

Psychosis Related to Ephedra-containing Herbal Supplement Use

Ruth Walton, MD, and Gail H. Manos, MD

Abstract: Ephedra, a psychoactive substance with stimulant properties, is found in many herbal products. Often perceived by the lay public as benign, the potential health-related dangers of using these products are beginning to be recognized. We review four cases associated with ephedra-containing herbal products and report three additional cases. Unlike the previously reported cases, the patients presented in this report developed persistent psychosis that required psychopharmaceutical management.

Ephedrine, a naturally occurring substance found in various species of the *Ephedra* genus (also known as *ma huang*), has been used in China for more than 2,000 years. It was introduced into Western medicine approximately 70 years ago as the first orally active sympathomimetic. Ephedrine is completely absorbed with oral administration, is distributed throughout the body, and crosses the blood-brain barrier. Ephedrine and other sympathomimetic drugs (eg, cocaine, methamphetamine) are derived from phenylethylamine. They differ only by a single substitution on the benzene ring, the terminal amino group, the α carbon, or the β carbon.¹

Although a urine drug screen that is positive for the presence of stimulants may suggest that ephedrine-induced psychosis is present, the symptoms may be indistinguishable from those of a primary psychotic disorder, and the presence of ephedrine may not account for the psychosis. Although cocaine and amphetamines are readily recognized as stimulants and are specifically tested for in urine drug screens, herbal substances that contain ephedrine may be overlooked. Ephedrine is not specifically tested for in urine drug screens but may result in a false-positive result for amphetamines on

qualitative tests. More specific quantitative tests can differentiate between amphetamines and ephedrine. Three cases of substance-induced psychosis in connection with the use of herbal dietary supplements are reported.

Case Reports

Patient 1

A 19-year-old man was referred for psychiatric evaluation because of decreased sleep, increasingly aggressive and disorganized behavior, and paranoid delusions during a 1-week period. It was reported that he recently had been using over-the-counter ephedra-containing herbal weight-training supplements (eg, Ripped Fuel, Twin Laboratories, Inc., Hauppauge, NY; Hydroxycut, MuscleTech Research and Development, Inc., Mississauga, ON, Canada) and had been escalating the doses and even inhaling the supplements through his nose in powder form. The patient's psychiatric history and substance use history were unremarkable. The family psychiatric history was negative.

His physical examination was unremarkable with the exception of an elevated lactic dehydrogenase level of 769 IU/L and an alanine transferase level of 142 IU/L, both of which returned to normal after 2 weeks of observation. His urine drug screen was initially positive for amphetamine, but confirmation studies (a more specific

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From the Department of Psychiatry, Naval Medical Center Portsmouth, Portsmouth, VA.

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Reprint requests to Gail H. Manos, MD, 2054 Hallmark Way, Chesapeake, VA 23323. Email: ghmanos@mar.med.navy.mil

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Key Points

- Ephedrine is a naturally occurring substance found in certain species of the ephedra plant, also known as *ma huang*.
- Many herbal products used to lose weight or enhance energy contain ephedra alkaloids.
- The actual amount of ephedrine in these products varies even within lots of the same product.
- Ephedra-containing herbal products have been associated with adverse effects such as psychosis.

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quantitative assay with the same sample) were negative for amphetamine.

He was observed in the hospital for 2 days without medications. He became increasingly hostile, assaultive, and disorganized. He was administered valproate, clonazepam, and haloperidol for persistent manic and psychotic symptoms. Gradually, his symptoms abated, and he was released for outpatient follow-up. The antipsychotic and benzodiazepine medications were discontinued after approximately 60 days without further psychotic symptoms. At the time of his last follow-up 5 months later, the patient remained on valproate only and was symptom-free.

Patient 2

A 21-year-old man who had experienced a brief psychotic episode after Hydroxycut use approximately 1 year earlier presented with recurrent manic and psychotic symptoms manifested by decreased sleep and increasing agitation with grandiose, persecutory, and referential delusions. During the year between psychotic episodes, the patient had used Hydroxycut in increasing doses for brief periods without psychotic symptoms until the most recent episode, which followed a 2-week Hydroxycut binge. There was no other substance abuse history. The family psychiatric history was unremarkable. The patient's physical examination and laboratory studies were unremarkable except for the presence of global cerebral atrophy seen on a computed tomographic scan.

Because his first episode of psychosis had resolved quickly after discontinuation of the Hydroxycut, the patient

initially was observed in the hospital for 5 days without medications. His psychotic symptoms did not abate, however, and he was administered olanzapine. He was discharged on the 10th hospital day with continued outpatient follow-up. He remained asymptomatic on medications until his medical discharge from the military 2 months later.

Patient 3

A 33-year-old man presented with a 2-week history of depressive symptoms, suicidal ideation, auditory hallucinations, and paranoid and grandiose delusions. These symptoms coincided with his use of the diet aid Metabolife, which contains ma huang. He denied other substance use and denied prior herbal supplement use. His psychiatric history and family psychiatric history were unremarkable. His physical examination and laboratory studies were unremarkable.

The patient was hospitalized, observed without medication use, and discharged after 5 days with apparent resolution of his symptoms. Ten days later, the patient presented in the emergency department complaining of recurrence of his previously described psychotic symptoms. He denied resumption of herbal product or other substance use. Treatment with antipsychotic medication was then initiated and titrated to effect with remission of symptoms during the next 3 weeks. Three months later, the patient remained asymptomatic and his medication was tapered during a 4-week period. He did well for an additional 4 months but was restarted on quetiapine after he experienced recurrence of paranoid ideation.

Discussion

There are numerous ma huang-containing herbal dietary supplements available on the market that are advertised for various uses, including bodybuilding, weight loss, enhanced energy, or improved memory (eg, Ripped Fuel, Hydroxycut; Metabolife, Metabolife International, Inc., San Diego, CA; Herbalife, Herbalife, Inc., Century City, CA; Energel, PVL Nutrients, Ltd., Port Coquitlam, BC, Canada; herbal ecstasy, herbal phen-fen). Ma huang, which is derived from plants of the genus *Ephedra*, contains the alkaloids norephedrine, norephedrine, pseudoephedrine, and ephedrine, with the first two being minor components and ephedrine accounting for 30 to 90% of the total alkaloid content. Pseudoephedrine, which is the second major constituent in most ma huang-containing products, is less potent and less likely to cause central nervous system stimulation.² The actual amount of ephedrine and other ephedra alkaloids found in a product depends on which *Ephedra* species is used (more than one species may be used in a given product), where the plant is

grown, the type of growing conditions, and the time of the harvest. These factors determine not only the differences in ephedrine content between products but also within batches of the same product. High-performance liquid chromatographic assessment of ma huang-containing herbal products have demonstrated 5- to 20-fold variance in ephedrine and pseudoephedrine content in products with the same amount of ma huang extract reported on the label and even within different lots of the same product.³

Ephedrine psychosis has been reported in multiple cases since its introduction into Western medicine as a bronchodilator in 1930. Whitehouse and Duncan⁴ reviewed 20 such cases and found that there was no personal or family history of psychosis in 18 of the cases, that 80% of the patients had taken ephedrine for more than 1 year, that a majority of patients had gradually increased the dose, and that the average dose before the psychotic episode was 510 mg. The typical clinical picture for these patients was that of paranoid psychosis, with roughly one-third having affective symptoms.

Cases of psychosis resulting from the use of synthetic norephedrine and pseudoephedrine have also been described. Lambert⁵ reported an example of this presentation in a case of paranoid psychosis in a 55-year-old man after abuse of Contac 400 (GlaxoSmithKline, Research Triangle Park, NC), which contained phenylpropanolamine (norephedrine). He also described the case of a 32-year-old policeman who developed visual hallucinations, auditory hallucinations, and paranoid delusions after abuse of Actifed (Pfizer, Inc., New York, NY), which contained pseudoephedrine.

The potential health risks arising from herbal substances containing botanical ephedrine have been recognized. Toxicity may occur at only two or three times the maximum therapeutic dose of 150 mg/d.⁶ Most reports have focused on medical complications such as stroke, seizure, hepatic toxicity, or even death.⁷⁻⁹ A search of English-language publications revealed only four previously reported cases of psychosis developing subsequent to use of ma huang-containing herbal products. Capwell¹⁰ reported the case of a 45-year-old man with a 2-month history of daily herbal diet supplement use who developed behavior and personality changes. After discontinuing use of the herbal supplement, the patient's symptoms resolved by the third day and remained symptom-free for more than 1 year. Doyle and Kargin¹¹ described the case of a 34-year-old man who jumped out an upstairs window to escape imagined attackers after using ma huang for 10 days. This patient's symptoms also rapidly resolved during a 2-week hospitalization. Katz¹² described the case of a 39-year-old man who developed manic and psychotic symptoms after bingeing for 72 hours on excessive amounts of Herbalife in both pill and concentrated powder form. This man's symptoms resolved rapidly within 24 hours after hospital admission. Jacobs and Hirsch¹³ presented the case of a 20-year-old man who became paranoid and psychotic after several months of using ma huang, ginseng, dehydroepiandrosterone, creatine, and coffee. Although initially treated with antipsychotic medication, the medication was discontinued as the patient's symptoms abated.

Conclusion

Psychosis associated with ma huang-containing herbal product use seems to be relatively rare, and in three of the four previously reported cases, symptoms resolved rapidly

without administration of antipsychotic medication after the substance use was discontinued. Our cases differed in that the psychotic symptoms did not remit quickly and antipsychotic medications were required to control the patients' symptoms. Although we think that the use of ephedra-containing herbal preparations accounted for the psychiatric symptoms observed, or that at least they were a contributing factor, it is possible that herbal use was only a fortuitous finding coincident to the onset of a primary psychotic disorder. Although psychosis as a result of the use of over-the-counter medications containing psychoactive substances has long been recognized, the clinician must recognize the risk that exists with the use of herbal products that contain ephedra alkaloids.

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