The prevalence of obesity in the United States has increased from approximately 23% in 1990 to 33.8% in 2008.1,2 Multiple over-the-counter products claim to aid in weight loss under the pretense of being “natural” and “safe”. According to a national survey conducted in 2005 and 2006, 33.9% of respondents (who had made a serious weight-loss attempt) reported having used such a product.3

Following the FDA’s ban on ephedra-containing dietary supplements due to serious cardiovascular and neurological adverse reactions,4 manufacturers substituted ephedra with other substances, such as Citrus aurantium and marketed these products “ephedra-free”.

We describe the development of severe psychosis in a middle aged woman after 2 weeks use of “ephedra-free” dietary supplements.

Case Report

Ms. P, a 52-year-old Caucasian woman with a history of anxiety, depression, and hypothyroidism, presented to the emergency department (ED) with a change in mental status. She was working in the operating room as a nurse when she saw occult messages on her identification badge from Satan that read “You will die.” She heard her body “ticking” all over, and saw laser-writing from aliens on the hospital floor, the door, and her arm. Her physical exam was significant only for tachycardia, high blood pressure, and unsteady gait. Her body mass index was calculated at 28.3. She appeared disoriented, anxious, depressed, and very paranoid. She denied suicidal or homicidal ideation or a history of suicide attempts. Her urine drug screen (UDS) was negative for amphetamines, cocaine, and opiates. She received lorazepam for agitation after refusing haloperidol, and agreed to be transferred to the Crisis Response Center (CRC) to be evaluated by a psychiatrist. In the CRC, she was guarded, suspicious, labile, irritable, and disorganized with looseness of associations. She was oriented to person, place, and time. She received lorazepam for agitation and was admitted voluntarily to the psychiatric unit.

Her preadmission medications included buspirone, levothyroxine, Jillian Michaels’ Fat Burner (two pills each morning) and Calorie Control (two pills three times a day). In her possession were a bottle of Jillian Michaels Maximum Strength Calorie Control and a bubble-pack containing nine capsules of Detox and Cleanse.”5 Both Ms. P and her husband denied current drug and alcohol abuse. Ms. P reported she first used diet pills in her late teens to lose weight and increase energy. She had abused phenylpropanolamine and over-the-counter diet pills 28 months prior, which led to her only previous psychiatric admission with similar symptomatology and a negative UDS. She followed up with her primary care and pain management physicians. Other past medications stopped more than 1 year ago included phentermine, buprenorphine/naloxone (for recent rib fractures after a fall), and bupropion. She denied having a history of eating disorders and there was no indication of the presence of a personality disorder.

Complete metabolic panel, complete blood count, vitamin B12, rapid plasma reagin, hepatitis B panel, human immunodeficiency virus, urinalysis, and human chorionic gonadotropin hormone were within normal limits. Her thyroid panel was unremarkable and there was no clinical evidence of levothyroxine abuse. Her UDS was positive for amphetamines > 1000 ng/mL and benzodiazepines. Magnetic resonance imaging of the head showed scattered...
areas of small vessel ischemic changes, but was otherwise unremarkable, and her physical and neurological examinations were unremarkable. Electrocardiogram demonstrated normal sinus rhythm.

Upon arrival to the inpatient unit, she isolated herself in her room, refused antipsychotics, and slept for most of the day. She remained psychotic (with visual and auditory hallucinations), disheveled, and tearful for approximately 2 days. By hospital day 3, her symptoms had improved. She admitted to having increased the dosages of the Fat Burner and Calorie Control” pills to obtain more energy 4 days prior to admission, when she had difficulty sleeping. She denied abusing the Detox and Cleanse pills. She was anxious, with logorrhea and circumstantial speech but she denied auditory or visual hallucinations. She continued to refuse medications.

UDS remained positive for amphetamines until hospital day 4 when Ms. P felt “much better.” She believed her symptoms were related to the diet pills and had no psychotic or mood symptoms. She was discharged home with arrangements for outpatient psychiatric treatment.

**Discussion**

Ms. P was consuming a weight loss dietary supplement that contained *Citrus aurantium* and caffeine. *Citrus aurantium* (also known as Bitter orange, Sour orange, and Seville orange) is responsible for one-third of the annual sales for weight loss products. It contains synephrine, a sympathetic α- and β-adrenergic receptor agonist that is structurally related to ephedrine. Despite little supporting evidence, ephedra-free products are portrayed almost uniformly as a safer alternative to ephedra, and several over-the-counter weight loss dietary supplements contain synephrine (Table 1).

Case reports have described an association of synephrine with ischemic cerebrovascular accident, myocardial infarction, and exercise-induced syncope with QTc prolongation. We are not aware of any reports of psychiatric symptoms associated with synephrine. However, given its structural similarity to ephedra, it is likely that patients who use synephrine could experience symptoms similar to ones associated with ephedra, including euphoria, neurotic behavior, agitation, depressed mood, giddiness, irritability, and anxiety.

*Citrus aurantium* contains other phytochemicals of interest, including p-octopamine, which is structurally similar to amphetamines. Ms. P was consuming a weight loss dietary supplement that contained *Citrus aurantium* and caffeine. *Citrus aurantium* (also known as Bitter orange, Sour orange, and Seville orange) is responsible for one-third of the annual sales for weight loss products. It contains synephrine, a sympathetic α- and β-adrenergic receptor agonist that is structurally related to ephedrine. Despite little supporting evidence, ephedra-free products are portrayed almost uniformly as a safer alternative to ephedra, and several over-the-counter weight loss dietary supplements contain synephrine (Table 1).

Case reports have described an association of synephrine with ischemic cerebrovascular accident, myocardial infarction, and exercise-induced syncope with QTc prolongation. We are not aware of any reports of psychiatric symptoms associated with synephrine. However, given its structural similarity to ephedra, it is likely that patients who use synephrine could experience symptoms similar to ones associated with ephedra, including euphoria, neurotic behavior, agitation, depressed mood, giddiness, irritability, and anxiety.

Citrus aurantium contains other phytochemicals of interest, including p-octopamine, which is structurally similar to amphetamines. Ms. P was consuming a weight loss dietary supplement that contained *Citrus aurantium* and caffeine. *Citrus aurantium* (also known as Bitter orange, Sour orange, and Seville orange) is responsible for one-third of the annual sales for weight loss products. It contains synephrine, a sympathetic α- and β-adrenergic receptor agonist that is structurally related to ephedrine. Despite little supporting evidence, ephedra-free products are portrayed almost uniformly as a safer alternative to ephedra, and several over-the-counter weight loss dietary supplements contain synephrine (Table 1).

Case reports have described an association of synephrine with ischemic cerebrovascular accident, myocardial infarction, and exercise-induced syncope with QTc prolongation. We are not aware of any reports of psychiatric symptoms associated with synephrine. However, given its structural similarity to ephedra, it is likely that patients who use synephrine could experience symptoms similar to ones associated with ephedra, including euphoria, neurotic behavior, agitation, depressed mood, giddiness, irritability, and anxiety.

**TABLE 1. Some popular Weight-Loss Dietary Supplements that Contain Synephrine**

- Biolean and Biolean II
- Advantra Z
- Nutrex Lipo 6
- Lean System 7
- Jillian Michaels’ Fat Burner
- JetFuel
- Thermorexin

---

**FIGURE 1. Comparison of Active Ingredient Synephrine and Ephedrine to Assay-Sensitive Amphetamines.**

![Synephrine](image1.png)  
(Synephrine (active component of “Bitter Orange”))

![Ephedrine](image2.png)

![d-Amphetamine](image3.png)

![d-Methamphetamine](image4.png)

![Methylenedioxyamphetamine (MDA)](image5.png)

![Methylenedioxyamphetamine (MDMA)](image6.png)
similar to tyramine and appears to stimulate primarily the β3-adrenergic receptor.4 It also contains 6',7'-dihydroxybergamottin, which is used to selectively block intestinal cytochrome P450 isozyme CYP3A4 in bioavailability studies, and bergaptten, which inhibits CYP3A4 in cultured intestinal epithelial cells. Subsequently, *Citrus aurantium* may increase blood levels of many drugs, including psychotropic medications.10 Ms. P was also consuming Jillian Michaels’ Detox and Cleanse, which contains Irish moss, ginger, dandelion, buckthorn, and garlic among other ingredients, but we could not find any evidence of possible toxicity associated with these components.

Ephedra-free dietary supplements also contain significant amounts of caffeine, which in toxic doses, can cause psychosis in people without psychiatric illness and worsen psychosis in patients with schizophrenia.11–15 Ms P’s diet supplement contained an average of 400 mg of caffeine per daily dose. Patients with psychosis resulting from diet pill consumption may present with vivid auditory and visual hallucinations and paranoid delusions, making the clinical picture of diet pill associated psychosis difficult to differentiate from a primary psychotic disorder.

Ms. P’s symptoms remitted as her UDS became negative. Most drug screens do not specifically test for ephedrine, but ephedrine may cause a false-positive result for amphetamines on qualitative tests.16 Because synephrine shares structural similarity to ephedrine, amphetamine, and phenylpropanolamine, it is possible that the synephrine also might have caused a false positive result (Figure 1). It is unknown why her UDS was initially negative at the Emergency Department (ED), as the ED and the CRC use the same UDS protocol.

The treatment of our patient was mainly supportive and consistent with the available literature in treatment of ephedra-induced psychosis.17 Antipsychotics and/or benzodiazepines may be used to control symptoms, and hospitalization may be required in cases of severe mania or psychotic symptoms and danger to harm one self or others. A careful physical examination should be performed to assess for medical complications of synephrine and caffeine, such as cardiac arrhythmias.

Ms. P appeared to be susceptible to synephrine and caffeine adverse neuropsychiatric effects and vulnerable to experience a drug-related psychotic reaction as evidenced by her previous episode. However, she believed these medications were “natural” and therefore safe, and did not hesitate to use them for weight loss. Consumers should be informed that the FDA does not regulate “ephedra-free” compounds and the safety of these products has not been properly studied. Moreover, this case highlights the importance of obtaining a thorough medication history including over-the-counter weight loss and herbal supplements in patients presenting with psychosis.

*This program was presented as a case report poster in the Philadelphia Psychiatric Society’ Colloquium of Scholars in March 2011.*

**Disclosure:** No funding was provided for this study. The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

**References**

Case Reports