Weight Loss Products Adulterated with Sibutramine: A Focused Review of Associated Risks

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Abstract

Obesity has been classified as a major worldwide epidemic and associated co-morbidities are Type 2 diabetes, cardiovascular disease and several inflammatory disorders. Weight loss drugs in conjunction with diet modification and exercise can reduce co-morbidity risk. Weight loss herbal medicine (WLHM) is perceived by obese and overweight patients as well as those that are not overweight as a natural safe way to lose weight. The wide availability of WLHM, especially through the internet, is of concern as it has been found that many of these products are adulterated with weight loss drugs. Sibutramine is the most commonly found adulterant in WLHM. This paper reviews the literature on the pharmacological and adverse effects of sibutramine, as well as the risk associated with the undisclosed adulteration of WLHM with sibutramine. Sibutramine is a serotonin-norepinephrine reuptake inhibitor that was found to effectively reduce weight but due to reported adverse effects and the death of several patients it was banned. Non-disclosure of this drug as a WLHM ingredient has resulted in an increase in reported serious adverse events. Of concern are the high levels of sibutramine in some of these products as well as the lack of conclusive data related to the risk associated with exposure during early pregnancy. Public awareness of the risk associated with the use of WUHM should be raised. Furthermore the possibility of a WLHM adverse effect or an adverse WLHM-drug interaction should be taken into consideration when patients present with symptoms often associated with sibutramine.

ABBREVIATIONS


INTRODUCTION

Over the past few decades the incidence of obesity has been on the increase in both developed and developing countries [1,2]. The Medical Research Council (MRC) of South Africa recently reported that 70% of all women above the age of 35 are either overweight or obese, compared to 40% of all men above the age of 35 [3]. In 2012 it was also reported that a third of children and adolescents were either overweight or obese [4]. The impact it has on general health and well-being is so staggering that obesity has been classified as a major worldwide epidemic [3,5]. Linked to obesity are several life-threatening diseases such as cardiovascular complications, diabetes, musculoskeletal disorders, inflammatory complications and various forms of cancer [1,6].

While lifestyle changes including diet and exercise are recommended for those that are overweight, for those that are obese, anti-obesity drug therapy has been proven to be beneficial in weight loss and weight maintenance when used in combination with such lifestyle modifications [7]. Numerous weight loss drugs have well-described side effects and a prescription from a medical practitioner is required. For these reasons as well as the social impact of being overweight, a large sector of the population are using natural WLHM. The extensive and effective marketing of such weight loss products in the media, the easy availability...
of WLHM either over the counter or via the internet, the cost as well as the perceived safety of WLHM is for many the first choice for weight loss [8]. WLHM formulations often contain vitamins, minerals, amino acids, herbal plant material or extracts [9]. Although the herbal medicine and the supplement industry is well regulated in many countries [10], WLHM is available on the internet and many of these products are fraudulently adulterated with conventional weight loss drugs. The most common weight loss drug that is used for adulteration is sibutramine [11]. Sibutramine although an effective weight loss drug was removed from the market due to various cardiovascular complications including hypertension, arrhythmias, stroke and even death [12,13].

This paper reviews the literature on the pharmacological and adverse effects of sibutramine as well as the risks associated with the undisclosed adulteration of WLHM with sibutramine.

**SIBUTRAMINE**

Sibutramine hydrochloride monohydrate (N-[1-[1-(4-chlorophenyl) cyclobutyl]-3-methylbutyl]-N,N-dimethylamine hydrochloride monohydrate; sibutramine) was originally studied in the 1980’s as a possible antidepressant, but eventually investigations were directed towards its potential use as a weight loss agent [14]. This change in research could most probably be attributed to the unanticipated weight loss observed in obese patients during the early depression trials. Sibutramine eventually received Food and Drug Administration (FDA) approval in 1997 for the treatment of obesity and was subsequently approved in approximately 40 countries around the world. Since its launch in 1998, more than three million prescriptions had been written by 2001 and numerous clinical trials data indicated that sibutramine, in conjunction with a low calorie diet, produced initial and sustained weight loss [14]. More than this, studies also indicated that weight loss induced by sibutramine was of great clinical significance as it also showed improvement in glycemic control and enhancement of insulin sensitivity, lipid profiles, and significant reductions in total cholesterol [14,15]. In 2005, Filippatos and colleagues published a review of the metabolic effects of sibutramine also including improvement in glycemic control, the effects on low density lipoprotein (LDL) and high density lipoprotein (HDL) and serum uric acid levels amongst others, after sibutramine treatment [16].

Sibutramine is part of a group of compounds known as serotonin-norepinephrine reuptake inhibitors [17], which are a class of antidepressants indicated in the treatment of a variety of conditions including depression, fibromyalgia, anxiety, panic disorder, schizophrenia, Tourette syndrome, cocaine and alcohol addiction, Parkinson’s disease, and epilepsy amongst others [18].

Sibutramine however, has been developed solely for the treatment of obesity. Its therapeutic effects are produced by inhibition of norepinephrine (NE) and serotonin (5-HT) and to a minor extent, dopamine (DA) reuptake at neuronal synapse sites in the central nervous system (CNS) with a reuptake inhibition rank order of NE>5-HT>DA [19]. Essentially this causes an increase in the synaptic concentrations of these neurotransmitters [20], which then leads to the subsequent activation of alpha (α)-adrenoceptors, beta (β)-adrenoceptors and serotonin receptor 2A and 2C subtypes (5-HT2A/2C) [17, 21-26]. These interactions produce an eventual increase in satiety and energy expenditure, with a subsequent decreased body weight [27].

**Pharmacology of sibutramine**

Sibutramine’s pharmacological effects can mostly be attributed to its metabolites. In the human gastro-intestinal tract, sibutramine is rapidly absorbed after oral administration, with a standard bioavailability of 77% [27,28]. After absorption, sibutramine is metabolized by the hepatic cytochrome P450 2B6 enzymes (CYP2B6), which demethylates the parent compound to form its pharmacologically active metabolites, M1 (N-[1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl]-N-methylamine) and, after successive demethylation, M2 (1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl-amine) [28].

M1 and M2 have been shown to be even more potent than sibutramine in inhibiting monoamine reuptake. Studies done by Cheetham et al. [29,30] in which they investigated the efficacy of various antidepressants on inhibiting the reuptake of the NE and 5-HT, including sibutramine and its two active metabolites, showed that the metabolites, M1 and M2, possessed potency comparable to many of the antidepressants currently in use. M1 and M2 is eventually hydroxylated and conjugated to glucuronide to form pharmacologically inactive metabolites M5 and M6. Approximately 85% of a single orally administered dose is excreted in the urine and faeces [26].

**Retraction of sibutramine**

Despite sibutramine’s success as a weight loss agent, it was removed from the Italian market in 2002. Fifty adverse events had been reported including tachycardia, hypertension and arrhythmias and two cardiovascular events lead to death. The European Medicines Agency (EMA) started comprehensive risk assessments of the drug, while it still remained available on the European market. Between February 1998 and September 2001 the United States Food and Drug Administration (USFDA) received reports of 397 adverse events, including 143 cardiac arrhythmias and 29 deaths and in Canada reports of 28 adverse events in patients using sibutramine were received including cases of stroke and eye hemorrhage [31]. In January 2010 the EMA withdrew sibutramine from the European market based on the initial findings of the Sibutramine Cardiovascular OUT come (SCOUT) trial done by the FDA [32]. This study aimed to investigate the associated cardiovascular consequences of weight management with and without sibutramine administration. More than 5700 subjects at high risk for cardiovascular events participated in this follow-up trial which extended over a mean period of 3.4 years. In investigators concluded that participants with pre-established cardiovascular complications had an increased risk of nonfatal myocardial infarction and stroke associated with long term sibutramine use [33]. Following these findings, Abbott Laboratories voluntarily withdrew their sibutramine-containing slimming drugs from the United States of America (USA), Australian, Taiwanese and South African market in 2010 after discussions with the Medicines Control Council (MCC) [34].

**Sibutramine adulteration and side effects**

A search of Google Scholar using text words, herbal,
sibutramine, adverse reaction from January 2012 until October 2014 identified 564 articles and includes the development of methodologies for the identification of sibutramine in herbal medicine and supplements or case studies of adverse drug reactions.

Mass spectrometric methodologies for the identification of pharmacological adulterants in WLHM have been extensively reviewed by Vaclavík et al. [35]. Evaluation of 66 cases of poisoning, Tang and co-workers identified sibutramine as the most common agent [36]. Mathon et al. in 2014 analysed 52 WLHM samples purchased via the internet and found that half of the samples contained sibutramine up to 35mg per capsule, a dose that exceeds normal therapeutic dosages [37]. Sibutramine was present in all 11 WLHM samples analysed by Wang et al [38] and concentrations varied from 3.31 mg/g to 96.2 mg/g. Not only is sibutramine a common ingredient of WLHM but the concentration found in these products is of concern.

Since the withdrawal of sibutramine in 2010, many case studies have been reported about the effects of sibutramine. These included a 32-year-old male who presented with dilated cardiomyopathy and a left ventricle thrombus formation after using a slimming product containing sibutramine that was bought via the internet [39]. A 37-year-old Korean man presented with transient thyrotoxicosis with thyroiditis after consuming 280 mg of sibutramine [40]. In another case a young and healthy Chinese lady developed a sudden cardiac arrest after taking sibutramine. A clinical case published in 2012 described the incidence of a 21-year-old woman which presented with somnolence, sinus tachycardia, and other symptoms associated with serotonin syndrome after an overdose of a non-prescription slimming product which contained sibutramine that was also purchased via the internet. These effects of sibutramine adulterated WLHM is probably under reported as many patients will discontinue the use of these products when feeling unwell.

Another concern is the exposure of the developing fetus to undisclosed ingredients in herbal medicines. In a study published in 2013, it was reported that during the period of 1998–2011, 509 infants among 392,126 births in the Swedish Medical Birth Register had been exposed to weight loss drugs during early pregnancy. Of these, 242 cases were only sibutramine exposure while 26 cases were exposure to orlistat and sibutramine [41]. A significantly increased risk for cardiovascular defects has been identified following in utero exposure to sibutramine. Da Silva and colleagues reported dosage dependant increase in genotoxicity with sibutramine in Swiss mice [42]. In addition, van der Schoor reported that in ovo exposure to sibutramine caused various malformations such as gastrochisis as well as histopathological lesions associated with severe liver failure and cardiac muscle dystrophy [43]. A list of the adverse effects of Sibutramine is shown in table 1.

**CONCLUSION**

Sibutramine is a common ingredient in WLHM that are widely available on the internet. Non-disclosure of this ingredient places a large sector at risk for adverse side effects such as cardiovascular complications amongst others. Of further concern is the concentration of sibutramine found in these products, which in some instances far exceeds the daily dosage. Although not conclusive, in utero exposure may increase the risk of birth defects. Adverse events may also occur with other drug types such as the interaction between monoamine oxidase inhibitors and undisclosed sibutramine [15]. Public awareness of the risk associated with the purchasing and use of these WLHM should be raised. Furthermore the possibility of a WLHM adverse effect or an adverse WLHM-drug interaction should be taken into consideration when patients present with sibutramine associated symptoms.

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