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EXPERT REVIEW

Lorcaserin and the Role of 5-HT$_{2C}$ Agonism in the Treatment of Obesity

Jason C.G. Halford and Joanne A. Harrold

Human Ingestive Behaviour Laboratory, Department of Experimental Psychology, University of Liverpool, Liverpool, United Kingdom. Corresponding author email: j.c.g.halford@liverpool.ac.uk; Web: http://www.liv.ac.uk/obesity

Abstract: The serotonin (5-HT) system is implicated in the control of human appetite expression. However, previous serotonergic approaches to obesity, d-fenfluramine and sibutramine, were withdrawn over issues of safety. Selectively targeting hypothalamic 5-HT$_{2C}$ receptors should reduce the side effects produced by previous treatment. Lorcaserin is the first of a new generation of highly selective 5-HT$_{2C}$ agonists to pass through clinical development. Data is limited but the drug produces significant reductions in energy intake. These appear small compared to those reportedly produced by sibutramine and there is little evidence to indicate behavioural specificity or a clear satiety effect. However, Lorcaserin produces significant placebo-subtracted weight loss over two years of treatment which may be greater than current treatments such as the lipase inhibitor orlistat. Drugs that strengthen satiety may help individuals resist the urge to over-consume and maintain the reduction in energy intake required for successful weight control. However, for a number of patients Lorcaserin proved to be ineffective. For a centrally acting agent the drug's effect on appetite and behaviour remain poorly characterised. In summary, Lorcaserin produces statistically significant effects on energy intake, but the clinical significance of these findings is still debatable. Furthermore, the history of serotonin drugs indicates caution is warranted.

Keywords: Lorcaserin, obesity, appetite, weight control, satiety, serotonin, 5-HT$_{2C}$

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Introduction: Lorcaserin

Lorcaserin ([1R]-8-Chloro-2,3,4,5-terehydro-1-methyl-1H-3-benzazpine) is a selective 5-hydroxytryptamine (5-HT, serotonin)$_{2C}$ receptor agonist developed to specifically target human appetite expression.[1] 5-HT is a monoamine neurotransmitter found both within the gastrointestinal enterochromaffin cells and central serotonergic neurones, and consequently has a wide range of physiological and behavioural functions.[2] 5-HT$_{2C}$ receptors reside within the central nervous system in locations associated with the regulation of eating behaviour and appetite including the hypothalamus. This has been demonstrated in numerous preclinical pharmacological and knock out model studies of behaviour and body weight regulation. The 5-HT$_{2C}$ receptor is thus a validated anti-obesity drug target. However, although 5-HT$_{2C}$ receptors are almost entirely limited to the CNS, they are involved in many differing functions and are not limited to appetite regulation. A number of selective 5-HT$_{2C}$ receptor modulating drugs have the potential to treat a variety of conditions by altering central serotonergic function. These include schizophrenia, addiction, depression and anxiety, Parkinson's disease and Alzheimer's, in addition to obesity.[2]

Lorcaserin is reported to possess a functional selectively for the 5-HT$_{2C}$ receptor over that of the 5-HT$_{2A}$ receptor (15 fold) and 5-HT$_{2B}$ receptor (100 fold) subtypes.[1] This selectivity should ensure it has no functional activity at other receptor types, specifically the cardiovascular side effects including valvulopathy, associated with activity at peripheral 5-HT$_{2B}$ receptors, and vasoconstriction and hallucinogenisis associated with activity at central 5-HT$_{2A}$ receptors. This should provide Lorcaserin with the efficacy of serotonergic anti-obesity drug predecessors, d-fenflurmaine and sibutramine, without accompanying safety concerns that led to their withdrawal. The drug has completed a number of clinical trials in the quest to receive regulatory approval. At least two twelve week phase 2 studies[1,3] and one two year phase 3 study[4] have now been published. However, it is also worth considering the roll of appetite expression in obesity and the history of 5-HT anti-obesity drug development in evaluating the therapeutic potential of Lorcaserin.

Background: Obesity and Eating Behaviour

As our environments have changed adult obesity has become increasing prevalent. From Western society to urban Sub-Africa the impact of adiposity on health outcomes poses one of the most serious changes national health care systems face. The solution, altering energy balance, reducing energy intake and increasing energy expenditure, appears simple. However, successfully losing weight and maintaining that weight loss is challenging for many individuals. Strong biological forces maintain current weight status, while powerful motivational factors promote over-consumption. Caloric restriction increases feelings of deprivation, cravings and pre-occupations with food.[5–7] Therefore, making lasting behavioural changes needed for long term weight control appears a considerable challenge. However, if feelings of appetite could be modified then reductions in caloric intake could be more easily sustained. Appetite suppressing agents, such as drugs that reduce hunger, enhance satiation within a meal and strengthen post meal satiety, could reduce meal intake, and suppress inter-meal consumption, significantly reducing daily caloric intake.[8] Consequently, putative satiety factors involved in energy regulation circuits within the hypothalamus have been key targets for appetite suppressing agents. Such drugs would have to combat the powerful biological forces and environmental factors that promote weight gain.

Recent data demonstrate individual eating behaviour is strongly heritable.[9,10] Behavioural susceptibility to weight gain is in part determined by genetic inheritance. Specific behavioural traits, in conjunction with the over-consumption of a high-fat energy-dense highly palatable diet, drive weight gain.[11,12] The association between traits such as weakened satiety response, eating speed, and enjoyment of food and specific genes may be critical in understanding individual risk.[8] This demonstrates the critical role behavioural phenotypes play in obesity, and why certain individuals struggle to control their weight. The obese have been reported to eat higher fat diets, take larger mouthfuls, chew less, eat faster and fail to slow down during eating, suggesting a deficit in the normal operation of satiation. Food type, gastric capacity, and deficiencies in the physiological and neurological responses to ingestion may promote, or at least allow, overconsumption when palatable energy

dense foods are available.[8] The hedonic experience of eating appears to easily override appetite regulation.[13] However, while strengthening satiety cannot over-ride the enjoyment of food, it could at least moderate the drive to consume. The critical role of eating behaviour in weight gain and the psychological consequences of dieting such as a feeling of deprivation, provide a rational for pharmacotherapy. A powerful drive to consume coupled with an environment of abundance is necessary for over-consumption. However, drugs that satisfy appetite, reducing feeling of hunger and strengthening satiety, should reduce the motivation to eat, even in situations that encourage over-consumption.

Background: Satiety Enhancing Drugs

The pharmacological treatment of obesity has been characterised by a cycle of drug approval and then post marketing withdrawal.[14] Monoamine acting drugs have had a history of use in weight control despite their psychological effects and abuse potential (Table 1). Arguably amphetamines constituted the first class of 'appetite suppressants', their effects on appetite and eating behaviour both being pronounced. Other noradrenergic acting drugs including noradrenalin releasing agents such as phentermine and diethylpropion, and noradrenalin and dopamine releasing agents such as phenylpropanolamine have also been used for weight control, but side effects such as cardiovascular stimulation, insomnia, anxiety and irritability were also associated with these drugs.[15] The weight loss inducing potential of low-dose phentermine is still being examined in combination with topiramate. However, the sympathetic activity induced by noradrenergic drugs remains an issue, particular in patient groups at greater risk of cardiovascular disease. The pre-

Table 1. Monoaminergic drugs used for weight control.

Drug	Action	Effect on human appetite	Side effects
Amphetamine	Catecholamine release and reuptake inhibition (Controlled substance)	Disrupts eating behaviour Suppresses appetite	Abuse potential Hyperactivity Cardiovascular stimulation
Phentermine	Noradrenalin release	Approved as appetite suppressant but effects on eating behaviour uncharacterised	Increase in blood pressure and heart rate Psychological dependence Insomnia and anxiety
Diethylpropion	Noradrenalin release (Controlled substance)	Approved as appetite suppressant but effects on eating behaviour uncharacterised	Stimulant Increase in blood pressure and heart rate Anxiety
Phenylpropanolamine	Noradrenalin and Dopamine releasing	Uncharacterised	Stroke risk Increase in heart rate and blood pressure Anxiety
Fenfluramine	Serotonin release 5-HT receptor stimulation (Withdrawn 1997)	Reduction in appetite Enhanced satiety	Heart value damage Pulmonary hypertension High blood pressure
d-Fenfluramine	Serotonin release and reuptake inhibition (Withdrawn 1997)	Reduction in appetite Enhanced satiety Mediated by 5-HT_{1B} and 5-HT_{2C} receptors	Heart value damage Pulmonary hypertension
Sibutramime	Serotonin and Noradrenalin reuptake inhibition (Withdrawn 2010)	Reduction in appetite Enhance within meal-satiation and satiety in part mediated by 5-HT_{2C} receptors Enhanced thermogenesis may also contribute to weight management	Cardiovascular side effects—increased risk of heart attacks and stroke

cise mechanisms underlying the hypophagic effects of many of these drugs are still poorly understood but these, along with the side effect profiles, are largely attributed to their nor-adrenergic and dopaminergic activity. Compared to serotonergic drugs their effects on human appetite expression also remain poorly characterised and given their side effect profile is it likely they lack behavioural specificity.

In the late 1960s the weight loss inducing potential of the 5-HT releasing agent fenfluramine was noted. This drug, which triggered the release and reduced the reuptake of monoamines, particularly 5-HT, produced distinct and selective effects on rodent feeding behaviour and human appetite.[16,17] These changes where analogous to those produced by ingestion suggesting that fenfluramine strengthened natural appetite suppression. Notably, fenfluramine displayed the behavioural specificity that marked it out amongst appetite suppressants and satiety enhancing agents. This led to further drug development and eventually the licensing of two drugs; the selective 5-HT releasing and re-uptake inhibiting agent d-fenfluramine and the selective nor-adrenergic and serotinergic reuptake inhibiting agent sibutramine. Both drugs produced clinically significant placebo subtracted weight loss of between 3.5 to 4.4 kg in clinical trials[18–20] but ultimately they proved to have problematic side effect profiles of their own. All forms of fenfluramine were withdrawn due to pulmonary hypertension.[21] Sibutramine was also withdrawn due to cardiovascular side effects.[22] Despite eventual failure, in terms of wide spread clinical use serotonin acting drugs remain the most successful class of appetite suppressants to date.[15]

Mechanism of Action: 5-HT$_{2C}$ Agonists, Appetite and Eating Behaviour

The serotonin system has numerous receptors subtypes (5-HT$_{1A}$, 5-HT$_{1B}$, 5-HT$_{1D}$, 5-HT$_{1E}$, 5-HT$_{1F}$, 5-HT$_{2A}$, 5-HT$_{2B}$, 5-HT$_{2C}$, 5-HT$_{3}$, 5-HT$_{4}$, 5-HT$_{5\alpha}$, 5-HT$_{5\beta}$, 5-HT$_{6}$ and 5-HT$_{7}$) of which 5-HT$_{1A}$, 5-HT$_{1B}$, 5-HT$_{2C}$ and 5-HT$_{6}$ have been specific linked to the control of energy intake. Of all these receptor subtypes it is 5-HT$_{2C}$ that is most clearly linked with the expression of satiety. For no other target, peripheral or central, does the wealth of data on the effects of drugs on rodent feeding behaviour or human appetite exist.[15] Blundell[23] proposed that the 5-HT system had not only an inhibitory role in feeding, but also was a key satiety factor. Specifically, he noted that the changes in caloric intake produced by the 5-HT interventions did not disrupt feeding behaviour, but altered it in a manner consistent with the behavioural effects of ingestion. Through behavioural pharmacology the role of the 5-HT$_{2C}$ receptor in satiety became apparent.[24–26] The satiety enhancing effects of serotonergic drugs were blocked in animals treated with 5-HT$_{2C}$ receptor antagonists[15,27,28] and absent in knock-out models lacking functional 5-HT$_{2C}$ receptors.[29] Rodent models of obesity also indicated potent clinical utility of selectively targeting 5-HT$_{2C}$ receptors. Vickers et al[30,31] demonstrated the preferential 5-HT$_{2C}$ receptor agonist Chlorophenylpiperazine—mCPP impeded rodent body weight gain. Similarly multiple doses of Lorcaserin (4.5, 9, 18 and 36 mg/kg) have also been shown to inhibit the development of dietary induced obesity.[32] Heisler and colleagues[33–35] demonstrated the role of downstream hypothalamic melanocortin 4 receptors (MC4R) in mediating 5-HT induced hypophagia. Activation of 5-HT$_{2C}$ receptors produces hypophagia by promoting the release of the endogenous agonist and inhibiting the release of the endogenous antagonist of the MC4R.

The effects of 5-HT drugs on human appetite expression are well documented. mCPP (the 5-HT$_{1B/2C}$ receptor preferential agonist) reliably reduces food intake in humans. Walsh et al[36] demonstrated that female participants dosed orally with mCPP (0.4 mg/kg) reduced their energy intake by 30% (approximately 1000 kJ) an effect associated with a significant reduction in pre-meal hunger ratings. In a subsequent study[37] employing both male and female lean and healthy volunteers food intake was reduced in both women (28%, 1205 kJ) and men (20% reduction, 1219 kJ) an effect again associated with a reduction in hunger ratings prior to the meal. This appetite effect occurred marginally after peak plasma levels of mCPP, and just prior to the lunch. In the obese Sargent et al[38] demonstrated that 14 days treatment with mCPP (20 mg twice daily for women, 25 mg twice daily for men) produced significant weight loss (0.8 kg) an effect again associated with a decrease in hunger ratings. Nonethess, the value of mCPP as a therapeutic option is limited by side effects such as light-headedness, anxiety and nausea[36,37] and transient increases in blood pressure and heart rate[39] indicating effects mediated by other 5-HT receptors subtypes.

Data on drug metabolism or the pharmacokinetic profile of Lorcaserin is unavailable. Additionally, the role of 5-HT_{2C} receptors in Lorcaserins effects on appetite remain to be demonstrated. In fact, the effects of Lorcaserin on eating behavior have not been well characterized until recently. Martin et al[3] examined the effects of 10 mg Lorcaserin on energy balance in 39 overweight and obese men and women during an 8 week, double-blind, placebo-controlled trial. During the initial week, weight maintenance was achieved. Compared to baseline, on day 7 treatment produced a significant reduction in lunch and dinner intake of 286 kcal. This was a larger (but not a significantly different) reduction than observed in the placebo group (147 kcal). As total energy intake in each condition were not provided it is difficult to grasp the magnitude of these effects but this may represent over a 10% reduction in energy intake from baseline and 5% from placebo. On day 8 a 600 kcal deficit weight reducing diet and exercise plan was introduced. Energy intake was measured again on day 56. On this occasion lunch and dinner energy intake was reduced by 470 kcals in the Lorcaserin condition compared to 205 kcal in the placebo. This may represent a difference in energy intake of up to 10% between conditions and proved significant. These effects on appetite were associated with a significant reductions in retrospective measures of 'prospective food consumption' ('how much could you have eaten') but had little effect on retrospective or real time measures of appetite (with the exception of prospective consumption at a single time point). No effects of treatment on blood pressure, respiratory quotient or energy expenditure were observed at day 7 or day 56. Over the 8 weeks treatment Lorcaserin produced a significantly larger reduction in body weight 3.8 kg (3.92%) compared to 2.2 kg (2.19%) in the placebo condition giving a Placebo-Subtracted Weight Loss (PSWL) of 1.6 kg.

These data suggest that Lorcaserin does significantly reduced energy intake, rather than alter energy expenditure, and that this accounts for the significant weight loss. The effects on energy intake are difficult to judge but may be comparatively small in magnitude compared to that produced by drugs such as fenfluramine, d-fenfluramine or sibitramine on ad libitum intake.[15] Sibutramine (10 mg) has been shown to reduce test meal energy intake by up to 16% in obese women.[40] There is also a lack of clear effects on appetite. No main effect or condition by time interaction was observed for any of the real time measures of appetite (hunger, fullness, prospective consumption, desire to eat), only for one measure (prospective consumption) applied retrospectively. However, analysis at single time points did reveal a significant reduction in actual prospective consumption prior to lunch suggesting a reduction in the motivation to eat did precede the significant reduction in lunch intake on day 56. The lack of difference in post meal ratings may reflect a natural adjustment in appetite due to the reduced energy intake.[40] However, none of this confirms the drug was specifically enhancing satiety. A more detailed analysis of pre and within meal changes in eating behaviour may provide a more equivocal characterization of the drug's effects on human appetite expression.[15,40,41]

Efficacy and Safety: 5-HT_{2C} Agonists and Weight Management

Beyond published data on the short term effect of mCPP on body weight over 2 weeks[38] little published data existed on 5-HT_{2C} agonists and body weight until the publication of some of the Lorcaserin trials data. Initial safety dose-escalation data demonstrate no effect of Lorcaserin on heart values or pulmonary artery pressure allowing the drug to move into phase 2 weight loss trials. In Phase 2a trials, a 15 mg dose produced a statistically significant mean weight loss of 1.3 kg (compared to 0.4 kg in the placebo group) over a 28 day treatment period (PSWL = 0.9 kg).[42] Smith et al[1] published the first weight control data. In a randomised, 12 week, placebo-controlled, double-blind, parallel groups design the group compared the effects of Lorcaserin 10 mg q.d., 15 mg q.d., and 10 mg b.i.d., against placebo on body mass in obese men and women. The intention to treat last observation carried forward analysis of weight loss demonstrated the effect of increasing doses of Lorcaserin. Over the 12 weeks, weight loss in the placebo condition was 0.2 kg (0.2%), compared to 1.7 kg in the 10 mg q.d. (1.7%, PSWL = 1.5 kg), 2.2 kg in the 15 mg q.d. (2.2%, PSWL = 2.0 kg), and 3.1 kg in the 10 mg b.i.d. (3.1%, PSWL = 2.9 kg) conditions. The reductions in body mass in all drug conditions were significantly greater than in the placebo. The effects of Lorcaserin on weight loss in 12 week phase 2b trials appears to be no greater than its 'antecedents' d-fenfluramine and sibutramine.[15,43]

In 2006 Lorcaserin entered the first of three phase 3 clinical trials (BLOOM **B**ehavioral modification and **L**orcaserin for **O**verweight and **O**besity **M**anagement) and the results of BLOOM have now been fully published.[4] In the study 3182 patients who were either obese or overweight with at least one comorbidity, were randomly assigned to receive 10 mg of Lorcaserin or placebo b.i.d. In the first year, average weight loss was 5.8 kg in the Lorcaserin group compared with 2.2 kg in the placebo group (PSWL = 3.6 kg) and more than twice the number of Lorcaserin-treated than placebo-treated patients lost >5% of their initial body weight, and twice as many lost >10% (22.6% Lorcaserin versus 7.7% placebo). In the group as a whole, Lorcaserin treatment for 1 year improved levels of fasting glucose, fasting insulin, total cholesterol, LDL cholesterol and triglycerides, and reduced waist circumference. No major increases in mood-related adverse effects were reported and rates of cardiac valvopathy, although slightly higher in year one in the Lorcaserin than the placebo group, were the same between the groups over the 2-year duration of the trial.[4] These data support the notion that selectively targeting the 5-HT_{2C} receptor is a safe treatment option.

As with other phase 3 anti-obesity drug trials the dropout rate was high, and only 55% of the patients in the Lorcaserin group and 45% of the placebo group completed the first year. Moreover, the period of active weight loss lasted 35 weeks on treatment and in the second year modest regain was observed. The weight loss observed across the study indicates that compliance with diet and exercise advice was less than full. Notably, 50% of patients treated with Lorcaserin failed to lose at least 5% of their initial body weight and many of these may have lost nothing or even gained weight.[4,44] Nevertheless, while the extent of weight loss may seem modest, it compares favorably to that produced by the lipase inhibitor orlistat and marginally less than that produced by sibutramine.[18–20]

Patient Perspective

To date Lorcaserin remains to be approved. With the recent withdrawal of sibutramine most patients now have no appetite suppressing agents, satiety enhancing or otherwise, available to them. The only pharmacotherapy option remains the lipase inhibitor Orlistat. There therefore is an unmet need for an effective satiety enhancing agent. Gaining control over appetite should have a clear benefit to those trying to restrict their energy intake. As Lorcaserin clinical data demonstrate even modest reductions in body weight significantly reduce a number of risk factors for ill health. However, the failure of many patients to lose weight in the phase 3 study indicated that many of them failed to adopt the necessary diet and lifestyle required. The high dropout rate also demonstrates that patients readily discontinue treatment. Failure to respond and high attrition are issues in both trials and real world use of all anti-obesity drugs. Even with pharmacotherapy successful weight management still demands considerable behaviour change. For patients the degree of weight loss achieved, even with drug therapy (potentially 5%–10%), is often disappointing. Appetite suppressants have the potential to be a useful adjunct to changing eating behaviour and increasing activity, but it remains unclear who these drugs benefit the most and how.

Concluding Remarks

Drugs which either directly or indirectly stimulate hypothalamic 5-HT_{2C} receptors in rodents produce both changes in the structure of feeding behaviour and reductions in food intake that are consistent with the satiety process. These drugs cause an enhancement of the post-meal satiety potency of fixed caloric loads; reduce pre-meal appetite and food intake at ad libitum meals in both lean and obese humans. A new generation of selective 5-HT_{2C} agonists have been developed and some have passed into clinical testing but only Locaserin has successful completed phase 3 clinical trials proving both effective and potentially safe. Lorcaserin does produce weight loss that is at least comparable in magnitude with some existing and previous pharmacological treatment options. However, the fact that the drug suited some patients very well but for some the agent appeared to have little effect indicated that for only some the treatment successful modified their eating behavior. For many the drug failed to modify responses to the demands of the environment that provoke overconsumption.[44] The nature of this drug's effect on human appetite expression remains to be disclosed and although it reduced energy intake its satiety enhancing effects and more general behavioural specificity remain to be proven.[8]

With regard to safety, cardiovascular events are very rare and remain difficult to detect in phase 3 trials. Moreover, standard adverse event reporting is not sufficient to exclude the possibility of adverse effects of drug on mood or cognition.[43] Nonetheless, the limited clinical data available support the notion that selectively targeting the 5-HT_{2C} receptor is a safe treatment option. However, the behavioral data is preliminary and there remains the real possibility that serious CNS related side-effects may yet be uncovered.

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