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Review Article

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Revisiting the Most Successful United States Food and Drug Administration-approved Anti-obesity Drug Sibutramine sulfate: A Comprehensive Pharmacotherapeutic Review

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ABSTRACT

Introduction: Serotonin (5-HT) and noradrenaline (NA) re-uptake inhibitor sibutramine works together. Sibutramine primarily affects food intake and energy expenditure by way of its two pharmacologically active metabolites, primary and secondary amines, which cause significant weight loss. In addition to stimulating thermogenesis and enhancing the physiological process of satiety, it can also increase the efferent sympathetic activity to brown fat that is thermogenically active.

Aim: Revisiting the Most Successful United States Food and Drug Administration-approved Anti-obesity Drug Sibutramine sulfate.

Methodology: For a duration of 10 years, literature is covered.

Results: Clinical studies using sibutramine show a dose-related decrease in body weight, with weight loss up to 11% below baseline that can last up to 18 months with ongoing therapy. Patients assigned to the sibutramine medication continued to lose weight throughout a 1-year period, reaching 15% below baseline, while the patients receiving the placebo treatment had some weight increase when weight loss is induced with a very low calorie diet (VLCDL). By lowering the biochemical risk factors for obesity, such as plasma triglycerides, total cholesterol, low density lipoprotein (LDL) cholesterol, glucose, and insulin, and raising HDL cholesterol, sibutramine enhances metabolic fitness.

Conclusion: Sibutramine has been shown to be a beneficial treatment for obese people with moderately high blood pressure, and it has even been shown to reduce blood pressure on average as a result of weight reduction. The potential for misuse that is associated with amphetamine is not present with sibutramine, and in investigations evaluating abuse potential, it is identical to placebo.

Keywords: Anti-obesity drugs, Metabolic fitness, Obesity, Obesity-related disorders, Sibutramine, Pharmacotherapeutics

INTRODUCTION

Obesity is a complex, chronic condition that has grown pandemic in most developed nations and poses a threat to spread globally.[1] Body weight over a body mass index (BMI) of 27 and an increase in waist circumference both increase the risk of illness and death (as an index of visceral localization of fat). Patients who are obese are more likely to develop coronary artery disease, hypertension, hyperlipidemia, diabetes mellitus, certain malignancies, cerebrovascular accidents, osteoarthritis, restrictive pulmonary disease, and sleep apnea.[2] There has been much discussion recently about these risks because not all studies agree that being slightly overweight increases the risk of death in young people and because, even if one manages to maintain weight loss, there are no clinical studies demonstrating long-term maintenance of weight loss, so the long-term reduction of cardiovascular risk factors has not been evaluated.[3] Williamson and coworkers noted that the association between intentional weight loss and longevity in middle-aged overweight women appears to depend on their health status: in women with obesity-related health conditions, intentional weight loss of any amount was associated with a 20% reduction in all-cause mortality, primarily because a 40-50% reduction in mortality from obesity-related cancers; in women with no pre-existing

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illness, intentional weight loss of any amount was associated with an association with an association between intentional weight loss and longevity in middle-aged.[4] So, it makes sense to consider weight loss as a way to enhance your health.[7] Every obesity therapy, but especially a drug's effectiveness, should be evaluated on the basis of something like this.

CHEMISTRY AND ACTIVITY-STRUCTURE RELATIONSHIP

A recently created innovative anti-obesity medication is called sibutramine hydrochloride monohydrate (N-[1-(4-chlorophenyl)cyclobutyl]-3-methylbutyl-N,N-dimethylamine hydrochloride monohydrate). It was originally created in 1980, put through its first biological test the following year, and was given to people for the first time in 1984. When given to both people and animals, sibutramine, a tertiary amine, and its metabolites one through six, secondary amines, quickly develop by demethylation. Metabolites 4, 5, and 6, which are glucuronides, are thought to be pharmacologically inert. Metabolites 1 and 2 are pharmacologically active **(Figure 1)**; metabolite 3 has not been found in human plasma. Sibutramine, also known as Metabolite 1 and Metabolite 2, is a racemic combination of two enantiomers that results from asymmetry within the molecule. This means that the carbon atom to which the amine group is connected is also a chiral centre for sibutramine. A number of kinds of anorectic medications, such as amphetamine, fenfluramine, and phentermine, include the β-phenylethylamine substructure, which is also present in sibutramine. The bulky substituents at the α- and β-positions are thought to be the cause of the significant pharmacological differences between sibutramine and amphetamine and its derivatives, according to structure-activity correlations. The venlafaxine antidepressant, which it has certain pharmacological qualities with, and sibutramine have structural similarities.

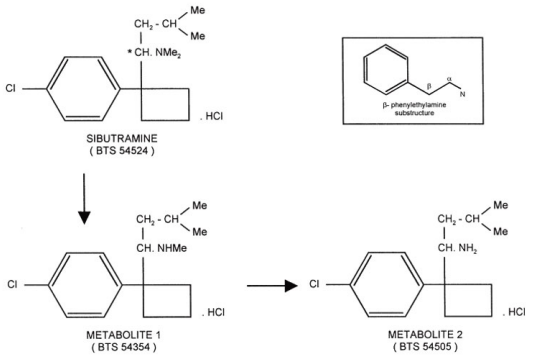

Figure 1: Chemical structure of sibutramine hydrochloride monohydrate (*N*-{1-[1-(4- chlorophenyl)cyclobutyl]-3-methylbutyl}-*N*,*N*-dimethylamine hydrochloride monohydrate) and its metabolites 1 and 2.

SITE OF ACTION: MONOAMINE REUPTAKE INHIBITION

The potent, selective reuptake inhibitors of noradrenaline (NA) and 5-hydroxytryptamine (5-HT), desipramine and fluoxetine, respectively, are comparable in strength to sibutramine *in vivo*. However, sibutramine's indirect effects result from its ineffective *in vitro* inhibition of monoamine reuptake in human and rat brain tissue **(Table 1)**. Its activity is primarily mediated *in vivo* by the metabolites 1 and 2, which impede the reuptake of dopamine (DA) and NA into rats, as well as 5-HT and other compounds, to a lesser extent (4–10-fold selectivity for NA over 5-HT or DA reuptake inhibition). The preference for NA and 5-HT over DA reuptake inhibition is about three times greater in human brain preparations. Sibutramine is a moderately ineffective monoamine reuptake inhibitor when compared to other common ones like nomifensine, desipramine, imipramine, and amitriptyline. Because sibutramines' metabolites 1 and 2 are strong NA reuptake inhibitors with a 10-fold preference for DA, sibutramines' action is mostly found in these compounds. Both metabolites are almost equally potent for the respective monoamines when combined with the selective NA reuptake inhibitor desipramine and the selective 5-HT reuptake inhibitor fluoxetine.[9,10] At doses up to 10,000 nM, sibutramine and Metabolites 1 and 2 do not promote the release of [3H]-NA, [3H]-5-HT, or [3H]-DA from brain slices. This characteristic sets them apart from anorectic medications like dexfenfluramine, which promotes the release of [3H]-5-HT at 1000 nM, and *D*-amphetamine, which does so at 100 nM.[11–14] *In vivo* animal studies of NA, 5-HT, or DA reuptake inhibition further support these findings.

Table 1: Potencies of sibutramine and its metabolites as monoamine reuptake inhibitors in human and rat brain.

	Noradrenaline	Serotonin	Dopamine
Human brain tissue			
Sibutramine	5451	298	943
Metabolite 1	20	15	49
Metabolite 2	15	20	45
Rat brain tissue			
Sibutramine	283	3131	2309
Metabolite 1	2.7	18	24
Metabolite 2	4.9	26	31

It is possible to show a difference in potency between the effects of sibutramines on NA or 5-HT reuptake and DA. Sibutramine and its metabolites have a wide range of neurotransmitter receptor affinities, including α1/α2/β1/

β2/β3-adrenoceptors, 5-HT1A, 5-HT1B, 5-HT2A, 5-HT2C serotonin receptors, D1 and D2 dopamine receptors, muscarinic receptors, H1 histaminergic receptor, and benzodia.[15,16] Sibutramine, like the majority of monoamine reuptake inhibitors, including fluoxetine, had no impact on 5-hydroxytryptophan (5-HTP) accumulation in either the frontal cortex or hypothalamus, but it does lower 5-HTP in the latter two, while *D*-fenfluramine decreased 5-HTP in both of these areas.[11] Furthermore, sibutramine and its metabolites 1 and 2 lower the levels of 3-methoxy-4-hydroxyphenylglycol (MHPG), a metabolite of NA, in mouse brains, indicating a potent effect on this neuronal system. Last but not least, intracerebral microdialysis was used to determine how sibutramine at pharmacologically efficacious levels affected 5-HT efflux in the hypothalamus of freely moving rats.[17] Sibutramine increased the levels of extracellular 5-HT in a dose-dependent manner. This impact had a somewhat lengthy duration, relatively gradual start, and moderate size. In contrast to sibutramine's activity, dfenfluramine's effects on 5-HT efflux were quick in start, relatively brief in duration, and of profound amplitude.[11–17]

PHARMACOLOGICAL PROPERTIES

Food intake and behavior

Lean rats get acute sibutramine treatment, which dose-dependently reduces their appetite.[18,19] Additionally, sibutramine has been demonstrated to decrease food intake in genetically or diet-induced obese mice.[20,21] Rolls and colleagues' sibutramine-treated people showed a considerable decrease in daily meal consumption. In fact, over the course of 14 days, 12 obese non-dieting women reported a substantial decrease in their daily calorie and gramme consumption compared to placebo, 10, or 30 mg of sibutramine.[22]

According to these findings, sibutramine lowers energy consumption in obese women who are not trying to lose weight. These substances significantly lower food intake in lean, developing rats in a dose-dependent manner, supporting the theory that sibutramine primarily exerts its effects *in vivo* via Metabolite 1 and 2. Both of these metabolites are roughly as powerful as sibutramine. Sibutramines' ability to reduce appetite is mediated by the central nervous system (CNS). When administered intracerebroventricularly, metabolites 1 and 2 diminish mice's food intake at levels that have no impact on their eating behaviour.[8]

A greater sense of fullness is the reason why sibutramine can help you eat less. Compared to untreated animals, rats that have received the medication before to feeding spend more time resting and grooming and less time eating. There was no mention of the drug's sedative effects. In contrast to *D*-effects amphetamine's on eating, sibutramine preserves the normal satiety sequence and decreases food intake by speeding up the physiological process of fullness. Indeed, after receiving the latter medication, rats quit feeding early, but their replacement of these behaviours with greater locomotor activity.[23]

Experiments using selective inhibitors of NA and 5-HT reuptake, such as nisoxetine and fluoxetine, respectively, have shown evidence for a synergistic interaction of NA and 5-HT reuptake in the suppression of food intake. Both medications affect how much food is consumed when taken alone, but when taken together, they have a powerful inhibitory effect. A role for NA and 5-HT in sibutramines' effects on food intake is also supported by experiments using monoamine receptor antagonists.[24,25] Thus, pretreatment with metoprolol, a β1-adrenoceptor antagonist, prazosin, an α1-adrenoceptor antagonist, or metergoline and ritanserin, two 5-HT receptor antagonists, prevents the sibutramine-induced decrease in food intake either completely or partially. The β2-adrenoceptor antagonist ICI 118,551, the α2-adrenoceptor antagonist RX 821002, or the DA receptor antagonists like remoxipride, which are known to counteract *D*-amphetamine- and mazindol-induced anorexia, do not prevent the impact of sibutramine on food intake.[26,27] Intriguingly, research on the function of 5-HT receptor subtypes in the effects of sibutramine were conducted using a variety of feeding paradigms (such as in rats that were starved of food and had been injected with the neuropeptide Yor muscimol) and 5-HT receptor subtype antagonists.[28] Particularly, the nonselective metergoline (5-HT2A/2C), ritanserin (5-HT2A/2C), and GR127935 (5-HT1B/1D) did not alter the impact of sibutramine, whereas SB206553 (5-HT2B/2C) lowered it marginally but considerably. The reduction in food intake brought on by sibutramine in neuropetide Y-injected rats was not altered by GR127935, indicating that 5-HT1 and 5-HT2 receptor subtypes are not significantly involved in the acute (2 hrs after injection) hypophagic effect of sibutramine, possibly with the exception of a possible partial involvement of 5-HT2B/2C receptors in sibutramines' hypophagia in food-deprived rats. These findings offer contradictory information about the effectiveness of metergoline and ritanserin in blocking the effects of sibutramine. According to the findings from Stricker-Kongrad and colleagues, ritanserin reversed the effects of sibutramine in a bell-shaped manner. This is unexpected given that evidence points to the drug's higher dosage having a greater effect on 5-HT2C receptors.[29] The pharmacological mechanisms of sibutramines' action have not yet been definitively characterised, which is supported by the evidence that the action of 5-HT reuptake inhibitors may change with prolonged administration. This could, therefore, influence at least the extent to which 5-HT mechanisms contribute to sibutramine's efficacy.

Sibutramine is also effective in *in vivo* animal models of noradrenergic or serotonergic reuptake inhibition, such as preventing ptosis brought on by reserpine, inducing thermogenesis, as well as inhibiting food intake, but it is ineffective in causing circling in unilaterally nigrostria.[16] Evidence from these experiments demonstrates a potency separation between sibutramines' actions as a reuptake inhibitor of NA or 5-HT and DA. As shown by the induction of ipsilateral circling in unilateral nigrostriatal-lesioned rats, a well-established model to determine enhanced CNS dopaminergic function, effective doses for the prevention of reserpine-induced ptosis,[23-30] inhibition of food intake, and induction of thermogenesis are 2-30-fold lower than those required to initiate even minimal DA reuptake inhibition.[31] In fact, under these experimental circumstances, the same range of dosages that affect food intake for *D*-amphetamine, mazindol, and nomifensine also caused ipsilateral turning.[32,33] In a similar vein, sibutramine does not enhance locomotor activity, but anorectic dosages of *D*-amphetamine and mazindol do.[32] These findings show that sibutramine has a significantly distinct pattern of behavioural effects than CNS stimulant medications.

Potential abuse liability

Drugs that have a high potential for misuse and have an impact on psychomotor performance are related with enhanced limbic dopamine activity.[34] Sibutramine and its metabolites do not increase dopamine release, as was previously described, hence abuse potential is not anticipated.

When tested in rat models and on human volunteers with a history of drug misuse, sibutramine doesn't seem to have any potential for abuse. 20 mg and 30 mg of sibutramine were tested with milligram-equivalent doses of *D*-amphetamine and placebo in recreational stimulant users to demonstrate that sibutramines had no stimulant or euphoric effects in humans. The Addiction Research Center Inventory (ARCI) scale, which has been validated, may be used to evaluate the abuse potential of a novel substance in people by comparing subjective experiences to a positive control.[35] Recreational drug users were selected for this study because they are thought to have more valid opinions on substances that are likely to be abused than uninformed participants. These analyses revealed that the sibutramine 20 mg dosage was equivalent to the placebo on all five subclasses of the ARCI scale, but significantly different from *D*-amphetamine.[36] The findings of the ARCI scales strongly showed that sibutramine, a weight-loss aid, did not have the same addiction potential as drugs in the amphetamine class.[37]

Thermogenesis

In rats, sibutramine increases oxygen consumption by around 20% during the next two hrs after therapy and the metabolic rate stays 30% higher than control values for at least six hrs after treatment. Rats' body temperatures therefore rise noticeably as well. Multiple pieces of evidence demonstrate that this stimulation is caused by a central sympathetic nervous system activation that abundantly innervates brown adipose tissue (BAT), which in turn stimulates the β3-adrenoceptors on brown adipocytes.[15–38] Basal energy expenditure (EE) and diet-induced thermogenesis in persons with normal weight or obesity were compared with the acute and long-term thermogenic effects of sibutramine and placebo.[39] In a randomised, double-blind, and placebo-controlled study, Hansen and colleagues found that sibutramine significantly increased basal metabolic rates (BMR) over those for placebo (over 5.5 h) in the fed and fasted states as well as in the final 3.5 h of this 5.5 h period and in the fed and fasted states, respectively. This illustrates a considerable rise in BMR brought on by sibutramine. It's interesting to note that Walsh and colleagues and Hansen and colleagues found that sibutramine inhibits the drop in energy expenditure associated with weight reduction in obese people, whether or not food restriction is used.

Brown adipose tissue metabolism

It is important to note that sibutramine has no effect on glucose utilisation in any other tissues other than BAT, where there is an 18-fold increase in glucose utilisation, when glucose utilisation was measured in anaesthetized rats using the labelled 2-deoxy-*D*-glucose method. The exceptions were small increases in glucose utilisation in the diaphragm and gastrocnemius muscle.[38–43]

This clearly suggests that sibutramine can increase BAT activity and, consequently, increase energy expenditure. BAT is a highly specialised tissue that is found in most hibernating mammals, including humans,[44] and it generates heat in response to exposure to cold weather or following a meal.[45] In addition to being present as islets inside the omental, perirenal, and periadrenal fat depots in adult humans, accumulation of BAT is also evident in the interscapular, perirenal, axillary, and cervical areas of babies.[46]

Brown adipocytes and BAT blood vessels, as well as the sympathetic neurons that abundantly and directly innervate them, release NA that stimulates thermogenesis in the BAT.[47] Chronic BAT stimulation, as seen in animals adapted to low environmental temperatures, causes a trophic response that includes marked mitochondrial proliferation, which involves an increased uncoupling of mitochondrial respiration and oxidative phosphorylation, and selective increases in transcription of thermogenetic genes, such as the mitochondrial uncoupling protein-1 (UCP1).[48] Apoptosis of brown fat cells triggered by tumor necrosis factor (TNF)-α, which is overexpressed in white adipose tissue, is therefore another reason why BAT in obese animals is often in a comparatively atrophied and thermogenically quiescent state in obese animals.[49-51] Since it has been demonstrated that

sympathetic activity in the BAT can prevent the brown fat apoptosis that is caused by TNF-α, sibutramine may be able to prevent the obesity-related shrinkage of the BAT.[52]

PHARMACOKINETIC ASPECTS

Sibutramine is quickly absorbed after oral consumption. A single oral dosage of 20 mg of sibutramine results in plasma concentrations of the drug-related substance those are maximum at 1 hr and an elimination half-life of around 1 hr. After 96 hrs, plasma cannot be identified with radio-labelled material. If sibutramine is found, it is only in trace levels, a sign of the drug's quick and thorough metabolism. Two pharmacologically active metabolites are produced in the liver after significant first pass metabolism (Metabolites 1 and 2). 77% of the given substance is retrieved from the urine, where sibutramine and its metabolites are mostly eliminated. In fact, a subsequent peak in plasma concentrations is observed six to ten hrs after dosage because these components are also discharged into the bile and then reabsorbed from the gut. The pharmacokinetics of Metabolite 1 and 2, which are known to be pharmacologically active in animal testing, have been studied following single doses of 12.5 mg, 25 mg, 50 mg, and 75 mg sibutramine due to the low quantities of the parent drug. Both metabolites enter the plasma quickly, reaching their highest levels between 3 and 5 hrs later and additional peaks between 6 and 9 hrs later that are thought to be caused by biliary recycling. With estimated terminal half values of 12.6 hrs for metabolite 1 hr and 13.3 hrs for metabolite 2, the metabolites are removed in a biphasic manner.[53] A 10-mg dosage of [14C]-sibutramine has been shown to have a total drug-related material terminal plasma half-life of 16 hrs. After repeatedly giving sibutramine doses of 20 mg once day for 14 days and 15 mg twice daily for up to 5 days, the pharmacokinetics of metabolite 1 and metabolite 2 were investigated. These dose regimens result in just traces of the parent chemical being found in the plasma. It takes both metabolites 72 hrs to reach steady state plasma concentrations, and steady state maxima are around twice as high as initial peak levels. Terminal half-lives of the metabolites after repeated dose are 15.7 hrs (Metabolite 1) and 22.7 hrs, and elimination is biphasic (Metabolite 2). Drugs with a high first-pass effect frequently see increases in terminal half-lives with repeated administration.

THERAPEUTIC EFFICACY

The cornerstone of treating obesity is behavioral adjustment to enhance nutrition and boost physical activity. In some obese individuals with a BMI more than 30, or in patients with a BMI greater than 27 who already have comorbidities, several specialists in the field of obesity treatment advice using medication as an addition to an organised programme of food and exercise.[54] The ordinary patient may realistically reduce just 10% of total body weight and comfortably maintain this with food and exercise, but the patient for whom medicine is indicated would need to lose at least 30% of total body weight to attain optimal body weight.[55] Since obesity-related comorbidities can be reduced with weight loss of as low as 5% of total weight, this should be the focus of obesity therapy rather than aesthetics. Evidence shows that anti-obesity drugs must be sustained to maintain weight loss in the majority of patients, same as hypertension medications must be kept to maintain reduced blood pressure.[56]

In clinical studies, sibutramine was administered to more than 8000 obese participants, and it was found to be associated with a dose-related reduction in body weight. For this article, published clinical studies proving the safety and effectiveness of sibutramine were reviewed.[22,57-72] Similar procedures were used in all of the trials: patients were given active medication or a placebo during the treatment phase, which was preceded by a run-in period of 1-3 weeks to set appropriate entry criteria and track the impact of dietary and/or behavioral modifications. A post-treatment visit to gauge weight change after discontinuing therapy was frequently conducted following the treatment period, which lasted 8 to 52 weeks. Adjunctive therapy in the form of dietary, exercise, and behavior modification guidance has been incorporated, albeit to variable degrees, in all clinical studies of sibutramine for weight control in overweight and obese patients. In double-blind, placebo-controlled studies in overweight and obese patients, once-daily sibutramine $ 30 mg for £ 52 weeks led to better weight reduction than with placebo.[57–59]

Sibutramine doses of less than 10 mg per day exhibited noticeably better benefits than placebo in obese individuals with or without coexisting illness, demonstrating that weight reduction is unquestionably dose-related.[22,57–59] Patients taking sibutramine 10-20 mg day-1 lost around 5-7.5 kg of body weight in trials lasting 8–12 weeks; equivalent weight reductions for placebo users ranged from 1.5–3.5 kg.[22,57] During a six-month treatment period, weight reduction persisted and was more pronounced with sibutramine (10–30 mg/day) than with a placebo. In a study done by Bray and colleagues, 1047 individuals with a BMI of 30 to 40 kg/m^2 were given a hypocaloric diet for 24 weeks, along with increased daily activity.[59] The trial was successfully completed by 683 subjects. Sibutramine dosages ranging from 5 mg per day to 30 mg per day resulted in statistically significant weight reduction when compared to placebo at all time points. The amount of weight lost at week four was a good indicator of the amount lost at week 24.

In a 12-week study in general practice, 485 patients took part and were randomly assigned to receive placebo, sibutramine

5 mg, 10 mg, or 15 mg once day. Final weight decreases after 12 weeks, from a mean baseline BMI of 33 kg m^2, were 1.4 kg in the placebo group, 2.4 kg in the 5 mg group, 5.1 kg in the 10 mg group, and 4.9 kg in the 15 mg group. The percentage of patients in this G.P. outpatient group who lost at least 5% of their body weight over a 12-month period with a placebo was 29%, 56% with sibutramine 10 mg, and 65% with sibutramine 15 mg.[60] Patients, who had previously lost weight following a 4-week period on a very low calorie diet in a French 1-year research, not only maintained the weight reduction throughout ongoing sibutramine double-blind medication, but also enhanced the weight loss. Patients who were randomly assigned to either placebo or sibutramine saw equivalent weight reduction following the VLCD phase.[61] At the research's endpoint, 86% of patients in the sibutramine group had dropped at least 5% of their body weight as compared to their weight at study entrance, as opposed to just 55% of those in the placebo group. Similar to this, by month 12, 75% of sibutramine group participants had maintained at least 100% of the weight reduction they had made with a VLCD, as opposed to 42% of placebo group participants. Due to lack of compliance or minor biochemical or metabolic changes across people, a fraction of patients receiving the majority of pharmacological therapy do not react to any specific target. "Non responders" in the aforementioned study were those who did not drop 1% of their body weight after receiving therapy for four weeks. The results at the end of 12 months showed that sibutramine 15 mg day-1 caused a weight reduction of roughly 8 kg after taking this into account and removing patients who did not lose 2 kg of weight at 4 weeks.[60]

Dexfenfluramine was one of the most often used medications to help people lose weight before it was taken off the market due to concerns about cardiovascular damage. Clinical studies have not shown definitively that sibutramine is more effective than dexfenfluramine.[62] One research compared the two medications and found that after 12 weeks, sibutramine 10 mg once day or dexfenfluramine 15 mg twice daily significantly increased weight loss compared to placebo.[60, 63]

TOLERABILITY AND SIDE EFFECTS

Headache, constipation, and nausea are the sibutramine side effects that are most frequently reported. More than 5% of people using sibutramine suffer certain neurological system side effects, such as lightheadedness, dry mouth, and sleeplessness.[59,71]

Overall, sibutramine single dosages up to 75 mg are well tolerated and seldom cause side effects. Additionally, sibutramine is well tolerated at repeated daily dosages up to a maximum of 20 mg per day, however some standing tachycardia is seen at these levels. When sibutramine at dosages of 5, 10, and 20 mg is administered repeatedly, heart rates rise by 6–13 beats per minute in comparison to placebo. 0.3% of sibutramine patients who experienced palpitations discontinued their medication therapy, whereas 0.4% of sibutramine patients who suffered tachycardia did the same.[67]

The medication's impact on blood pressure may be understood as a delicate balancing act between an expected lowering effect based on its effects on weight and a stimulating effect based on the suppression of NA re-uptake. Sibutramine raises both systolic and diastolic blood pressure by a mean of 2 mmHg at dosages of 10-15 mg once a day, however there is no clinical risk in normotensive people compared to the 0.6-0.7 mmHg mean declines in resting diastolic and systolic blood pressure caused by placebo. 113 obese individuals with hypertension were given either sibutramine 10 mg daily or a placebo for 12 weeks after a 3-week washout period; the mean weight reduction for sibutramine patients was 4.4 kg, compared to 2.2 kg for placebo users. Standing and supine diastolic blood pressure reductions with sibutramine were 3.7 and 4.0 mmHg and 6.1 and 5.7 mmHg with a placebo; these reductions were not statistically different. This study is comforting in that it shows that sibutramine and a placebo both have a beneficial effect on blood pressure in hypertensive individuals.[72]

When obese individuals with hypertension begin taking sibutramine, blood pressure and pulse rate should be monitored since blood pressure increase or tachycardia is frequently observed in the first eight weeks of medication. Additionally, it is advised to use clinical judgement in individuals with documented coronary heart disease who are overweight.

Dexfenfluramine and fenfluramine have recently been taken off the global market due to their link to valvulopathy. So it makes sense to research how sibutramine affects the structure of the heart. Sibutramine doesn't seem to have a negative impact on heart valve function.[73] A double-blind, placebo-controlled, parallel-arm, 12-month trial including 210 obese individuals with type 2 diabetes mellitus is now underway. For a mean of 7.6 months, 133 of them were given sibutramine, and 77 were given a placebo. All of them received transthoracic echocardiographic imaging and colour Doppler interrogation to evaluate the structure and function of their cardiac valves. Based on these findings, both therapy groups had a low incidence of illness affecting the left heart valve. There were 5 aortic insufficiency instances in all, 4 of which were mild and 1 of which was severe (in a recipient of a placebo). Because norfenfluramine has a high affinity for this 5-HT receptor subtype, it has been hypothesised that sibutramine and its metabolites will not have the same affinity for the valvular 5-HT2B receptors. This 5-HT receptor subtype has been linked to the purported valvular fibroplasia caused by fenfluramine.[74]

CONTRAINDICATIONS

In individuals undergoing other centrally acting appetite suppressants and within two weeks of monoamine oxidase inhibitor treatment, sibutramine is contraindicated. Patients with a history of coronary artery disease, congestive heart failure, dysrhythmias, stroke, severely impaired renal function, or severely impaired hepatic function shouldn't take it. Patients with a history of hypertension can be cautiously administered sibutramine, but it is not advised for individuals whose hypertension is uncontrolled or just moderately under control. Patients with narrow angle glaucoma, those with a history of seizures, and those with bipolar illnesses should use sibutramine with caution.

POTENTIAL DRUG INTERACTIONS

Sibutramine should be used with caution in individuals who may also be taking phenylpropanolamine, ephedrine, or pseudoephedrine, medications that raise blood pressure and heart rate. Since the cytochrome P450 enzymes are involved in the metabolism of sibutramine, medications that compete with these enzymes, such as cimetidine, erythromycin, and ketoconazole, may make sibutramine more active.

CONCLUSION

The realisation that obesity is a chronic, complex condition that responds poorly to existing therapy modalities (diet, exercise, and behavior) has sparked a resurgence in interest in medication usage. Only a small number of medications have been created or licenced to treat obesity in the previous 30 years. The development of these medications has been considerably hampered by international laws and treatment recommendations. For instance, until recently, several regulations mandated that these medications continuously reduce weight. However, other medications that manage chronic conditions like diabetes mellitus or hypertension are anticipated to maintain a target level rather than further lower high blood pressure or high blood glucose levels. According to the current thinking on weight reduction, obese individuals shouldn't be expected to attain their "ideal" bodyweight but rather should be urged to resist gaining more weight at first, then to drop moderate amounts of weight, and to keep this weight off. There are currently limited possibilities for pharmacologically treating obesity. The only other newly authorised anti-obesity medication with central action for uses longer than three months was dexfenfluramine. However, due to possible cardiovascular safety issues, it has been voluntarily pulled from the market worldwide along with fenfluramine, and more testing is being done. Sibutramine and dexfenfluramine both have a centrally acting effect on satiety, albeit their respective mechanisms of action vary. These agents seem to have little capacity for misuse. There is currently a paucity of comprehensive published evidence demonstrating sibutramine's long-term tolerability and the consequences of withdrawal after extended usage. Throughout the pharmaceutical sector, new drugs are being developed, and a number of therapeutic agents are on the horizon. The development of fully sequenced genomes and new genomics and proteomics technologies, which allow analyses of gene transcription profiles and protein interactions in intricate cell circuitries, will lead to new target selection for drugs able to treat obesity and allow obese people to be classified according to their likely response to an anti-obesity drug.

CONFLICT OF INTEREST

No conflict of interest declared.

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AUTHOR CONTRIBUTION DETAILS

Yadav L: Writing the manuscript

Sahu S: Literature Review

Agrawal B: Guidance, Topic suggestion, Addressing revisions

Meshram R: Grammar improvement and Plagiarism reduction

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