CASE IN POINT

Supplements Are Not a Synonym for Safe: Suspected Liver Injury From Ashwagandha

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Background: As patients look more to alternative herbal and dietary supplements to boost energy and mood, reports are increasing of unintended adverse effects, particularly to the liver.
Case Presentation: We report a case of a 48-year-old man with a history of severe alcohol use disorder who presented to the emergency department with a cholestatic pattern of liver injury in the setting of alcohol and use of a testosterone-boosting supplement containing ashwagandha.
Conclusions: Drug-induced liver damage should be considered in patients with alcohol use disorder who present with a cholestatic pattern of liver injury. Although many natural substances are well tolerated, others can have unanticipated and harmful adverse effects and drug interactions. Future research should identify not only potentially harmful substances, but also which patients may be at greatest risk.

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Many patients take herbals as alternative supplements to boost energy and mood. There are increasing reports of unintended adverse effects related to these supplements, particularly to the liver.[1-3] A study by the Drug-Induced Liver Injury Network found that liver injury caused by herbals and dietary supplements has increased from 7% in 2004 to 20% in 2013.[4]

The supplement ashwagandha has become increasingly popular. Ashwagandha is extracted from the root of *Withania somnifera* (*W somnifera*). It is purported to have health benefits, such as improving men's health and increasing strength, memory, and learning abilities while decreasing anxiety and counteracting chronic fatigue.[5,6] *W somnifera* generally has been considered safe, though recently, a few case reports suggest that it may lead to a cholestatic pattern of injury.[5-7]

To date, the factors defining the population at risk for ashwagandha toxicity are unclear, and an understanding of how to diagnose drug-induced liver injury is still immature in clinical practice. The regulation and study of the herbal and dietary supplement industry remain challenging. While many so-called natural substances are well tolerated, others can have unanticipated and harmful adverse effects and drug interactions. Future research should not only identify potentially harmful substances, but also which patients may be at greatest risk.

CASE PRESENTATION

A 48-year-old man with a history of severe alcohol use disorder (AUD) complicated by fatty liver and withdrawal seizures and delirium tremens, hypertension, depression, and anxiety presented to the emergency department (ED) after 4 days of having jaundice, epigastric abdominal pain, dark urine, and pale stools. In the preceding months, he had increased his alcohol use to as many as 12 drinks daily due to depression. After experiencing a blackout, he stopped drinking 7 days before presenting to the ED. He felt withdrawal symptoms, including tremors, diaphoresis, abdominal pain, nausea, and vomiting. On the third day of withdrawals, he reported that he had started taking an over-the-counter testosterone-boosting supplement to increase his energy, which he referred to as TestBoost—a mix of 8 ingredients, including ashwagandha, eleuthero root, Hawthorn berry, longjack, ginseng root, mushroom extract, bindii, and horny goat weed. After taking the supplement for 2 days, he noticed that his urine darkened, his stools became paler, his abdominal pain worsened, and he became jaundiced. After 2 additional days without improvement, and still taking the supplement, he presented to the ED. He reported having no fever, chills, recent illness, chest pain, shortness of breath, melena, lower extremity swelling, recent travel, or any changes in medications.

The patient had a 100.1 °F temperature, 102 beats per minute pulse; 129/94 mm Hg blood pressure, 18 beats per minute respiratory rate, and 97% oxygen saturation on room air on admission. He was in no acute distress, though his examination

TABLE 1 RUCAM Adverse Drug Reaction Causality Assessment[a,16]

Cholestatic or mixed pattern of injury			
	Exposure		
Periods	**Initial exposure, d**	**Subsequent exposure, d**	**Points**
Start	5-90 < 5 or > 90	1-90 > 90	+2 +1
Stop	< 31	< 31	+1
Peak ALT or bilirubin minus upper limit of normal			
After discontinuing drug	Decrease by 50% or more within 180 d		+2
	Decrease by less than 50% within 180 d		+1
	Unchanged or increase or no available information		0
Alcohol or pregnancy risk factors	Yes No		+1 0
Age	> 54 y < 55 y		+1 0
Presence of other drugs	None or information not available Drug with suggestive timing Known hepatotoxin with suggestive timing		0 -1 -2
	Drug with other evidence for a role (eg, rechallenging)		-3
Other etiologies	Ruled out HAV, HBV, acute HCV, biliary obstruction, alcoholism, recent hypotension and CMV, EBV, HSV		+2
	Ruled out all of the following: HAV, HBV, acute HCV, biliary obstruction, alcoholism, recent hypotension		+1
	4 to 5 of the following ruled out: HAV, HBV, acute HCV, biliary obstruction, alcoholism, recent hypotension		0
	< 4 of the following ruled out: HAV, HBV, acute HCV, biliary obstruction, alcoholism, recent hypotension		-2
	Nondrug cause highly probably		-3
Available documented information	Reaction in product label Reaction published; no label Reaction unknown		+2 +1 0
Drug re-administration	Positive Compatible Negative Not done or not interpretable		+3 +1 -1 0

Abbreviations: ALT, alanine aminotransferase; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HS, herpes simplex virus; RUCAM, Roussel Uclaf Causality Assessment Method.
[a]Adapted from Hayashi PH. Causality assessment in drug-induced liver injury. *Semin Liver Dis*. 2009;29(4):348-356. doi:10.1002/cld.615

was notable for generalized jaundice and scleral icterus. He was mildly tender to palpation in the epigastric and right upper quadrant region. He was alert and oriented without confusion. He did not have any asterixis or spider angiomas, though he had scattered bruises on his left flank and left calf. His laboratory results were notable for mildly elevated aspartate aminotransferase (AST), 58 U/L (reference range, 13-35); alanine transaminase (ALT), 49 U/L (reference range, 7-45); and alkaline phosphatase (ALP), 98 U/L (reference range 33-94); total bilirubin, 13.6 mg/dL (reference range, 0.2-1.0); direct bilirubin, 8.4 mg/dL (reference range, 0.2-1); and international normalized ratio (INR), 1.11 (reference range, 2-3). His white blood cell

TABLE 2 RUCAM Scoring

Scoring, range, 0-14	
Total points	**Likelihood**
0	Unrelated
1-2	Unlikely
3-5	Possible
6-8	Probably
> 8	Highly probable

and platelet counts were not remarkable at 9790/µL (reference range, 4500-11,000) and 337,000/µL (reference range, 150,000-440,000), respectively. Abdominal ultrasound and computed tomography (CT) revealed fatty liver with contracted gallbladder and no biliary dilatation. Urine ethanol levels were negative. The gastrointestinal (GI) service was consulted and agreed that his cholestatic injury was nonobstructive and likely related to the ashwagandha component of his supplement. The recommendation was cessation with close outpatient follow-up.

The patient was not prescribed any additional medications, such as steroids or ursodiol. He ceased supplement use following hospitalization; but relapsed into alcohol use 1 month after his discharge. Within 3 weeks, his total bilirubin had improved to 2.87 mg/dL, though AST, ALT, and ALP worsened to 127 U/L, 152 U/L, and 140 U/L, respectively. According to the notes of his psychiatrist who saw him at the time the laboratory tests were drawn, he had remained sober since discharge. His acute hepatitis panel drawn on admission was negative, and he demonstrated immunity to hepatitis A and B. Urine toxicology was negative. Antinuclear antibody (ANA) test was negative 1 year prior to discharge. Epstein-Barr virus (EBV), cytomegalovirus (CMV), ANA, antismooth muscle antibody, and immunoglobulins were not checked as suspicion for these etiologies was low. The Roussel Uclaf Causality Assessment Method (RUCAM) score was calculated as 6 (+1 for timing, +2 for drop in total bilirubin, +1 for ethanol risk factor, 0 for no other drugs, 0 for rule out of other diseases, +2 for known hepatotoxicity, 0 no repeat administration) for this patient indicating probable adverse drug reaction liver injury (Tables 1 and 2). However, we acknowledge that CMV, EBV, and herpes simplex virus status were not tested.

The 8 ingredients contained in TestBoost aside from ashwagandha did not have any major known liver adverse effects per a major database of medications. The other ingredients include eleuthero root, Hawthorn berry (*crataegus laevigata*), longjack (*eurycoma longifolla*) root, American ginseng root (American panax ginseng—*panax quinquefolius*), and *Cordyceps mycelium* (mushroom) extract, bindii (*Tribulus terrestris*), and *epimedium grandiflorum* (horny goat weed).[6] No assays were performed to confirm purity of the ingredients in the patient's supplement container.

Alcoholic hepatitis is an important consideration in this patient with AUD, though the timing of symptoms with supplement use and the cholestatic injury pattern with normal INR seems more consistent with drug-induced injury. Viral, infectious, and obstructive etiologies also were investigated. Acute viral hepatitis was ruled out based on bloodwork. The normal hepatobiliary tree on both ultrasound and CT effectively ruled out acute cholecystitis, cholangitis, and choledocholithiasis and there was no further indication for magnetic resonance cholangiopancreatography. There was no hepatic vein clot suggestive of Budd-Chiari syndrome. Autoimmune hepatitis was thought to be unlikely given that the etiology of injury seemed cholestatic in nature. Given the timing of the liver injury relative to supplement use it is likely that ashwagandha was a causative factor of this patient's liver injury overlaid on an already strained liver from increased alcohol abuse.

The patient did not follow up with the GI service as an outpatient. There are no reports that the patient continued using the testosterone booster. His bilirubin improved dramatically within 1.5 months while his liver enzymes peaked 3 weeks later, with ALT ≥ AST. During his next admission 3 months later, he had relapsed, and his liver enzymes had the classic 2:1 AST to ALT ratio.

DISCUSSION

Generally, ashwagandha has been thought to be well tolerated and possibly hepatoprotective.[7-10] However, recent studies suggest potential for hepatotoxicity, though without clear guidance about which patients are most at risk.[5,11,12] A study by Inagaki and colleagues suggests the potential for dose-dependent mechanism of liver injury, and this is supported by in vitro CYP450 inhibition with high doses of *W Somnifera* extract.[11,13] We hypothesize that there may be a multihit process that makes some patients more susceptible to supplement harm, particularly those with repeated exposures and with ongoing exposure to hepatic toxins, such as AUD.[14] Supplements should be used with more caution in these individuals.

Additionally, although there are no validated guidelines to confirm the diagnosis of drug-induced liver injury (DILI) from a manufactured medication or herbal remedy, the Council for International Organizations of Medical Sciences (CIOMS) developed RUCAM, a set of diagnostic criteria for DILI, which can be used to determine the probability of DILI based on pattern of injury.[15] Although not widely used in clinical practice, RUCAM can help identify the possibility of DILI outside of expert consensus.[16] It seems to have better discriminative ability than the Maria and Victorino scale, also used to identify DILI.[16,17] While there is no replacement for clinical judgment, these scales may aid in identifying potential causes of DILI. The National Institutes of Health also has a LiverTox online tool that can assist health care professionals in identifying potentially hepatotoxic substances.[6]

CONCLUSIONS

We present a patient with AUD who developed cholestatic liver injury after ashwagandha use. Crucial to the diagnostic process is quantifying the amount ingested before presentation and the presence of contaminants, which is currently difficult to quantify given the lack of mechanisms to test supplements expediently in this manner in the clinical setting, which also requires the patient to bring in the supplements directly. There is also a lack of regulation and uniformity in these products. A clinician may be inclined to measure ashwagandha serum levels; however, such a test is not available to our knowledge. Nonetheless, using clinical tools such as RUCAM and utilizing databases, such as LiverTox, may help clinicians identify and remove potentially unsafe supplements. While there are many possible synergies between current medical practice and herbal remedies, practitioners must take care to first do no harm, as outlined in our Hippocratic Oath.

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Author disclosures

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Ethics and consent

The patient gave verbal consent to Dr. Fujimoto. The patient would not return to hospital or accept an email to sign a paper consent. There is no identifiable patient information in this case report.

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