

## CASE REPORT

# Sibutramine (Hidden Ingredient)-Induced Psychosis, Associated with the Use of Herbal Slimming Product, A Case Report

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## Abstract

Adulteration of herbal products with active pharmaceutical ingredients and banned substances is an emerging health hazard. Many of commercially available weight loss preparations were found to contain hidden ingredients, not disclosed on labelling. Sibutramine is an anti-obesity agent, often found in many over-the-counter slimming products as a hidden ingredient. We report a case of acute life-threatening psychosis after intake of slimming product adulterated with sibutramine. A 29-year-old woman presented with agitation, hallucination, delusions and floating ideas of persecution. The symptoms developed over 2 months after starting intake of a non-prescription slimming product (Burning Fat Slimming Capsule) obtained from the Internet. The product was later found to contain sibutramine. The overall clinical presentation was compatible with psychotic symptoms associated with sibutramine intake. These psychotic symptoms improved after a short course of antipsychotic medication, together with stopping intake of the slimming product. The mechanisms involved in sibutramine-associated psychotic disorders may be explained by its blocking effects on reuptake of norepinephrine, serotonin and dopamine; the neurotransmitters related to psychosis. The temporal relationship between onset of behavioural changes and sibutramine intake in the slimming capsules, support the suggested relationship between use of sibutramine and pathogenesis of psychosis. Moreover, the fact that remission of psychotic symptoms occurred and maintained after stopping sibutramine could suggest a causal role in this condition. This case highlighted the health threat posed by non-prescription slimming products sold over the Internet. Thus, patients presenting with psychotic symptoms should be enquired about recent use of complementary medications, slimming and/or herbal remedies.

**Keywords:** Sibutramine; Psychosis; Slimming Products; Hidden Ingredients

## Introduction

A wide variety of herbal and traditional unlicensed health products are freely available on the market via the internet in many countries. These illegal products include anabolic steroids, erectile dysfunction preparations and numerous types of weight loss pills [1]. The products are usually imported in bulk from abroad and sold freely through the internet. The sale of health products, herbal preparations and adulterated medicines are increasing online, making it big business supported by a huge number of websites and social media platforms [2].

Herbal and unlicensed medicines are often contaminated with hidden active ingredients not mentioned on labels, such as sildenafil, the active ingredient of viagra; plant extracts ephedra, synephrine, and yohimbe, which are classed as prescription-only medicines because of their serious cardiac complications [3]. Many of the commercially available weight loss preparations were found to contain hidden ingredients, which are not disclosed on labelling, such as sibutramine, a weight-loss drug previously available as a prescribed drug. Moreover, some of these illegal slimming medicines may also contain banned substances and dangerous levels of heavy metals [4]. Those who commonly buy these preparations from websites, place themselves at risk of obtaining imitation or fake medicine (which may be sub-standard, unregulated and trade in illicit or sub-standard products) [5]. Purchasing medicine over the internet may seem cheaper and more convenient than going to a health care professional and community pharmacies, however the dangers outweigh the benefits by far [4,6].

Sibutramine is a serotonin and norepinephrine reuptake inhibitor, developed initially as an antidepressant in the 1980s, but subsequently used for weight management as an appetite suppressant [7]. Sibutramine was licensed as a weight-reducing agent

by the USA Food and Drug Administration (FDA) in 1997, and marketed under the name Meridia in the USA, and Reductil in Europe and other countries. The drug was also found to be effective for weight management in people with schizophrenia on antipsychotic medications, such as Olanzapine, but its implications on psychotic symptoms needed further exploration [8]. Sibutramine was withdrawn from the market in October 2010, after several reports of serious adverse health effects related to the drug, including tachycardia and hypertension, together with significant risks of coronary artery disease, congestive heart failure, arrhythmias or strokes [9]. Sibutramine use has also been involved in many psychiatric complications, including depression, panic attacks, mania and psychosis [10-17].

The aim of this report is to present a case of an acute life-threatening psychosis in a young woman, without a previous history of any psychotic illness, after intake of a slimming product adulterated with sibutramine. The goal will attempt to elucidate the possible mechanisms, management and outcomes of such conditions.

## Case history

Ms X is a 29-year-old woman who was brought to the emergency department (ER) of the general hospital by her parents, in a severely agitated condition. She was administered haloperidol (Serenace aqueous ampoule) 2mg intravenously (IV) and referred to a psychiatric hospital. On the first assessment at the ER of the psychiatry hospital, Ms X was awake and alert but agitated and talkative. She was having auditory hallucinations and delusions about her husband's behaviour. She was admitted to the ER department and prescribed risperidone 2mg orally at night, Olanzapine 5mg dispersible sublingual tablets, as needed, for her agitated condition and diazepam 5mg IV, as needed for insomnia. She received these drugs for two days before she was referred to the psychiatric inpatient ward.

History obtained from her parents, indicated that she attained a high school education, then married and has five children. She appeared to have adjusted fairly well to her life. This patient had never had a past history of psychiatric disorders or substance abuse. There was no family history of mood or psychotic disorders. Four months prior to this scenario, Ms X became more conscious of her weight and started dieting with restrictions of caloric intake. On further questioning, it was revealed that she had started taking herbal diet pills for weight loss (Burning Fat Slimming Capsules) two to three times a day, which she had obtained over the internet, two months prior to her hospital admission. At that time, after starting intake of the slimming capsules, the patient experienced nervousness, insomnia, hyperactivity, and obsession. She started talking about persecutory ideation and increasing disbelief regarding her husband's behaviour and relationships with other women. The family noticed that she became more aggressive with her children and unmanageable at home. A month later, she left the husband and home and went to live with her parents. The parents believed that she may have been possessed and took her for an exorcism session; she didn't improve. The change in behaviour and abnormal symptoms developed gradually over the last two months, coinciding with the intake of her slimming medication while trying to lose weight.

On physical examination of Ms X, it was revealed she was a thin, pale, young lady, who was agitated and restless with increased energy, talkativeness and disorganised speech and floating ideas of persecution. Baseline investigations included a complete blood count, kidney and liver function tests, an ECG, urine testing for substances, (including amphetamine, cocaine, marijuana), and a CT of the head; all were within normal limits, apart from mild anaemia (Hb concentration was 10.4 mg/dl). After the medical workup, she was diagnosed provisionally as having psychotic symptoms associated with the intake of potentially adulterated slimming pills, with primary psychosis as a differential diagnosis. This woman was advised to stop taking the slimming capsules and prescribed risperidone (Risperdal tablet) 4mg orally each night, Aripiprazole (Abilify tablet) 15mg orally every day (add on antipsychotic to reduce risperidone-induced hyperprolactinemia) and chlorpromazine (Largactil tablet) 25mg at night, as well as oral ferrous sulphate, folic acid and multivitamin capsules.

During hospitalisation, her psychotic symptoms and agitation gradually decreased within the first week and disappeared after two weeks. Her antipsychotic treatment plan was changed as the oral risperidone was switched to an intramuscular long acting risperidone (Risperdal Consta) 25mg intramuscular injection every two weeks, aiming to improve patient compliance, and a withdrawal of chlorpromazine with close observation for relapse of psychotic symptoms. The patient did well, and was discharged to her parents in a stable condition after 18 days in hospital. She was advised to continue the same treatment until her outpatient appointment. Two weeks following discharge, treatment was slowly tapered down until it stopped after six weeks without recurrence of any psychotic symptoms. The woman was closely followed up by her own psychiatrist for more than six months and reviewed several times, remaining in full remission after weaning off all psychotropic medication. She did not exhibit any relapse of her previous symptoms.

The herbal slimming capsules were sent to the hospital pharmacy for investigation. A toxicology analysis of the slimming capsules using high-performance liquid chromatography (HPLC) was completed confirming the inclusion of sibutramine as a hidden ingredient in the product. Quantitative analysis of the amount of sibutramine, in the slimming products was not performed because no more capsules were available. Thus, the most likely explanation for this patient's psychotic symptoms was related to the use of sibutramine-contaminated slimming capsules. The diagnosis was revised to sibutramine-induced psychosis, and the woman was advised to avoid reuse of this slimming product.

## Discussion

Sibutramine is an anti-obesity agent, often found in many over-the-counter slimming products as a hidden ingredient. It is a  $\beta$ -phenylethylamine drug structurally related to the psychostimulants, amphetamine and ketamine. Sibutramine was previously approved as an appetite-suppressant with a favourable safety profile in pre-marketing studies [18]. It works to decrease body weight via dual mechanisms, suppression of appetite and thermogenesis. Sibutramine has also been advocated for use in management of metabolic syndromes [19]. However, with widespread use of the drug, its psychiatric effects started to emerge and sporadic cases of sibutramine-associated psychotic complications have been reported in the literature. The variety of psychiatric disturbances reported with use of sibutramine include cases of panic attacks, mania and psychosis, but many of the patients had mania-like psychotic symptoms similar to those induced by amphetamine [10-17].

The mechanisms involved in sibutramine-associated psychotic disorders have not been clearly clarified but may be explained by its blocking effects of reuptake of norepinephrine, serotonin and dopamine; the neurotransmitters related to psychosis. Sibutramine, a racemic mixture of cyclobutanemethanamine, produces a potent serotonin and norepinephrine reuptake inhibition, besides a significant dopamine reuptake inhibition [19,20]. Receptor binding studies of sibutramine demonstrated that serotonin and norepinephrine reuptake inhibitory effects as more potent than the dopaminergic reuptake inhibitory effects. Experimental studies, however, showed a potent dose-related dopaminergic reuptake inhibition in the striatal and hypothalamic areas [21]. In addition, sibutramine could stimulate release of catecholamine from presynaptic nerve endings like amphetamines [22]. It is likely that the increased dopaminergic neurotransmission could contribute to the anti-obesity effect, as well as the psychotic symptoms associated with use of sibutramine [23].

The psychotic symptoms in patient X improved after a short period of antipsychotic medication and did not relapse after stopping treatment. Moreover, the temporal relationship between onset of behavioural changes and sibutramine intake in the slimming capsules, support the suggested relationship between use of sibutramine and pathogenesis of psychosis. The woman has neither past history of psychotic disorder nor a history of psychotic illness in her family, making the diagnosis of primary psychosis less likely. Moreover, the fact that remission of psychotic symptoms occurred and maintained after stopping sibutramine could suggest a causal role in this condition. Further studies are warranted to establish the causal relationship between sibutramine and psychosis and explain precisely the involved mechanisms.

## Conclusion

The adulteration of herbal products with active pharmaceutical ingredients and banned substances is an emerging health hazard. Although sibutramine was withdrawn from the market in 2010, it is still found as a hidden ingredient in many slimming products claimed to be herbal in origin. Patients presenting with psychotic symptoms should be asked about recent use of complementary medications, slimming and/or herbal remedies. If this recommendation is not taken into account, dire health consequences on people may occur. The main conclusion of this report is to identify patients presenting with active psychotic symptoms and enquire about recent use of complementary products. Such simple questioning by a careful physician can have profound impact on the patient's diagnosis and treatment. It is also crucial to educate individuals to take great care when buying medicines online in which many internet-based pharmacies often sell unapproved or counterfeit medicines, potentially presenting a significant health risk (evidence indicates risks outweigh benefits).

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