R E V I E W

The use of serotonergic drugs to treat obesity – is there any hope?

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Abstract: Surgical interventional strategies for the treatment of obesity are being implemented at an increasing rate. The safety and feasibility of these procedures are questionable for most overweight or obese individuals. The use of long-term pharmacotherapy options, on the other hand, can target a greater portion of the obese population and provide early intervention to help individuals maintain a healthy lifestyle to promote weight loss. Medications that act on the central serotonergic pathways have been a relative mainstay for the treatment of obesity for the last 35 years. The clinical efficacy of these drugs, however, has been encumbered by the potential for drug-associated complications. Two drugs that act, albeit by different mechanisms, on the central serotonergic system to reduce food intake and decrease body weight are sibutramine and lorcaserin. Sibutramine is a serotonin and norepinephrine reuptake inhibitor, whereas lorcaserin is a selective $5HT_{2C}$ receptor agonist. The recent worldwide withdrawal of sibutramine and FDA rejection of lorcaserin has changed the landscape not only for serotonin-based therapeutics specifically, but for obesity pharmacotherapy in general. The purpose of this review is to focus on the importance of the serotonergic system in the control of feeding and its potential as a target for obesity pharmacotherapy. Advances in refining and screening more selective receptor agonists and a better understanding of the potential off-target effects of serotonergic drugs are needed to produce beneficial pharmacotherapy.

Keywords: 5-hydroxytryptamine, serotonin 1B, fenfluramine, dexfenfluramine, satiety, dorsal raphe

Introduction

Obesity in the past several decades has become increasingly prevalent in the adult population of several countries, such as the US, Mexico, and the UK.[1–3] The alarming rate of childhood obesity in these and other countries only exaggerates the health concern worldwide.[4–6] In fact, the World Health Organization projects 700 million adults will be clinically obese (BMI $\geq$ 30, body mass index; kg/m^2) by 2015.[7,8] Individuals who are obese or even overweight (BMI 25–29.9) are at an increased risk of developing one or more chronic diseases, including diabetes mellitus type II, coronary heart disease, hypertension, and various cancers.[9–11] Several studies have indicated that weight loss, even a 5% to 10% weight reduction, either lowers the risk of developing these comorbidities or helps in their therapeutic management.[12–16] The overall societal healthcare burden and the individual risk to a person's health and wellbeing caused by excessive weight gain, therefore, can be dramatically reduced by effective interventional strategies aimed at reducing body weight.

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The type and degree of interventional strategies recommended by a clinician to treat obesity can vary depending on the severity of weight gain and obesity-related complications. The initial approach involves having patients reduce their total caloric intake by eating more nutritious foods while increasing their physical activity. Other behavioral approaches may involve self-monitoring of eating behaviors, cognitive therapies, and lifestyle modification support.[12] In addition, pharmacotherapy can be initiated if moderately overweight individuals (BMI 27–29.9) have difficulty losing weight or are at a high risk for developing an obesity-related comorbidity. Pharmacotherapy is typically initiated in obese individuals with a BMI of ≥30 as part of a comprehensive treatment approach.[12,17] In more severe obese individuals with a BMI of >40 (also known as class III obese) or a BMI > 35 with one or more obesity-related comorbidities, bariatric surgical options are considered as well.[12,13,18,19] Bariatric surgery, in particular gastric bypass, compared with other interventional strategies is the most clinically effective at decreasing body weight and reducing the incidence and risk of most obesity-related comorbidities.[19–21] Bariatric surgery, however, poses a mortality risk (as high as 10%) to patients undergoing the procedure and the immediate and the long-term cost-effectiveness is only significantly apparent in individuals with a BMI ≥ 40.[22–24] In addition, there is a suggested higher risk of suicide in patients undergoing bariatric surgery. A recent survey of 16,683 bariatric operations found there were 31 suicides in the 3-year post-surgery period (13.7 per 10,000 among men and 5.2 per 10,000 among women), which is a much higher rate than general age and sex-matched population in the US (2.4 per 10,000 among men and 0.7 per 10,000 among women).[25] Nonetheless, obese individuals with a BMI ≥ 40 represent only 10% to 12% of the adult overweight or obese population in the US, suggesting that bariatric surgery is not a feasible weight loss interventional strategy for most of the afflicted population.[26] Hence, overweight or moderately obese individuals would benefit tremendously from effective pharmacotherapy before their weight gain becomes unmanageable or they develop associated comorbidities. When combined with other interventional strategies, in this sense, pharmacotherapy can help achieve or maintain ideal weight loss and possibly avoid more invasive life-threatening surgical interventions.

The development of effective long-term pharmacotherapy for obesity is a difficult task because mechanisms that promote sustained weight loss are often accompanied by mild to severe adverse events. The purpose of this review is to primarily focus on two obesity medications, sibutramine and lorcaserin, which act on the central serotonergic systems to reduce body weight. While the relevance of pharmacotherapy for obesity is certain to change in the next few years, particularly as a consequence of the withdrawal of sibutramine and an FDA advisory panel's concerns over lorcaserin, this review will highlight the importance of serotonergic systems and the pharmacotherapy potential for serotonergic drugs in the long-term treatment of obesity.

Pharmacotherapy for the long-term treatment of obesity

The clinical endpoint for effective pharmacotherapy, as stipulated by the Food and Drug Administration (FDA, USA) and National Institute for Health and Clinical Excellence (NICE, UK), is based on *mean efficacy* and *categorical efficacy*. Mean efficacy is defined as a medication-associated (ie, greater than placebo) weight reduction of 5%. Categorical efficacy is defined as a significantly greater proportion (at least 35%) of those individuals receiving the medication compared with placebo controls maintaining a 5% weight loss from their initial weight.[13,27] A mean efficacy of a 5% medication-associated weight reduction has been a difficult criterion to achieve in most large scale clinical trials and an overall efficacy of a medication is generally assessed more by a risk-benefit approach. Until fall 2010, the only two prescribed medications for the long-term treatment of obesity were orlistat and sibutramine. These drugs have completely different mechanisms of action, but each has shown to produce a varying degree of clinical efficacy at reducing body weight when administered along with interventional strategies aimed at changing a patient's diet, physical activity, and eating behaviors.

Orlistat or tetrahydrolipstatin is a derivative of lipstatin, an inhibitor of lipases isolated from the Gram-positive bacterium *Streptomyces toxytricini*.[28] Orlistat reduces the absorption of dietary fat by selectively and irreversibly binding to pancreatic and gastric lipases in the intestinal lumen. Inhibition of these lipases prevents the breakdown of triglycerides and diacylglycerides into free fatty acids for epithelial absorption and subsequent utilization.[29] Orlistat (120 mg 3 times daily) reduces the absorption of dietary fat by approximately 30% and has been demonstrated to result in an approximately 3% greater orlistat-associated reduction in body weight in long-term (52-week) randomized double-blinded studies.[30–32] The most commonly reported adverse events with orlistat treatment in a large number of subjects (as high as 30% above the control group) were related to mild to moderate gastrointestinal disturbances.[30] Aside from rare cases of

acute liver injury, orlistat is a moderately well-tolerated, relatively safe drug producing modest long-term weight loss.[33] A similar favorable assessment of orlistat's risk-benefit analysis is shared by drug regulatory agencies in the US, European Union, and Australia, which have all approved over-the-counter dosages of the drug.[33–35]

Sibutramine, on the other hand, was indefinitely suspended in August 2010 for the treatment of obesity by the European Union drug regulatory agency based on several reports of cardiovascular complications; the agency cited the "drug's benefits do not outweigh the risks".[36] In October 2010, following the findings of a comprehensive study examining the potential cardiovascular risks and a split decision of an FDA advisory panel, Abbott Laboratories, the manufacturers of sibutramine, withdrew sibutramine from the US, Australia, and other countries.[37] Sibutramine is in a class of drugs known as monoamine reuptake inhibitors and most drugs of this class are prescribed for the treatment of depression.[38–40] The effectiveness of monoamine reuptake inhibitors is achieved by augmenting central nervous system (CNS) concentrations of monoamine neurotransmitters, such as dopamine (DA), norepinephrine (NE), and serotonin (5-hydroxytryptamine; 5HT). Sibutramine was ineffective in vivo as an antidepressant, but produced sustained weight loss by reducing food intake and increasing energy expenditure.[38,41] Sibutramine and its active amine metabolites alter serotonergic and noradrenergic, but not dopaminergic, activity in brain areas that are involved in the control of appetite.[38,42,43] Long-term treatment (~52 weeks) with sibutramine (10 or 15 mg once daily) in randomized placebo-controlled studies has been shown to reduce body weight by 5% to 10% more than placebo control subjects.[44,45] A meta-analysis examining 10 long-term weight-loss studies with sibutramine (15 mg once daily), however, found more modest weight loss, with a 4.3% sibutramine-associated reduction in body weight.[17] Since its FDA approval in 1997, the widespread use of sibutramine to treat obesity was limited because the drug increased heart rate and blood pressure and was not indicated in obese or overweight patients with a history of cardiovascular disease.[46,47] Prompting the withdrawal of sibutramine was a recently completed multicenter trial examining sibutramine on cardiovascular OUTcomes (SCOUT) in subjects with either a history of at least one risk factor for cardiovascular disease. The findings from this study demonstrated an overall 16% increase in the relative risk of cardiovascular events (ie, nonfatal myocardial infarction and stroke) with sibutramine treatment. Moreover, the sibutramine-associated weight loss at the end of the trial was modest, with approximately 3% greater weight loss than the placebo group.[48] The small weight-loss benefit and increased risk of cardiovascular events in at risk obese patients in such a large study led to an unfavorable assessment by an FDA advisory panel and subsequent withdrawal of the medication.

Lorcaserin (ADP356) is another potential treatment for obesity that acts on the central serotonergic system to reduce food intake and body weight. Lorcaserin is a selective serotonin receptor ($5HT_{2C}$) agonist and is believed to reduce food intake predominantly by influencing hypothalamic pathways involved in appetite.[49] In a phase III clinical trial with 3182 overweight or obese subjects (known as BLOOM; Behavioral modification and Lorcaserin for Overweight and Obesity Management), there was a 4% lorcaserin (10 mg twice daily)-associated weight reduction at 52 weeks. Despite this modest weight loss, lorcaserin was associated with few subject-reported and no cardiovascular-related adverse events.[50] The toxicology data in rodents presented to the FDA advisory panel, however, demonstrated a significant number of neoplasms in mammary and brain tissue of rats treated with lorcaserin (10 mg/kg, 30 mg/kg, 100 mg/kg per day) for 2 years.[51] Based on the modest weight loss and the problematic carcinogenicity findings, the FDA advisory panel recommended that lorcaserin not be approved for the long-term treatment of obesity, and that decision was supported by the FDA's complete response letter to the New Drug Application (NDA) filed for lorcaserin, which requested more data addressing these issues.[52]

Serotonin in the control of feeding behavior and metabolism

Serotonin (5HT) was initially isolated from beef serum in 1948 during the process of determining an active substance involved in vasoconstriction.[53,54] Although 5HT has extensive biological actions in peripheral tissue and as a vasoactive amine, its role as a neurotransmitter in the CNS as a modulator of behavior and mood has received considerable attention.[55] The 5HT-containing neurons are organized into nine nuclei (B1–B9) and are located in the midbrain and hindbrain areas. The dorsal raphe (B7), in particular, is a midbrain nucleus that contains a substantial portion of the total brain 5HT and has distinct projections to hypothalamic nuclei and other feeding-related forebrain areas.[56,57] Obesity, either by genetic or diet-induced means, has been demonstrated to alter 5HT dorsal raphe neurons and 5HT terminal regions. For instance, the genetic obese fatty Zucker rats were shown to have hyperexcitable dorsal raphe neurons and greater

feeding-induced hypothalamic 5HT levels compared with lean Zucker rats.[58,59] Continuous infusions (14-day) of 5HT into a target hypothalamic region, ventromedial nucleus, has been shown to reduce food intake and body weight of lean Zucker rats, but not obese Zucker rats.[60] Related to this, increases in 5HT transporter binding have been reported in the dorsal raphe of rats made obese by feeding a high-energy diet (68% carbohydrate and 13% fat) for 7 weeks. Taken together, these data suggest a dysregulation of central serotonergic pathways as a consequence of obesity.[61]

The direct functional involvement of 5HT in the modulation of feeding behavior was suggested by early experiments examining the anorectic potency of fenfluramine.[62,63] Fenfluramine (3-trifluoromethyl-N-ethylamphetamine) is structurally similar to *d*-amphetamine, but fenfluramine is more potent as an anorectic agent without an abuse potential.[64–66] Fenfluramine is a racemic compound with its active enantiomer being the *d*-isomer or dexfenfluramine.[67] The mechanism of action for dexfenfluramine is the release of 5HT (and to a much lesser extent NE), whereas amphetamine is less selective and releases NE and DA from nerve terminals. Fenfluramine, dexfenfluramine, and *d*-amphetamine are classified as monoamine releasing agents, but specifically are transporter substrates causing the displacement of monoamines from intracellular storage *independent* of neuronal activity.[40,62,68] In addition, active metabolites of fenfluramine and dexfenfluramine (eg, nor-fenfluramines) act as agonists at postsynaptic serotonin receptors to potentiate the serotonergic actions of the parent drugs.[66,69] Dexfenfluramine also has actions to enhance energy expenditure since the body weight produced by the drug is greater than that achieved by pair-feeding animals.[65,70,71] This enhanced energy expenditure partly occurs via increased fat oxidation.[72] Fenfluramine was approved in 1973 and dexfenfluramine was approved in 1996 as medications for treatment of obesity in the US. Fenfluramine and later dexfenfluramine were part of an "off-label" combinational drug therapy with phentermine, an amphetamine analog stimulant FDA-approved for the short-term (up to 3 months) treatment of obesity, and the drug combination was known as "fen-phen" or "dexfen-phen".[66,73] Although the combinational therapies were effective in the long-term management (up to 12 months) of obesity and were widely prescribed, the therapies were associated with a significant increased risk of developing primary pulmonary hypertension and valvular heart disease.[74–80] These adverse events were discovered to be caused by fenfluramine and dexfenfluramine and the two drugs were subsequently withdrawn from the market in 1997 at the FDA's recommendation.[81]

Not only did experimental findings with fenfluramine and dexfenfluramine suggest that targeting the serotonergic systems produced clinically significant body weight reductions, these drugs also implicated 5HT's involvement in the inhibitory control of eating. Acute peripheral injections of fenfluramine and dexfenfluramine have been demonstrated to increase hypothalamic concentrations 5HT.[82,83] Also, when dexfenfluramine is chronically administered to rodents it reduces meal sizes and meal duration, and progresses the behavioral sequence of satiety, suggesting that the drug acts on the physiological functions involved in the normal cessation of a meal.[84–86] That is, when rats are allowed to eat until satiety they display a temporal sequence of behaviors as meal consumption is terminating that begins with a reduction in eating followed by increases in grooming and other activities, and then a period of rest.[84,85,87] This behavioral sequence is disrupted with amphetamine and food adulterated with bitter-tasting quinine, suggesting the anorectic responses produced by these agents are mediated differently from those involved with satiety.[85,88] Generally speaking, it has been demonstrated that serotonergic compounds, which specifically and dose-dependently increase 5HT signaling to reduce food intake, maintain the integrity of the behavioral satiety sequence at a related range of doses.[84,85,89] Similar reductions in eating rate and increased subjective satiety ratings have been demonstrated in human subjects administered fenfluramine and other serotonergic drugs, confirming the behavior interpretations made in rodents.[70,90–92] Correspondingly, certain pharmacological conditions that decrease CNS levels of 5-HT promote overeating.[57] Centrally injected selective serotonin depleting agents, such as *p*-chlorophenylalanine or 5,7-dihydroxytryptamine pretreatment with desmethlyimipramine, resulted in pronounced hyperphagia and increased body weight in rats.[93,94]

Sibutramine was approved for the long-term treatment of obesity by the FDA in November 1997 (coincidentally, dexfenfluramine was withdrawn in September, 1997). Sibutramine also increases the extracellular 5HT to reduce food intake, but does so by a different mechanism of action than dexfenfluramine. Acting as a NE and 5HT reuptake inhibitor, sibutramine (and its active metabolites) prevents the extracellular removal of monoamines and their effectiveness, and therefore is *dependent* on neuronal activity of 5HT neurons. Using anorectic doses of fenfluramine or sibutramine in rats, the magnitude of release of 5HT in the hypothalamus was shown to be 10- to 15-fold higher with fenfluramine (3 mg/kg) than with sibutramine (10 mg/kg).[82] The reduced magnitude of 5HT release with sibutramine is mediated, in

part, by indirect activation of somatodendritic autoreceptors, which modulate the intrinsic activity of 5HT neurons.[82,95] This autoreceptor inhibition is not evident with monoamine releasers (eg, fenfluramine or dexfenfluramine) because their mechanism of action is not dependent on neuronal activation.[82] Sibutramine, similar to serotonin-selective reuptake inhibitors (SSRI), was believed to mediate its actions by increases in basal or tonic levels of 5HT with repeated treatment. It appears that autoreceptor desensitization in the dorsal raphe rather than increased 5HT actions in the terminal is more likely involved in the sustained actions of SSRIs, but this needs further delineation for the anorectic actions of sibutramine.[38,96,97] It is worth noting that SSRIs do not have a sustained effect on weight loss, hence it has been concluded that the combined actions on the 5HT and NE transporters are needed for the weight loss efficacy of sibutramine.[39,98,99]

Sibutramine has been reported to improve glucose regulation and lipid profiles in obese subjects, but the enhancement of these factors appears to be a consequence of weight loss rather than the direct actions of sibutramine on metabolism.[38,100] Sibutramine has been demonstrated, however, to improve obesity-related energy expenditure. Dietary weight loss is accompanied by a decrease in energy expenditure, which tends to be an obstacle for optimal weight loss.[101] Several studies have indicated that sibutramine attenuates the decline in energy expenditure that follows weight loss.[102,103] The increased energy expenditure has been shown to be mediated by central modulation of sympathetic outflow, the thermogenic effects being blocked by antagonism of β_3 adrenoceptor in rats.[104] On the other hand, the effect of sibutramine on heart rate and blood pressure appears to be a paradoxical interplay between reduced central and increased peripheral sympathetic regulation, but this needs further clarification.[56,105–108]

The assortment of central and peripheral biological actions of 5HT is mediated by at least 14 different classified receptors that are differentiated based on structure, function, and intracellular signaling.[109,110] The two receptors most critically involved in the control of feeding behavior and body weight homeostasis are the $5HT_{1B}$ and $5HT_{2C}$ receptors.[111] Recent findings have also implicated $5HT_{2B}$ receptors in the anorectic properties of dexfenfluramine; however, this receptor has been strongly implicated in the cardiopulmonary adverse effects of dexfenfluramine.[112–114] The role of the $5HT_{2B}$ receptor is likely to be a mechanism involved in potentiating 5HT release from serotonergic neurons, but its feasibility as a target for obesity certainly requires further examination.[112]

The $5HT_{1B}$ receptor (classified at one time as the human $5HT_{1D\beta}$ receptor[115,116]) is a G-protein couple receptor (GPCR) that negatively couples to adenylyl cyclase to inhibit cAMP formation. Like receptors of the $5HT_1$ class, the $5HT_{1B}$ receptor has a high affinity for 5HT and is encoded by a gene sequence without introns.[110] Located on nerve terminals, the $5HT_{1B}$ receptor functions as an autoreceptor to inhibit the release of 5HT from serotonergic neurons or as heteroreceptors to inhibit the release of other (nonserotonin) neurotransmitters.[109,110,117] The involvement of the $5HT_{1B}$ receptor in feeding behavior was initially implicated using preferential antagonists with affinity for the receptor, such as (+/−) cyanopindolol and methiothepin, to block the anorectic actions of dexfenfluramine, whereas the selective agonist, CPP94235 (3-(1,2,5,6-tetrahydro-4-pyridyl)-5-propoxypyrrolo[3, 2-b] pyridine), reduced meal size and decreased feeding duration.[118–121] Further evidence for a role in feeding behavior was demonstrated with the generation of the $5HT_{1B}$ receptor knockout mouse. Following administration of fenfluramine (3 or 10 mg/kg), for instance, $5HT_{1B}$ receptor knockout mice were unresponsive to its anorectic actions and demonstrated reduced or no neuronal activation in feeding related brain areas compared with wild types.[122] It also has been reported that $5HT_{1B}$ receptor knockout mice, compared with age-matched wild type mice, have higher body weights and consumed more food and water, but these findings are not consistently reported with $5HT_{1B}$ knockout mice.[122,123]

The actions of the $5HT_{1B}$ receptor in the CNS have been demonstrated to directly influence pathways involved in food intake and body weight homeostasis. Separate populations of neurons in arcuate nucleus (ARC) of the hypothalamus express the orexigenic peptides neuropeptide Y/agouti-related peptide (NPY/AgRP) or the precursor pro-opiomelanocortin (POMC) to the anorectic peptide alpha-melanocyte stimulating hormone (α-MSH). These two groups of neurons are activated or inhibited by other CNS pathways or peripheral circulating factors to control feeding behavior and energy expenditure. For example, the POMC-containing neurons release α-MSH to acts on melanocortin (MC) MC3/MC4 receptors lead to downstream effects that reduce food intake and increase energy expenditure. Reciprocally, increases in food intake and reduction in energy expenditures are demonstrated following activation of adjacent NPY/AgRP neurons. While NPY acts on a distinct set of receptors, AgRP is an endogenous antagonist for MC3/MC4 receptors.[124–127] In a series of experiments it was determined 5 HT_{1B} receptors are expressed on AgRP neurons and 5HT

terminals are in close proximity to ARC neurons that contain AgRP. Furthermore, it was demonstrated that CPP 94235, a selective $5HT_{1B}$ receptor agonist, reduces the membrane potential (ie, hyperpolarizes) of ARC neurons that express NPY/AgRP and reduces the inhibitory inputs on POMC neurons.[128] Moreover, mice with disruptions in the MC4 receptor were unresponsive to the anorectic effects of dexfenfluramine or CPP 94253.[128] Such data strongly suggest that 5HT actions are mediated by the $5HT_{1B}$ receptor signaling to increase the MC4 receptor-mediated melanocortin pathways.

In contrast to the $5HT_{1B}$ receptor, the $5HT_{2C}$ receptor is a GPCR with cellular excitatory activation that leads to the accumulation of inositol phosphates and downstream activation of phospholipase C. Originally classified as the $5HT_{1C}$ receptor based on its binding affinities for 5HT, the receptor was re-classified as $5HT_{2C}$ after gene sequencing revealed it had introns in various coding regions and was structurally and functionally similar to receptors in the $5HT_2$ class.[110] Similar to $5HT_{1B}$, the role of the $5HT_{2C}$ receptor was implicated in feeding by several experiments using preferential and selective agonist and antagonists.[120,129,130] Experiments utilizing $5HT_{2C}$ receptor knockout mice have demonstrated hyperphagia and an obese phenotype.[131–133] These mice also are less responsive to the anorectic properties of dexfenfluramine (3 mg/kg) and preferentially selective agonists.[132,134] It has been shown that the $5HT_{2C}$ receptor mediates the activity of ARC neurons, in a mechanism that is complementary to that of the $5HT_{1B}$ receptor. For instance in the ARC, the $5HT_{2C}$ receptor was also found in up to 80% of POMC neurons and activation of the $5HT_{2C}$ receptor increased the firing rate of POMC neurons. Upstream activation of MC receptors was also needed because dexfenfluramine action can be blocked by antagonism of MC3/MC4 receptors, while the anorectic responses of MTII, an MC3/MC4 receptor agonist, were indistinguishable between wild type and $5HT_{2C}$ receptors knockout mice.[135] Together with the findings for the $5HT_{1B}$ receptor, this suggests that 5HT activates POMC neuron and inhibits NPY/AGRP to reduce the expression of feeding behaviors. Such findings support the pharmacological studies that suggest that the $5HT_{1B}$ and $5HT_{2C}$ receptors reduce food intake by independent mechanisms.[136]

Serotonin has also been implicated in glucose regulation by action at the $5HT_{2C}$ receptor. Early findings with $5HT_{2C}$ receptor knockout mice indicated that these animals had elevated fasted blood glucose and insulin levels and impaired glucose tolerance compared with wild types.[133] Using the preferential, mCPP (m-chlorophenyl-piperazine), or the selective, BVT.X, $5HT_{2C}$ ligands, it was demonstrated that

$5HT_{2C}$ receptor compounds improved glucose homeostasis in diet-induced or mutant obese animals. This was accomplished by using low doses of the compounds, which did not affect food intake. The mechanisms were shown to be mediated by activation of POMC neurons and of downstream activation of MC4 receptors located in the intermediolateral cell nucleus of the spinal cord, suggesting $5HT_{2C}$ receptor agonist alters sympathetic outflow to improve glucose homeostasis.[137] A similar mechanisms of MC4 activation to increase sympathetic outflow is speculated to account for the hyperthermic effects noted with several selective $5HT_{2C}$ receptor agonists, but this has not been experimentally determined.[138,139] Lorcaserin (APD-356), a $5HT_{2C}$ agonist, has not only completed a phase III study to determine effectiveness for the treatment of obesity (BLOOM), but is also undergoing a phase III study for the management of obesity and glucose regulation outcomes in subjects with diabetes mellitus type II (BLOOM-DM).[51] Preliminary findings indicate improvements in fasting blood glucose levels and HbA_{1c} levels in obese diabetic subjects treated with lorcaserin (10 mg twice daily).[140]

Chemistry and related pharmacology of sibutramine and lorcaserin

Sibutramine hydrochloride (BTS 54 524; N-1-(1-[4-chlorophenyl]cyclobutyl)-3-methylbutyl-N,N-dimethylamine hydrochloride monohydrate) is a racemic compound that is structurally similar to other β-phenylethylamine drugs, such as metamphetamine, phentermine, and dexfenfluramine (see Figure 1).[41,141] It is suggested that the chlorine on the 4 position of the phenyl
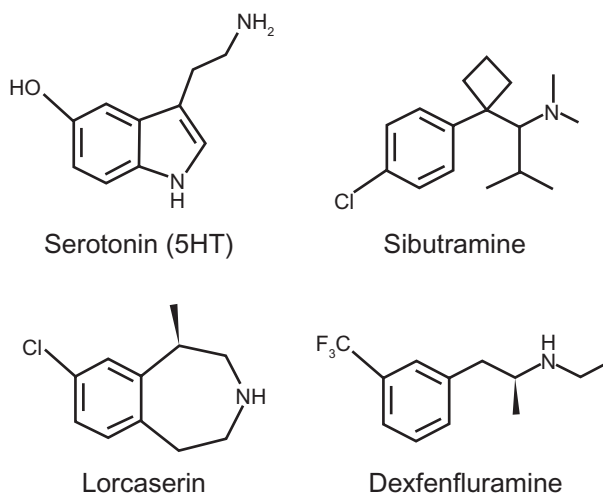
Figure 1 Chemical structure of serotonin (5-hydroxytryptamine; 5HT) and serotonergic compounds that have been used for, or have the potential to treat, obesity.

ring imparts affinity for the serotonin transporter, since it has been demonstrated that a halogenated-substituted phenyl rings is needed for SSRI specificity.[142] In vitro and in vivo data have demonstrated that sibutramine weakly inhibits monoamine uptake in human and rat tissue.[40,143,144] For instance, in vitro inhibition (half maximal inhibitory concentration, IC_{50}) in rat brain tissue of sibutramine is 2.17 µM for NE, 477 µM for 5HT, and 10.8 µM for DA.[143] Sibutramine, though, is metabolized by the liver primarily by the P450 isozyme CYP2B6 into two active metabolites that are more potent monoamine inhibitors than the parent compound.[40,143–145] Sibutramine metabolism takes place by a series of demethylations, first to the primary (M1) metabolite (BTS 54 354; N-1-(1-[4-chlorophenyl] cyclobutyl]-3-methylbutyl-N-methylamine hydrochloride monohydrate) and then to secondary (M2) metabolite (BTS 54 505; N-1-(1-[4-chlorophenyl] cyclobutyl]-3-methylbutylamine hydrochloride monohydrate). The M1 metabolite demonstrated an in vitro inhibition of 0.14 µM for NE, 3.9 µM for 5HT, and 0.16 µM for DA, whereas the M2 metabolite in vitro inhibition was 0.06 µM for NE, 5.1 µM for 5HT, and 0.31 µM for DA.[143] In vivo data indicate the two active metabolites of sibutramine are approximately equipotent for NE and 5HT inhibition with inactive inhibition for DA.[40,143] The active metabolites display a similar degree of inhibition for 5HT as SSRI compounds.[40,83] In humans the elimination half-life of oral administration of sibutramine is 1.1 hours while the half-lives of the active metabolites are much longer, at 14 hours and 16 hours for M1 and M2, respectively.[146] In a recent positron emission tomography study in human subjects (n = 11), it was determined that brain serotonin transporter occupancy was significantly positively correlated ($r^2 = 0.59$, $P = 0.003$) with plasma M2 levels, suggesting that 5HT inhibition is mediated predominately by M2.[147]

Lorcaserin hydrochloride [(1R)-8-chloro-2,3,4,5 tetrahydro-1-methyl-1H-3-benzazepine] is a substituted 3-benzazepine, structurally resembling serotonin and nor-dexfenfluramine (dexfenfluramine metabolite). The compound is synthesized from a substituted phenylethylamine precursor with the chlorine substitution at the 8-position yielding high affinity and selectivity for the $5HT_{2C}$ receptor.[148] In fact, lorcaserin demonstrated ~10-fold higher affinity for the human $5HT_{2C}$ receptor compared with the $5HT_{2A}$ and $5HT_{2B}$ receptors (K_i values of 15 nM, 112 nM, and 174 nM, respectively) and >40-fold higher affinity compared with other 5HT receptors.[149] Using in vitro functional assays examining inositol phosphate accumulation in HEK cells transfected with specific human 5HT receptors,

lorcaserin was 18-fold and 104-fold more potent at the $5HT_{2C}$ than at the $5HT_{2A}$ and $5HT_{2B}$ receptors, respectively.[149] Lorcaserin is metabolized by the liver and the M1 metabolite is a sulfamate, which is inactive with no apparent affinity for any of the $5HT_2$ receptors.[149,150] The elimination half-life of orally administered lorcaserin in humans is 11.1 hours and the half-life of the M1 metabolite is 41.3 hours.[51]

Clinical efficacy studies for sibutramine and lorcaserin

The efficacy of sibutramine for weight loss with diet intervention was tested in several clinical trials in obese subjects. In one double-blind randomized trial, sibutramine at 5 mg or 20 mg once daily was compared with placebo in 3 groups of subjects. Notably, medications were administered over an 8-week period during the holiday season with Thanksgiving falling between week 2 and 3, Christmas between week 6 and 7, and New Year's falling on weeks 7 and 8. Weight loss in the 5 mg sibutramine group (n = 18) was approximately 2% greater than in the placebo group (n = 19), while weight loss in the 20 mg sibutramine group (n = 18) was approximately 4% greater than in placebo.[151] In another multi-center double-blind randomized study using a wider dose range of sibutramine (6 doses between 1 and 30 mg once daily) in a large sample size (n = 1043) for a longer duration (24 weeks) the efficacy of sibutramine was further assessed. There was a dose-dependent relationship for weight loss with sibutramine over the trial. Doses of 1 mg or 5 mg produced an approximately 2% greater weight loss than in those individuals receiving placebo, while doses of 10 mg, 15 mg, 20 mg, and 30 mg produced an approximately 4% to 7% greater weight loss than in placebo. The categorical efficacy with 10 to 30 mg of sibutramine demonstrated that >58% of the population maintained 5% weight loss from baseline and >17% of the population maintained 10% weight loss from baseline over the 24 weeks. After the 24-week treatments there was a single-blind phase "washout" period of 6 weeks during which placebo was administered to all subjects. At the end of this period subjects regained weight, those losing the most during treatment regaining the most weight during the washout period.[152] In a smaller study (n = 173) conducted in the same fashion, after a 6-week washout period from 24 weeks of sibutramine treatment ≥40% of the subjects from the 10- to 30-mg sibutramine group maintained a 5% weight loss from baseline and ≥12% maintained a 10% weight loss from baseline.[153] The greatest amount of weight loss with sibutramine appears to occur during the first 12 weeks of treatment, weight stabilizing or increasing slightly with longer treatment.[17,45,48,152]

In a meta-analysis that examined the data from 10 double-blind randomized control studies (n = 2623) it was revealed that long-term treatment (1 year or more) with sibutramine (10–20 mg once daily) lost 3.7% to 5.0% more weight than individuals receiving placebo. In addition, from the same data set, approximately 35% more individuals receiving sibutramine than subjects receiving placebo maintained a ≥5% weight loss and 18% more than placebo maintained a ≥10% weight loss from baseline. In comparison, data from 13 studies (n = 4948) found that the FDA-approved gastrointestinal lipase inhibitor orlistat produced a weight loss 2.9% to 3.4% greater than in individuals receiving placebo. Proportionally, only approximately 21% more individuals taking orlistat maintained a ≥5% weight loss and approximately 12% maintained a ≥10% weight loss from baseline.[17] Sibutramine was also more effective at reducing body weight directly compared with another serotonergic drug used to treat obesity, dexfenfluramine. This comparison was only with a single dose of both drugs, rather than a range of doses. For this study, 2 groups of obese subjects received either sibutramine (10 mg once daily; n = 112) or dexfenfluramine (15 mg twice daily; n = 114) for 12 weeks. Because there was no placebo control group, weight loss was compared with baseline values within groups. Sibutramine treatment produced a 5.4% weight loss, dexfenfluramine a 4.2% weight loss. Sibutramine was also associated with a greater proportion of subjects maintaining a ≥5% weight loss for the study duration, (46% compared with 34% for dexfenfluramine).[154]

The first double-blind placebo controlled randomized clinical trial for lorcaserin examined the efficacy of three doses (10 mg or 15 mg once daily, 10 mg twice daily) in obese individuals (n = 469) for 12 weeks. For this study no diet or lifestyle intervention strategy was endorsed by the experimenters for the study participants. Lorcaserin produced a dose-dependent reduction in weight, with a 1.4%, 2.3%, and 3.1% greater weight loss than placebo for the 10 mg (once daily), 15 mg (once daily), and 10 mg (twice daily) doses, respectively. The proportion of subjects losing ≥5% body weight from baseline was 12.8% (10 mg once daily), 19.5% (15 mg once daily), and 31.2% (10 mg twice daily).[150] In a multicenter double-blind placebo-controlled randomized clinical trial in a larger number of obese subjects (n = 3182), the efficacy of lorcaserin (10 mg twice daily) was compared with placebo for 1 to 2 years. In addition to including diet and lifestyle interventional strategies, the efficacy of lorcaserin was further assessed by having a randomized portion of subjects in lorcaserin groups reassigned to placebo at the end of year 1

and followed for an additional 1 year. Efficacy, therefore, was assessed in 2 groups, lorcaserin compared with placebo, in year 1 and 3 groups at the end of year 2, lorcaserin compared with placebo compared with lorcaserin–placebo. At the end of year 1, lorcaserin resulted in 4.0% greater weight loss than placebo. A ≥5% weight loss from baseline body weight was achieved in 47.5% of subjects receiving lorcaserin compared with 20.3% receiving placebo. Only 22.6% of the lorcaserin group compared with 7.7% of the placebo maintained ≥10% weight loss from baseline. At the end of year 2, the degree of weight loss was maintained in the group continuing to receive lorcaserin, but weight gain was apparent in the group that was switched to placebo. The group that received lorcaserin–placebo had an identical weight loss to the placebo group by 28 weeks after the reassignment.[50] There are no reported studies, either experimentally or from a meta-analysis, comparing the weight loss efficacy of lorcaserin with other medications for the treatment of obesity.

Safety and tolerability

Medications acting on serotonergic systems have received considerable scrutiny for cardiopulmonary complications because of the increased incidence of primary pulmonary hypertension and valvulopathies associated with earlier obesity medications, fenfluramine and dexfenfluramine. Sibutramine or lorcaserin has not been associated with any reported cases of confirmed pulmonary hypertension. In addition, pulmonary artery pressure has not been demonstrated to change with long-term treatment with either medication.[50,155] Likewise, sibutramine has not been demonstrated to influence cardiac valve function or result in any evident valvulopathies.[156] In a multicenter study examining weight loss efficacy of lorcaserin (see above), the occurrence of valvulopathy at 52 weeks was 2.7% in the subjects receiving lorcaserin (10 mg twice daily) and 2.3% in the placebo group.[50] Preliminary findings at 52 weeks in the BLOOM-DM (n = 604) study for lorcaserin, however, have shown that the incidence of valvulopathies was 2.9% in subjects receiving lorcaserin (10 mg twice daily) and 0.5% in the placebo group.[140] Although the study was not powered to determine a statistical difference in valvulopathies between groups, this almost 6-fold difference in incidence rates certainly raises concerns that likely need to be addressed in future lorcaserin studies. Notwithstanding, other documented safety issues and potential health risks have resulted in the withdrawal of sibutramine and the FDA rejection of lorcaserin.

At the time of FDA approval for sibutramine it was well demonstrated that the drug was associated with increased heart

rate and blood pressure. Initially, the NDA for sibutramine contained 5 doses (5 mg, 10 mg, 15 mg, 20 mg, and 30 mg once daily). Because of the potential dose-dependent cardiovascular risk balanced against the potential benefit for the treatment of obesity, only 3 doses (5 mg, 10 mg, and 15 mg once daily) were approved by the FDA in 1997.[152,157] Sibutramine, though, carries a bold-type warning that blood pressure and heart rate should be monitored in patients receiving the drug and it is contraindicated in individuals with a history of coronary artery disease, congestive heart failure, arrhythmias, or stroke.[47] In a meta-analysis of 7 double-blind randomized control studies examining sibutramine treatment (≥1 year) in obese individuals, the drug was found to increase systolic blood pressure by 1.7 mm Hg, diastolic pressure by 2.4 mm Hg, and resting heart rate by 4.5 bpm compared with placebo.[17] The increase in heart rate and blood pressure is likely to influence cardiovascular function. The recently completed SCOUT trial was conducted in 16 countries, initially enrolling >10,000 subjects, to examine the long-term effects (mean treatment was 3.4 years) of sibutramine on cardiovascular outcomes in overweight and obese subjects. Unlike other clinical studies with sibutramine, eligible subjects had to have a history of cardiovascular disease and/or diabetes mellitus type II with one risk factor for cardiovascular disease. As previously demonstrated, sibutramine was associated with an increase in blood pressure and heart rate; the drug also resulted in an increased rate of nonfatal myocardial infarction (+0.9%) and stroke (+0.7%).[48] The most frequently reported adverse events with sibutramine are dry mouth, insomnia, and constipation. Typically, these events are dose-related, the 15 mg dose having a placebo-subtracted reported frequency of ~20%, ~5%, and ~5%, respectively.[47,152]

The major safety concerns for the lorcaserin (10 mg twice daily) NDA are findings from the carcinogenicity studies in rodents. In particular, 2-year treatment with lorcaserin resulted in a higher combined incidence rate of mammary fibroadenomas and adenocarcinomas in female rats at the 10 mg/kg, 30 mg/kg, and 100 mg/kg compared with vehicle-treated animals. In the male rats at the 30 mg/kg and 100 mg/kg doses, there was also a higher incidence rate of combined mammary tumors and skin benign fibromas. In addition, male rats receiving the 100 mg/kg dose showed an increased incidence rate of astrocytomas, squamous carcinomas, Schwannomas, combined hepatocullular neoplasms, and follicular cell adenomas. Over the 2-year study, the survival rate for both genders of rats was strongly negatively influenced by lorcaserin. In fact, the female

survival rate was 18.4% for 10 mg/kg, 7.7% for 30 mg/kg, and 0% for 100 mg/kg while the vehicle survival rate was 35%. Only the high dose appeared to influence the survival rate of males, which was 5.3% compared with 33.8% of the vehicle group. Necropsy findings confirmed that lorcaserin-induced tumors were associated with the excessive mortality observed with both genders of rats.[51] In a multicenter phase III clinical trial with lorcaserin (10 mg twice daily) treatment (≥1 year) the most frequently subject-reported adverse event was headache (7.2% in lorcaserin compared with 4.3% in placebo). The frequency of headaches in the treated population, as well as other less frequent subject-reported adverse events, had a tendency to decrease with lorcaserin treatment length.[50]

Both sibutramine and lorcaserin appear to be well tolerated by obese subjects. The reported 1-year attrition rate appears to be about 35% for sibutramine and about 45% for lorcaserin.[17,50] Certainly more long-term studies are needed to determine accurate drop-out and nonresponder rates with lorcaserin.

Patient-focused perspectives

Improvements in the quality of life, attitudes, and mood have been demonstrated to occur in overweight or obese patients with weight loss.[158–160] Long-term pharmacotherapy for obesity, including sibutramine and lorcaserin, at doses that are effective at reducing body weight are also associated with improvements in the quality of life and subjective attitude scores.[17,50,161] What is unclear is whether the medications per se or the medication-associated additional weight loss is responsible for the improvement in quality of life and patient attitude. Experiments addressing this issue with sibutramine have had mixed findings. In one study (n = 376), 6-month treatment with sibutramine (10 mg) combined with high-frequency contact with a dietician resulted in greater weight loss than the group receiving sibutramine only. Although quality of life assessment was significantly improved from baseline (ie, before intervention and/or sibutramine), there was no difference in scores between groups.[161] This implies that sibutramine treatment alone had an impact on quality of life not directly related to the degree of weight loss. In contrast, a 12-month study (n = 236) in obese subject with diabetes mellitus type II, treatment with sibutramine (15 mg) produced significantly greater weight loss (7.3%) than the placebo group (2.4%), but did not change health-related quality of life ratings.[162] Sibutramine (15 mg) treatment compared with placebo for 6 months also failed to improve quality of life scores in a population of bulimic patients

(n = 304), but effectively reduced body weight and reduced the severity and frequency of binge eating episodes.[163]

Conclusion

Pharmacotherapy would greatly benefit effective interventional nonsurgical strategies for the management of obesity. As a result of the US and European drug regulatory agencies scrutinizing more closely the approval and the continued use of these medications, the approved drug market for the treatment of obesity has been reduced to one medication, orlistat. Aside from the frequently reported gastrointestinal disturbances and the well-documented modest long-term drug-associated weight loss (~3%), orlistat is relatively safe. The continued approval of orlistat as a prescribed and over-the-counter treatment for obesity demonstrates that the weight-loss efficacy standards of the FDA and European regulatory agencies, 5% drug-associated weight loss and >35% of the treated population losing 5% of body weight, are not a contingent criteria for drug approval. The rationale in orlistat's case is that any safe weight loss is beneficial. In order for drug manufacturers to develop and screen potential medications that receive approval by these agencies, the efficacy guidelines should be clearly revised to include the acceptable margin of drug-associated weight loss. In doing so and under the "any weight loss is beneficial" premise, this is likely to produce pharmacotherapy with reduced efficacy for weight loss, but with fewer and less severe adverse effects.

While drug regulatory agencies examine the risk–benefit analysis of each approved and proposed medication for the treatment of obesity, the unapproved herbal and "natural" dietary supplements consumer market is driven almost entirely by demand. In a study of 35,000 US adults approximately 34% had used dietary supplements for weight loss and approximately 50% of the entire sampled population overestimated the safety and efficacy of these unapproved weight loss supplements.[164] Herbal and dietary supplements reduce appetite and promote weight loss by various mechanisms, some of which are not clearly defined or systematically examined.[165] A number of these supplements (eg, "bitter orange" and other stimulants) promote weight loss by increasing autonomic activity (including increases in resting heart rate and blood pressure).[166,167] Unlike patients that received sibutramine, however, individuals taking dietary supplements are likely not being observed regularly by a health care provider to monitor heart rate and blood pressure. Indeed, the risk of nonfatal myocardial infarction and stroke has not been assessed with herbal remedies and dietary

supplements used to suppress appetite. In the past, the FDA has been reactive, rather than proactive, in regulating diet supplements (eg, ephedra). Taken in the broader context of a demonstrated need and willingness of the consumer market for substances that promote weight loss and the availability of the unregulated alternatives, an argument can be made that *withdrawal* of sibutramine is likely to be more detrimental to the overweight and obese population than the risks associated with sibutramine treatment. Another option not exercised by the FDA and other regulatory agencies is to include a "black box" warning on sibutramine, which appears to be more than reasonable considering the medication has been on the US market for 13 years. The data from the SCOUT clinical trial should be considered "worst case scenario", since the primary outcome event was the incidence of nonfatal myocardial infarction, nonfatal stroke resuscitation after cardiac arrest, and cardiovascular death in subjects with a history of and/or risk factors for cardiovascular disease. What is also unclear is whether the cardiovascular risks associated with sibutramine are long lasting or permanent after cessation of sibutramine treatment. Overall, the rationale of the FDA for the withdrawal of sibutramine seems unwarranted and unnecessary considering the medication, certainly since its approval in 1997, has always been associated with increases in cardiovascular-related adverse effects.

In contrast, the decision of the FDA not to approve lorcaserin pending further data is entirely reasonable. The carcinogenicity findings in rats are too difficult to rectify without a defined mechanism of action, as is the related low survival rate. The low survival rate with lorcaserin is rather surprising considering that calorie restriction with weight loss decreases mortality and leads to a longer life span.[168,169] A recent study re-examining the toxicology data from a 2-year study in rodents (n = 520 mice and n = 520 rats) found that sibutramine had no effect (either positive or negative) on longevity or mortality rate.[170] In the toxicology studies with lorcaserin, on the other hand, the reduced survival rate trends exactly with the dose-dependent drug-induced tumor load, suggesting the cause of the increased mortality is likely a result of lorcaserin carcinogenicity. Further testing is undoubtedly needed to clearly determine whether the tumor burden was caused by lorcaserin or was related to toxicity as a result of the maximum tolerated dose being exceeded.

Therapeutically targeting the serotonergic systems will continue to be a viable approach for the treatment of obesity. This does not mean that other neurotransmitter systems or even combination therapies may prove to be more efficacious in combating obesity with fewer side effects.

Even so, serotonin actions in producing subjective feelings of satiety by modulation of the neural mechanisms of appetite are beneficial not only for reducing and maintaining body weight, but also for controlling eating behavior. Because of the adverse effects associated with nonspecific serotonin drugs, such as dexfenfluramine and sibutramine, the recent direction of drug development has focused on specific receptor agonists. Recent findings with lorcaserin, the $5HT_{2C}$ agonist, need further clarification while a specific $5HT_{1B}$ receptor agonist has yet to be clinically developed. Although the immediate hope for a serotonin-based pharmacotherapy seems remote, given what is known about the serotonin systems and the control of appetite, the long-term probability is that a new serotonin-based therapeutic will emerge. In the short-term, the landscape of obesity pharmacotherapy would be better served by a clarification of reasonable efficacy standards by regulatory agencies.

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