggression, anxiety
Kratom (*Mitragyna speciosa*)	Mu-opioid agonism and partial agonism; alpha-2 agonism	Stimulant (low doses); opioid agonism, analgesia, and sedative effects (higher doses)	Euphoria, CNS stimulation, seizures, hallucinations, psychosis, confusion, agitation, headache, dizziness, syncope; withdrawal symptoms include myalgia, insomnia, fatigue
Ma Huang (*Ephedra sinica*)	Active ingredient ephedrine is a sympathomimetic agent structurally similar to amphetamine; stimulates short-term release of dopamine and norepinephrine and long-term monoamine depletion	Weight loss, respiratory conditions	Psychosis, euphoria, depression, mania, severe agitation, irritability, anxiety, addiction
Nutmeg (*Myristica fragrans*)	Myristicin, active ingredient, mechanism is unknown; possible serotonin antagonism	Sedation, possible hallucinogenic effects	CNS depression, agitation, hallucination

Table continued

Supplement/ substance	Mechanism of action	Common uses	Select neuropsychiatric adverse reactions
Purple passionflower (*Passiflora incarnata*)	Inhibits uptake of GABA into neuronal synapses; has affinity for GABA-A and GABA-B receptors	Anxiety, sleep, opioid withdrawal	Confusion, dizziness, sedation, ataxia
Peyote (*Lophophora williamsii*)	Active ingredient mescaline (an exogenous phenylethylamine); sympathomimetic and hallucinogenic activity similar to LSD	Hallucinogenic effects, may also be used for physical and psychological effects in religious rituals	Mydriasis, agitation, hallucinations
Salvia species (*Salvia divinorum*)	Activity at kappa opioid receptors, allosteric modulation of cannabinoid type 1 receptors; also inhibits leukotrienes and cytokines	Hallucinogenic effects, depression, inflammatory conditions, pain	Headache, restlessness, hyperactivity, disorientation, loss of coordination, dizziness, slurred speech, altered perceptions and hallucinations, mood changes, psychosis
St. John's Wort (*Hypericum perforatum*)	Inhibits uptake of norepinephrine and dopamine; potential effects with serotonin inhibition	Depression, anxiety	Sedation, fatigue, headache, insomnia, restlessness; rare reports of suicidal ideation and psychosis
Tetrahydrocannabinol (THC)	Binds to CB1 receptors in brain	Euphoric effects, pain, anxiety	Dizziness, dry mouth, fatigue, headache, increased appetite, nausea, paranoia and dissociative thinking, sedation
Valerian (*Valeriana officinalis*), edible valerian (*Valeriana edulis*)	Unknown; may increase amount of GABA in synaptic cleft	Insomnia, anxiety	Sedation, mental slowness, dizziness, vivid dreams, excitability
Yohimbe (*Pausinystalia yohimbe*)	Active ingredient yohimbine is an alpha-2 adrenoceptor antagonist	Weight loss, sexual dysfunction	Anxiety, irritability, impulsivity, mania, addictive behaviors

GABA: gamma-aminobutyric acid; LSD: lysergic acid diethylamide

Source: References 12-19

acid-B receptor agonist in the brain, spinal cord, and autonomic nervous system. Phenibut was developed in the Soviet Union in the 1960s, and outside of the US it is prescribed for anxiolysis and other psychiatric indications.[22] In the US, phenibut may be used as a nootropic or as a dietary supplement to treat anxiety, sleep problems, and other psychiatric disorders.[22] It may also be used recreationally to induce euphoria. Chronic phenibut use results in tolerance and abrupt discontinuation may mimic benzodiazepine withdrawal symptoms.[13,22]

Educating patients about supplements

One of the most critical steps in assessing a patient's supplement use is to directly ask them about their use of herbal or over-the-counter products. Research has consistently shown that patients are unlikely to disclose supplement use unless they are specifically asked.[23,24]

Additional strategies include[25,26]:

- Approach patients without judgment; ask open-ended questions to determine their motivations for using supplements.

continued

Clinical Point

Asking open-ended, nonjudgmental questions can help determine a patient's motivation for using supplements

Clinical Point

Supplements may contain unknown or toxic ingredients, or have inconsistent amounts of the intended substance

- Explain the difference between supplements medically necessary to treat vitamin deficiencies (eg, vitamin D, calcium, magnesium) and those without robust clinical evidence.
- Counsel patients that many supplements with psychoactive properties, if indicated, are generally meant to be used short-term and not as substitutes for prescription medications.
- Educate patients that supplements have limited evidence regarding their safety and efficacy, but like prescription medications, supplements may cause organ damage, adverse effects, and drug-drug interactions.
- Remind patients that commonly used nutritional supplements/dietary aids, including protein or workout supplements, may contain potentially harmful ingredients.
- Utilize evidence-based resources such as the Natural Medicines Comprehensive Database[14] or the National Center for Complementary and Integrative Health (https://www.nccih.nih.gov) to review levels of evidence and educate patients.
- When toxicity or withdrawal is suspected, reach out to local poison control centers for guidance.
- For a patient with a potential supplement-related substance use disorder, urine drug screens may be of limited utility and evidence is often sparse; clinicians may need to rely on primary literature such as case reports to guide management.
- If patients wish to continue taking a supplement, recommend they purchase supplements from manufacturers that have achieved the US Pharmacopeia (USP) verification mark. Products with the USP mark undergo quality assurance measures to ensure the product contains the ingredients listed on the label in the declared potency and amounts, does not contain harmful levels of contaminants, will be metabolized in the body within a specified amount of time, and has been produced in keeping with FDA Current Good Manufacturing Practice regulations.

Related Resources

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Drug Brand Names

Butalbital/acetaminophen/caffeine/codeine • Fioricet with Codeine

CASE CONTINUED

In the ED, the consulting psychiatry team discusses Mr. D's use of phenibut with him, and asks if he uses any additional supplements or nonprescription medications. Mr. D discloses he has been anxious and having trouble sleeping, and a friend recommended phenibut as a safe, natural alternative to medication. The team explains to Mr. D that phenibut's efficacy has not been studied in the US and that based on available evidence, it is likely unsafe. It may have serious adverse effects, drug-drug interactions, and is potentially addictive.

Mr. D says he was unaware of these risks and agrees to stop taking phenibut. The treatment team discharges him from the ED with a referral for outpatient psychiatric services to address his anxiety and insomnia.

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Clinical Point

If patients want to take supplements, recommend they purchase USP-verified products