

Letter to the Editor

First-episode mania with psychotic features induced by over-the-counter diet aids containing sibutramine

To The Editor,

Consumption of over-the-counter drugs or medicinal products in Turkey has been increasing following Turkish legislation on the classification of medicinal products in 2005, which regulates the marketing of over-the-counter drugs (Turkish Pharmacists' Association 2009). Moreover, many international pharmaceutical products are easily obtained via suppliers on the Internet (Morris and Avorn 2003). Herbal medicines are marketed in drugstores and herbal stores, and via advertisements in the print media and on the Internet (De Smet 2004).

In Turkey over-the-counter drugs and herbal medicines can be imported with the approval of the Ministry of Agriculture and Rural Affairs, bypassing the Ministry of Health (Turkish Pharmacists' Association 2009). Due to this approval and licensing process, products claimed to be herbal in origin and that potentially affect the central nervous system (CNS) can be obtained without adequate oversight. Some of these products are marketed as diet aids.

Laboratory investigation of such products in many countries found that some contained pharmacological agents that affect the CNS and those particular products were confiscated (Müller et al. 2009). Three products marketed as diet aids were confiscated in Turkey in August 2010 following the probable association of one of those products with the death of an enteritis case in Kastamonu province (Ministry of Health 2010). Laboratory analysis showed that the three confiscated products contained sibutramine (Ministry of Health 2010).

Sibutramine, which is indicated for the treatment of obesity (body mass index >30 , or >27 in obesity cases with comorbid hypertension, hyperlipidemia, and diabetes mellitus), acts as a serotonin and noradrenalin re-

uptake inhibitor in the synaptic cleft via its primary and secondary metabolites (Luque and Rey 1999).

The effect of sibutramine on the CNS makes it relevant to psychiatric practice. While 10-15 mg per day of sibutramine is used for the treatment of obesity (Luque and Rey 1999), over-the-counter products illegally contain sibutramine in undisclosed concentrations. Various investigations reported that the concentration of sibutramine was 2-3-fold higher in products marketed as herbal medicines than in originally licensed medicines (Jung et al. 2006, Müller et al. 2009).

Case reports on hypomania, mania, and psychotic episodes associated with sibutramine have increased along with the increase of its use in pharmaceutical products and as an undisclosed ingredient in quasi-herbal products (Tafilinski and Chojnacka 2000; Benazzi 2002; Cordeiro and Vallada 2002; Litvan and Alcoverro-Fortuny 2007; Rosenbohm et al. 2007; Yuen et al. 2007; Gazdag and Szabo 2008; Lee et al. 2008; Rocha et al. 2008; Naik et al. 2010). Additionally, there are case reports of mixed (Eker et al. 2003) and depressive mood episodes (Şengül and Balci-Şengül 2007), as well as a psychotic episode (Dogangun et al. 2008) associated with use of sibutramine in Turkey.

The purpose of this letter is to highlight the clinical features of a 19-year-old female that presented to our outpatient clinic and was diagnosed as first-manic episode with psychotic features following the use of a diet aid for 3 months that was confiscated by the Ministry of Health in August 2010.

The high-school-educated female patient presented to the outpatient clinic in July 2010 with symptoms of elevated mood, irritability, grandiosity, excessive talkativeness and pressured speech, decreased need for sleep, psychomotor agitation, and increase in goal-directed activity. She didn't have a history of psychiatric admission or treatment. Clinical evaluation of the patient and interviewing her parents revealed a depressive episode that lasted 3 months when she was 16 years old, and was not treated, but led to one year fail. It was learned that the patient had been using a diet aid branded "Pepper Time"

for the previous 3 months. A treatment regime that included olanzapine 10 mg per day and lorazepam 5 mg per day was initiated. Lorazepam dose was decreased over time and was withdrawn after 3 weeks of use. Olanzapine was decreased to 7.5 mg per day after achievement of almost complete remission after 4 weeks of treatment.

After her manic episode symptoms subsided, further clinical evaluation revealed that the patient decided to use the quasi-herbal diet aid (Pepper Time) after her close friend lost 10 kg using the same product. The patient researched Pepper Time via the Internet and bought it at a local drugstore in April 2010. She used the product regularly, but stopped 2 days before presentation. During the 3 months she used Pepper Time, she discontinued its use for 5-6 days each month while experiencing menstrual bleeding.

Beginning with the first week of usage, she not only experienced a decrease in her appetite, but also changes that included acceleration of thoughts, 2 hours decrease in need for sleep, and accelerated speech. Moreover, she had an increase in self-care, was spending more money than usual without concern, and started keeping a diary in order to write down the details of every moment she was experiencing. All of these symptoms tended to diminish during the 5-6 days each month she stopped taking the product; however, the symptoms would re-emerge after she began to use the product again.

After 3 months of use, the patient began to experience difficulty in making up her thoughts and constructing understandable sentences, and compressive talkativeness, taking continuous notes on her diary, thoughts on amending and orienting the individuals with those notes, and feeling of a special mission to reclaim failures. During the week preceding presentation, she was sleeping only 1-2 hours per night. She also began to smoke cigarettes regularly and used cannabis twice during this 3-month period.

There was no family history of mental disorder among her first-degree relatives. All laboratory tests (liver, kidney, thyroid, vitamins, and complete blood count) were within normal limits. Some of the clinical features the patient presented with suggested a probable causal association between sibutramine intake and manic episode due to the following: emergence of manic episode after the intake of the product (temporality), progression of subclinical experiences into full-blown syndrome with continued use (dose-response), and a decrease in manic symptoms with cessation of the diet aid and initiation of pharmacotherapy (exposure).

Over-the-counter marketing and use of health-related products can lead to severe complications, as the presented patients' clinical features highlight (De Smet 2004). Use of products with ingredients that affect the CNS can induce various symptoms, ranging from sub-clinical experiences in the absence of help-seeking behavior to clinical symptoms leading to need for care (Müller et al. 2009). Nonetheless, it is not possible to assess the whole picture about the outcomes associated with use of such products, since most of these products are out of control and could be easily delivered through various sources (Müller et al. 2009).

Furthermore, probable harmful effects of these products are usually far from gaining public attention unless a lethal outcome associated with use occurs and authorities change relevant legislations after such serious outcomes. At the same time, completion of license approvals in an institution unaffiliated with Ministry of Health leads to and calls for major complications in Turkey.

Considering the use of sibutramine, as described in the presented case and in other case-reports, we have some suggestions that might be applied in Turkey. First, all health-related products should be evaluated via analysis, as required by the Ministry of Health. Licensed approval after such a procedure may decrease the risks associated with unregulated medicinal products. Second, ingredients in over-the-counter products must be disclosed in detail and a medical warning leaflet for consumers must be included in the packaging. Third, the mental health history of patients must be evaluated before the use of products with a CNS-active ingredient, and patients must be informed about any probable risks. Fourth, government institutions must inform the public about the possible side effects of "herbal" products and provide information on their drug interaction profiles. Fifth, current legislation on the marketability of some over-the-counter drugs in shops other than drugstores is candidate to cause some undetectable and uncontrolled health related risks. As such, the government must regularly inform public on probable risk associated with the marketability of health and related products.

Implementation of the above-mentioned suggestions would surely help patients in their health care search for their particular complaints, and would prevent them to pay mild or serious burdens.

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