Hypertensive Emergency Caused by Sexual Enhancement Supplements

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ABSTRACT

Introduction: In the United States, major depression ranks second among all diseases and injuries as a cause of disability and 40% of patients using antidepressants experience sexual dysfunction.

Case Presentation: A 41-year-old woman with past history of depression and anxiety presented with hypertensive urgency after ingesting a sexual enhancement supplement—BioXgenic—for the first time. Shortly after, computed tomography showed a basal ganglia hemorrhage. After many weeks of rehabilitation, some cognitive deficits remained.

Discussion: The US Food and Drug Administration (FDA) does not regulate supplements. The sexual enhancement supplement ingested had monoamine oxidase inhibitor properties and precipitated a hypertensive emergency with an intracerebral hemorrhage. Reducing medication dosage, switching medication, using drug holidays, and changing the time of administration may help alleviate sexual side effects.

Conclusion: Physicians should inquire about dietary supplements and warn about the risks, encourage patients to report adverse effects with the FDA, and refer to the FDA's Tainted Supplements database for known adulterated supplements.

INTRODUCTION

The dietary supplement market is larger than ever. In 2020, the global dietary supplements market was estimated at $140.3 billion and is projected to continue growing and expanding due to rising health concerns and changing lifestyles.[1] Pivotal legislation that laid the groundwork for this booming market included the 1976 "Proxmire Amendment" and the Dietary Supplement Health and Education Act (DSHEA) of 1994. The Proxmire Amendment, which became section 411 of the Federal Food, Drug, and Cosmetic Act,[2] prohibited the US Food and Drug Administration (FDA) from requiring and limiting potency of vitamins and minerals in food supplements and regulating them as drugs. The DSHEA created specific labeling requirements, provided a regulatory framework, and authorized the FDA to establish good manufacturing practice regulations for dietary supplements.[3] It also established that dietary supplements are meant to supplement the diet; contain 1 or more dietary ingredients, including vitamins, minerals, herbs, amino acids, or other substances; are meant to taken by mouth; and are labeled as a dietary supplement. This distinction in labeling resulted in different rules and regulations than those for food and drugs. Dietary supplements do not have to prove efficacy before reaching consumers, whereas drugs are tested for efficacy and safety before they can be sold. Dietary supplement labels may include a health claim, which purports to reduce risk of a disease or health-related condition; a nutrient claim, which describes the relative amount of a nutrient or dietary substance in a product; and a structure or function claim, which describes how a product may affect the organ systems of the body but cannot mention any specific disease. It also must include the following disclaimer: "This statement has not been evaluated by the FDA. This product is not intended to diagnose, treat, cure, or prevent any disease" on the label.[3]

Although dietary supplements may be "natural," as noted

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Published online November 22, 2021.

above, they are not regulated by the FDA and can have unexpected adverse effects and drug interactions, such as kidney toxicity,[4] liver toxicity,[5] anaphylaxis,[6] and drug interactions.

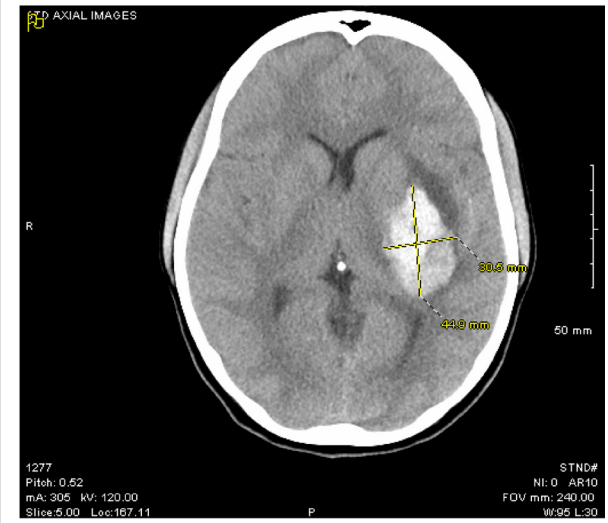
People turn to herbal supplements for many reasons, including sexual dysfunction. In the United States, major depression ranks second among all diseases and injuries as a cause of disability, and second-generation antidepressants are the first line of pharmacologic treatment. These include selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), atypical antidepressants, and serotonin modulators. Unfortunately, many serotonergic antidepressants can interfere with different aspects of sexual functioning, including desire, arousal, and orgasm. In fact, a review of research studies showed that 40% of patients using antidepressants experienced some form of sexual dysfunction,[7] which can negatively affect one's quality of life and lead to medication nonadherence. It also may prompt patients to try herbal supplements to improve sexual dysfunction.

CASE PRESENTATION

A 41-year-old woman with past history of depression, anxiety, substance use disorder in remission on medication-assisted treatment, and attention deficit hyperactivity disorder (ADHD) presented to urgent care with acute nausea, vomiting, flushing, and rash after ingesting a sexual enhancement supplement—BioXgenic—for the first time. Her home medications included bupropion 150 mg daily, clonidine 0.1 mg orally twice a day, as needed for anxiety, desvenlafaxine 200mg daily, trazadone 100 mg nightly, lisdexamfetamine dimesylate 100 mg daily, and buprenorphine 8 mg daily. Within an hour of presenting to the emergency department (ED), her blood pressure was 201/108, pulse 61, respiratory rate 16, and oxygen saturation 100%. A urine drug screen was positive for amphetamines due to the lisdexaferamine dimesylate; she was not taking any illicit drugs and did not drink alcohol.

Within 2 hours of her arrival to the ED, she reported a headache and then became somnolent with a new facial droop and right-sided weakness on exam. Computed tomography (CT) showed a 3.8 cm left basal ganglia hemorrhage (see Figure), and she had a Glasgow Coma Scale score of 11 with incomprehensible speech. She was transferred to a neurological intensive care unit, where she was found to have anisocoria, disconjugate gaze with left adduction deficit, right upper and lower facial weakness, right-sided motor deficits, and a right extensor plantar reflex. Due to location of brain bleed, she was not a candidate for neurosurgical intervention and was treated supportively with mannitol, permissive hypernatremia, and antihypertensives. Upon admission, she was too obtunded for safe oral intake so feeding tube was placed, and all psychiatric medications were held initially. Throughout her 16-day hospital stay, she slowly improved and was discharged to inpatient rehabilitation with aphasia with

Figure. Non-Contrast Head Computed Tomography of Intracerebral Hemorrhage



intact comprehension, a mild right facial droop, intact cranial nerves, and right-sided hemiparesis. After many weeks of inpatient and outpatient rehabilitation, her speech was comprehensible and motor function had improved enough for her to ascend a flight of stairs, but some subtle cognitive deficits remained.

DISCUSSION

Upon presentation, the patient's leading diagnosis included either an allergic reaction or a drug reaction due to the dietary supplement she had ingested about 2 hours prior. However, illicit drug use, reflex hypertension caused by clonidine, and alcohol withdrawal also were considered. A urine drug screen was ordered and was positive only for amphetamines caused by lisdexaferamine dimesylate, which she was taking for ADHD. A thorough social history also was taken to rule out any other illicit drug use and possible alcohol withdraw. Clonidine is known to cause reflex hypertension, but the patient's prescription history showed that it had been prescribed at a dose of 0.1mg orally twice a day as needed for anxiety 2 years earlier, and medication refill history indicated she was using less than 10 doses per month, so it is unlikely that this contributed to her hypertensive emergency. Although lisdexamfetamine can cause increased heart rate and blood pressure, she had been taking this medication for years, whereas she had just taken the herbal dietary supplement—BioXgenic—for the first time prior to admission. The emergency physician also spoke with poison control and was informed that the supplement is known to cause hypertension and tachycardia. Concerning ingredients listed on the supplement's label include American ginseng and epimedium, which is also known as "horny goat weed." Ginseng has been documented in scientific literature for causing adverse effects, including nausea, diarrhea, euphoria, insomnia, headaches, hypertension, hypotension,

Published online November 22, 2021.

mastalgia, vaginal bleeding, and blood pressure abnormalities.[8] Interactions also have been documented with the use of phenelzine, warfarin, clomipramine, imatinib, oral hypoglycemics, insulin, and caffeine, as well as about use in patients with hypertension or bleeding.[9] Epimedium is an herb used in traditional Chinese medicine to treat fatigue and sexual problems; known side effects include sweating or feeling hot, rapid irregular heartbeat, increased energy, and mood changes.[10]

Supplements may contain inconsistent amounts of active ingredients, have unknown potential side effects, or interact with prescribed medications, so they should be used with caution. A recent study identified unapproved pharmaceutical ingredients in herbal supplements from 2007 through 2016; 776 tainted dietary supplements were identified by the FDA, and 45.5% of these products were marketed for sexual enhancement.[11]

Our patient had a long history of refractory depression, which led to aggressive titration of her SNRI. Unfortunately, sexual side effects are often dose dependent. The sexual enhancement supplement she purchased contained herbs that likely interacted with her current medical regimen: ginseng and epimedium. These herbs may have contained monoamine oxidase inhibitor properties and precipitated a hypertensive emergency with an intracerebral hemorrhage. The antiplatelet effect of her serotonergic antidepressant also likely contributed to her hemorrhagic stroke.[12]

CONCLUSIONS

In the US, more than 50% of adults consume dietary supplements.[11] Thus, physicians should always inquire about dietary supplement use and warn patients about risks. A systematic review of adverse effects, poisonings, and interactions of plant food supplements in 2014 found a total of 492 papers, with 81.7% described cases due to adverse effects directly associated with the botanical and 18.1% to interactions with conventional drug. These papers identified 66 different plants used as supplements; the most sited were green tea, black cohosh, *Cinnamomum zeylanicum* (Ceylon cinnamon), bitter orange, Eastern purple coneflower, ginkgo/maidenhair tree, soybean, liquorice, devil's claw, St John's wort, ginseng, valerian, vitex or "chaste tree," and grape.[9] The FDA relies on post-market surveillance to identify unsafe or contaminated supplements, so physicians should encourage patients to read dietary supplement labels, research the ingredients while keeping a close eye out for the botanicals mentioned above, and encourage patients to report to the FDA any adverse effects or complaints pertaining to dietary supplements. Physicians also should refer to the FDA's Center for Drug Evaluation and Research's Tainted Supplements database for known adulterated dietary supplements.[13]

Our patient experienced antidepressant-induced sexual dysfunction, which led to her purchase and ingest the supplement BioXgenic, precipitating a hypertensive emergency. Prescribing physicians should have candid conversations with patients about adverse effects of serotonergic antidepressants to determine if sexual effects are a concern. There is not a one-size-fits-all approach to managing antidepressant-induced sexual dysfunction, but reducing the medication dosage, switching medication, using drug holidays, and timing administration of medication to be further from the time of anticipated sexual activity may help to alleviate symptoms, prevent self-medication, and improve a patient's quality of life.

Funding/Support: None declared.

Financial Disclosures: None declared.

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Published online November 22, 2021.