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Review Article

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 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 symptoms often associated with sibutramine.

ABBREVIATIONS

α:alpha, β: beta, CNS: central nervous system, CYP2B6: cytochrome P450 2B6, DA: dopamine, EMA: European Medicines Agency,FDA:Food and Drug Administration,5-HT: serotonin, 5-$HT_{2A/2C}$: serotonin receptor 2A and 2Csubtypes,M1: *N*-{1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl}-*N*-methylamine,M2: 1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl-amine, MCC: Medicines Control Council, MRC:Medical Research Council,NE: norepinephrine, SCOUT: Sibutramine Cardiovascular OUTcome,SNRIs: serotonin-norepinephrine reuptake inhibitors; adulteration, USA: United States of America,USFDA:United States Food and Drug Administration WLHM: weight loss herbal medicine.

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]. Sibutarmine 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 glycaemic 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 2Csubtypes (5-$HT_{2A/2C}$) [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. 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 Vaclavik *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]. A37-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 6 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 gastroschissis 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.

Table 1: Adverse effects of sibutramine [2,30,40].

Cardiovascular effects	Tachycardia Hypertension Arrhythmias Chest pain Increase risk for myocardial infarction Increase blood pressure Stroke
Other	Insomnia Nausea Dry mouth

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.

REFERENCES

1. Obesity and overweight. 2014
2. James WP, Astrup A, Finer N, Hilsted J, Kopelman P, Rössner S. Effect of sibutramine on weight maintenance after weight loss: a randomised trial.STORM Study Group.Sibutramine Trial of Obesity Reduction and Maintenance.Lancet. 2000; 356: 2119-2125.
3. Child K. Obesity in SA tips the scales. Times live.2013.
4. Ogden CL, Carroll MD, Kit BK2, Flegal KM1. Prevalence of childhood and adult obesity in the United States, 2011-2012. JAMA. 2014; 311: 806-814.
5. Pi-Sunyer FX. The obesity epidemic: pathophysiology and consequences of obesity. Obes Res. 2002; 10 Suppl 2: 97S-104S.
6. Crujeiras AB, Pardo M, Roca-Rivade A, Navas-Carretero S, Zulet MA, Martinez JA, et al. Longitudinal variation of circulating irisin after an energy restriction-induced weight loss and following weight regain in obese men and women. Am J Hum Biol. 2014; 26: 198–207.
7. Padwal RS, Majumdar SR. Drug treatments for obesity: orlistat, sibutramine, and rimonabant. Lancet. 2007; 369: 71-77.
8. Li M, Cheung BM .Pharmacotherapy for obesity.Br J Clin Pharmacol. 2009; 68: 804-810.
9. Vaysse J, Balayssac S, Gilard V, Desoubdzanne D, Malet-Martino M, Martino R. Analysis of adulterated herbal medicines and dietary supplements marketed for weight loss by DOSY 1H-NMR.Food AdditContam Part. AChem Anal Control Expo Risk Assess. 2010; 27: 903-916.
10. European Herbal & Traditional Medicine Practitioners Association.
11. Deconinck E, Cauwenbergh T, Bothy JL, Custers D, Courselle P De Beer JO. Detection of sibutramine in adulterated dietary supplements using attenuated total reflectance-infrared spectroscopy. 2014; 100: 279–283.
12. Wooltorton E .Obesity drug sibutramine (Meridia): hypertension and cardiac arrhythmias.CMAJ.2002; 166: 1307-1308.

13. Inchiosa MA. Experience (mostly negative) with the use of sympathomimetic agents for weight loss.IJO. 2010; 20: 1-4.

14. Luque CA, Rey JA. The discovery and status of sibutramine as an anti-obesity drug. Eur J Pharmacol. 2002; 440: 119-128.

15. Florentin M, Liberopoulos EN, Elisaf MS. Sibutramine-associated adverse effects: a practical guide for its safe use. Obes Rev. 2008; 9: 378-387.

16. Filippatos TD, Kiortsis DN, Liberopoulos EN, Mikhailidis DP, Elisaf MS. A review of the metabolic effects of sibutramine. Curr Med Res Opin. 2005; 21: 457-468.

17. Jackson HC, Needham AM, Hutchins LJ, Mazurkiewicz SE, Heal DJ. Comparison of the effects of sibutramine and other monoamine reuptake inhibitors on food intake in the rat. Br J Pharmacol. 1997; 121: 1758–1762.

18. United States patent. Serotonin and norepinephrine reuptake inhibitor and uses thereof. 2009.

19. Luscombe GP, Slater NA, Lyons MB, Wynne RD, Scheinbaum ML, Buckett WR. Effect on radiolabelled-monoamine uptake in vitro of plasma taken from healthy volunteers administered the antidepressant sibutramine HCI. Psychopharmacology. 1990; 100: 345-349.

20. Nutt DJ. The neuropharmacology of serotonin and noradrenaline in depression. Int Clin Psychopharmacol. 2002; 17 Suppl 1: S1-12.

21. Buckett WR, Thomas PC, Luscombe GP .The pharmacology of sibutramine hydrochloride (BTS 54 524), a new antidepressant which induces rapid noradrenergic down-regulation.Prog Neuropsychopharmacol Biol Psychiatry. 1988; 12: 575-584.

22. Heal DJ, Frankland ATJ, Gosden J, Hutchins LJ, Prow MR, Luscombe GP, et al. 1992, A comparison of the effects of sibutramine hydrochloride, bupropion and methamphetamine on dopaminergic function: evidence that dopamine is not a pharmacologic target for sibutramine. Psychopharmacology. 1992; 107: 303–309.

23. Heal DJ, Prow MR, Gosden J, Luscombe GP, Buckett WR. 1992b, A comparison of various antidepressant drugs demonstrates rapid desensitization of a2-adreno-ceptors exclusively by sibutramine hydrochloride. Psychopharmacology. 1992; 107: 497–502.

24. Fantino M and Souqet AM. Effects of metabolites 1 and 2 of sibutramine on the short-term control of food intake in the rat (abstract). Int J Obes. 1995; 19: 145.

25. Jackson HC, Bearham MC, Hutchins LJ, Mazurkiewicz SE, Needham AM, DJ Heal. Investigation of the mechanisms underlying the hypophagic effects of the 5-HT and noradrenaline reuptake inhibitor, sibutramine, in the rat. Br J Pharmacol.1997; 121: 1613–1618.

26. Stock MJ .Sibutramine: a review of the pharmacology of a novel anti-obesity agent.Int J Obes Relat Metab Disord.1997; 21 Suppl 1: S25-29.

27. Luque CA, Rey JA. Sibutramine: a serotonin-norepinephrine reuptake-inhibitor for the treatment of obesity. Ann Pharmacother. 1999; 33: 968-978.

28. Bae SK, Cao S, Seo KA, Kim H, Kim M-J, Shon J-H, et al. Cytochrome P450 2B6 catalyzes the formation of pharmacologically active sibutramine (N-{1-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl}-N,N-dimethylamine) metabolites in human liver microsomes. DMD. 2008; 36; 1679–1688.

29. Cheetham SC, Viggers JA, Slater NA, Heal DJ, Buckett WR. [3H] Paroxetine binding in rat frontal cortex strongly correlates with [3H]5-HT uptake: effect of administration of various antidepressant treatments.Neuropharmacology. 1993; 32: 737–743.

30. Cheetham SC, Viggers JA, Butler SA, Prow MR and Heal DJ. [3H] Nisoxetine-A radioligand for noradrenaline reuptake sites: correlation with inhibition of [3H] noradrenaline uptake and effect of DSP-4 lesioning and antidepressant treatments. Neuropharmacology. 1996; 35; 63-70.

31. Wooltorton E .Obesity drug sibutramine (Meridia): hypertension and cardiac arrhythmias.CMAJ.2002; 166: 1307-1308.

32. Inchiosa MA. Experience (mostly negative) with the use of sympathomimetic agents for weight loss.IJO. 2010; 20: 1-4.

33. James WP, Caterson ID, Coutinho W, Finer N, Van Gaal LF, Maggioni AP. Effect of sibutramine on cardiovascular outcomes in overweight and obese subjects. N Engl J Med.2010; 363: 905-917.

34. Van Heerdern IV. Simply Slim in the firing line. Health. 2010.

35. Vaclavik L, Krynitsky AJ, Rader JI. Mass spectrometric analysis of pharmaceutical adulterants in products labeled as botanical dietary supplements or herbal remedies: a review. Anal Bioanal Chem. 2014; 406: 6767-6790.

36. Tang MH, Chen SP, Ng SW, Chan AY, Mak TW. Case series on a diversity of illicit weight-reducing agents: from the well known to the unexpected.Br J Clin Pharmacol. 2011; 71: 250-253.

37. Mathon C, Ankli A, Reich E, Bieri S, Christen P. Screening and determination of sibutramine in adulterated herbal slimming supplements by HPTLC-UV densitometry. Food Addit Contam Part A Chem Anal Control Expo Risk Assess. 2014; 31: 15-20.

38. Wang MY, Anderson G, Nowicki D, Jensen J. Hepatic protection by noni fruit juice against CCl(4)-induced chronic liver damage in female SD rats. Plant Foods Hum Nutr. 2008; 63: 141-145.

39. Heo SH, Kang MH. A case of dilated cardiomyopathy with massive left ventricular thrombus after use of a sibutramine-containing slimming product. Korean Circ J. 2013; 43: 632-635.

40. Kim SK, Lee SM, Yoo SS, Hahm JR, Jung JH, Kim HS. Transient thyrotoxicosis from thyroiditis induced by sibutramine overdose: a case report. Hum Exp Toxicol. 2013; 32: 890-892.

41. Källén BAJ. Antiobesity drugs in early pregnancy and congenital malformations in the offspring. Obes Resh Clin Pract. 2013.

42. da Silva CJ, dos Santos JE, Satie Takahashi C .An evaluation of the genotoxic and cytotoxic effects of the anti-obesity drugs sibutramine and fenproporex.Hum Exp Toxicol.2010; 29: 187-197.

43. Van der Schoor C.An in vivo and in ovo evaluation of the toxicity of Sibutramine [dissertation].University of Pretoria, 2014.

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