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# The effects and safety of lorcaserin, a 5-HT 2C receptor agonist, on a rat model of diet-induced obesity

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## Abstract

Food and Drug Administration (FDA)-,approved for the management of obesity. This study used male Sprague-Dawley rats as a model for diet-induced obesity (DIO) and looked at the effects of a 28-day lorcaserin treatment. The researchers used a reverse translational approach. Cardiovascular function was one of many safety endpoints that were evaluated in an effort to determine the drug's effectiveness. When compared to controls given a vehicle, lorcaserin (1-2 mg/kg SC b.i.d.) considerably decreased percentage body weight growth (10.6% 0.4%), 7.6% 1.2% LOR 1, and 5.4% 0.6% LOR 2. Quantitative magnetic resonance (QMR) imaging measurements of body composition showed that this shift was caused by a deliberate decrease in fat mass. A little impact on caloric consumption was seen. Echocardiography did not show any signs of valvulopathy, namely aortic or mitral valve regurgitation, after the therapy period was over. Over the course of 7 days of therapy, the pharmacokinetics of the current regimen were established; there was no sign of drug accumulation, and plasma concentrations of Cmin and Cmax ranged from 13 to 160 ng/mL (1 mg/kg b.i.d.) and 34 to 264 ng/mL (2 mg/kg b.i.d.), respectively. All things considered, the results of these trials demonstrate that lorcaserin had an impact in the DIO model that was comparable to the one described in clinical trials (i.e., 3.0-5.2 percent body weight change vs. 3.2 percent). Taking into account nonspecific medication effects like malaise, the current results show that the DIO model has fair forward translational utility to assist predict clinical outcomes of a novel chemical entity, highlighting the translational usefulness of obesity models like DIO.

Abbreviations

5-HT, 5-hydroxytryptamine (serotonin); DIO, diet-induced obesity; QMR, quantita- tive magnetic resonance; FDA, Food and Drug Administration; EMA, European medi- cines agency; LDL-C, low-density lipoprotein-cholesterol; SC, subcutaneous; AV, atrioventricular; AUC, area under curve; RBC, red blood cell; WBC, white blood cell; $C_{min}$, minimum drug plasma concentration; $C_{max}$, maximum drug plasma concentra- tion; NA, noradrenaline; NCE, new chemical entity; OGTT, oral glucose tolerance test.

## Introduction

Type 2 diabetes, dyslipidemia, atherosclerosis, hypertension, stroke, specific malignancies, diminished affect, sleep apnea, and osteoarthritis are among the numerous serious clinical conditions that obesity can cause, making it the top preventable cause of death globally (Heal et al. 2009, 2013; Powell et al. 2011). There is a great medical need to treat obesity; at present, almost 35% of individuals in the US are considered obese, and there are few pharmaceutical choices available to help them (Flegel et al. 2010; Powell et al. 2011). Regulatory agencies like the FDA and EMA consider a new drug's ability to treat obesity, but they also look for evidence of improvement in comorbidities like lipid content, glycemia, and blood pressure, in addition to a substantial weight loss (usually 5% from a placebo-corrected baseline) (Heal et al. 2009; Kennett and Clifton 2010).

Extensive research on the effectiveness of dexfenfluramine, a 5-hydroxytryptamine (serotonin) (5-HT) releaser/reuptake inhibitor, has been conducted up to 1997. Heart problems, such as valvulopathol and pulmonary hypertension, led to the withdrawal of

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(dex)fenfluramine (Connolly et al. 1997). With the hope that the mechanisms underlying the anorectic effect might be differentiated from the cardiovascular effects, researchers set out to determine which receptor(s) were responsible for (dex)fenfluramine's therapeutic effectiveness. The finding that the 5-HT2C receptor primarily regulates effects on feeding and body weight supported this prediction (Vick-ers et al. 1999, 2001; Heisler et al. 2002), while the activation of the 5-HT2B receptor is likely to contribute to cardiovascular safety concerns (Hutcheson et al. 2011 for review). This, in conjunction with related studies on the effects of 5-HT systems on the eating process (Blundell and Halford 1998), led to the pursuit of functionally selective 5-HT2C receptor agonists as potential new treatments for obesity. Lorcaserin was the first selective 5-HT2C receptor agonist medication to get FDA approval for the treatment of obesity in 2012. Two big pivotal Phase III studies in "normal" obese people (Smith et al., 2010; Fidler et al., 2011) and one in a group of people with type 2 diabetes (O'Neil et al., 2012) supported approval. The results were nearly identical to those of (dex)fenfluramine, according to a meta-analysis of these studies (Chan et al., 2013), which showed a weight reduction of 3.32 kg when compared to a placebo. Additionally, secondary outcome measures such as blood pressure, total cholesterol, LDL-C, and triglycerides, as well as total cholesterol, showed modest improvements (Chan et al. 2013). Crucially, based on the data collected from clinical studies that have been carried out and are now ongoing in about

Lorcaserin does not seem to generate the cardiac valvulopathy or pulmonary hypertension associated with usage of (dex)fenfluramine, according to a study of 3500 people treated with the authorized 10 mg b.i.d regi-men for at least 1 year (Weissman et al. 2013).

In order to find novel therapies for obesity, animal models are crucial. While many clinical studies on lorcaserin's effects have been published (Smith et al. 2009, 2010; Fidler et al. 2011; O'Neil et al. 2012), there is a dearth of preclinical evidence about the drug's impact on obesity models. In two separate studies, the effects of a 28-day lorcaserin therapy were detailed: one in Levin rats given a high-fat diet (Thomsen et al., 2008) and another in Sprague-Dawley rats given a standard diet (Smith et al., 2008). Although lorcaserin did a good job of reducing food intake and body mass in both studies, the doses used (9-36 mg/kg b.i.d., Smith et al. 2008; 4.5-18 mg/kg b.i.d., Thomsen et al. 2008) were much higher than in other reports (0.3-3 mg/kg; Levin et al. 2011; Higgins et al. 2012, 2013a) and were within a dose-range where side effects like motor changes and malaise could have increased the apparent efficacy. In this diet-induced obesity (DIO) investigation, we aimed to assess the effects of lorcaserin on caloric intake and body mass using dosages that are more in line with previous research (i.e., 1-2 mg/kg SC b.i.d.). In addition, this model investigated the impact of lorcaserin on heart function as measured by echocardiography, plasma lipid profile, and fat-to-lean mass ratio. We also examined the medication plasma levels that the treatment regimen achieved over a 24-hour period. This research set out to compare the results we've gotten from using lorcaserin in other (acute) models of feeding behavior with those from prior clinical trials and to facilitate a back translation to those results (Higgins et al. 2012, 2013a). Enna and Williams (2009) and Day et al. (2011) both emphasize the need of backtranslating clinical data to the analogous animal model for validation and to establish the utility of the model as a guide for efficient transition of an NCE from preclinical to clinical proof-of-concept testing.

Procedures and Supplies

Pets and dwellings

The investigation was conducted with male Sprague-Dawley rats kept in individual solid bottom per-specex cages (dimension: 19″ L 9 10″ D 9 8″ H) purchased from Charles River in St. Constant, Quebec. At the beginning of the trial, the rats were about 7 weeks old and weighed between 170 and 200 grams. Housed

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in a climate-and humidity-controlled facility, the animals followed a 12-hour light-dark cycle (lights on from 5:00 to 17:00 h). Research Diets D12492 was used to provide a high-fat diet to 26 rats.

10 rats were given a conventional diet (LabDiet 5001: 4.07 kcal/g) throughout the trial, whereas the other rats were given a high-calorie diet (5.24 kcal/g). Regarding animal experimentation, all research adhered to the relevant Institutional and Canadian Council on Animal Care (CCAC) standards.

Glucose tolerance test, oral glucose tolerance, and dietary and fluid consumption monitoring
Every day, we weighed the food in the hopper or the water bottle to determine our meal and water intake. We hypothesized that the difference between the two scores represented the amount ingested. At 1:00 p.m., these consumptions and weight were recorded.
Sarstedt Microvette CB300 tubes (Sarstedt Canada Inc., Saint L'eonard, QC, Canada) were used to collect blood from saphenous vein bleeding. A lab in Mississauga, Ontario, Canada called Antech Diagnostics analyzed the levels of cholesterol and triglycerides. A glucometer and Accu-Check Aviva test strips (Accu-Chek Aviva, model type 0353231003; Roche Diagnostics, Mississauga, ON, Canada) were used for in-house blood glucose measurement.
Oral glucose challenges were also administered to the animals at regular intervals. Blood was drawn 30 minutes before and just before an oral glucose load (2 g/kg; 5 mL/kg dosage volume) after an overnight fast. Following the methods previously described, blood was drawn at 15, 30, 60, 120, 180, and 240 minutes and blood glucose levels were measured.

Magnetic resonance imaging for structural health
A 1.5 T magnet (GE Excite MRI system, Milwaukee, WI) and a human quadrature knee coil were used to acquire full body magnetic resonance images while the patient was under mild general anesthesia (Buprenorphine: 0.05-0.1 mg/kg, Midazolam: 1-2 mg/kg, and Dexmedetomide: 0.02-0.05 mg/kg administered intramuscularly). We took pictures of both fat and water, with the water serving as the focal point, and pictures of fat alone, with the fat serving as the focal point. For the purpose of quantifying visceral and subcutaneous fat volumes, the image acquisition settings were a TR of 1500 msec, TE of 10 msec, and a 15 9 15 cm field of view with a 256 9 196 matrix.
Visceral and nonvisceral areas were manually separated from the photos. The liver was added to the area of interest by hand. To separate fat from nonfat tissues, we used ratio images and fat volumes, following the method outlined by Johnson et al. (2008). Then, we used volume averaging correction to get the total fat volume for each compartment. Figure 1 displays several segmented photos as an example. Particle MRS (magnetic resonance spectroscopy) information was also

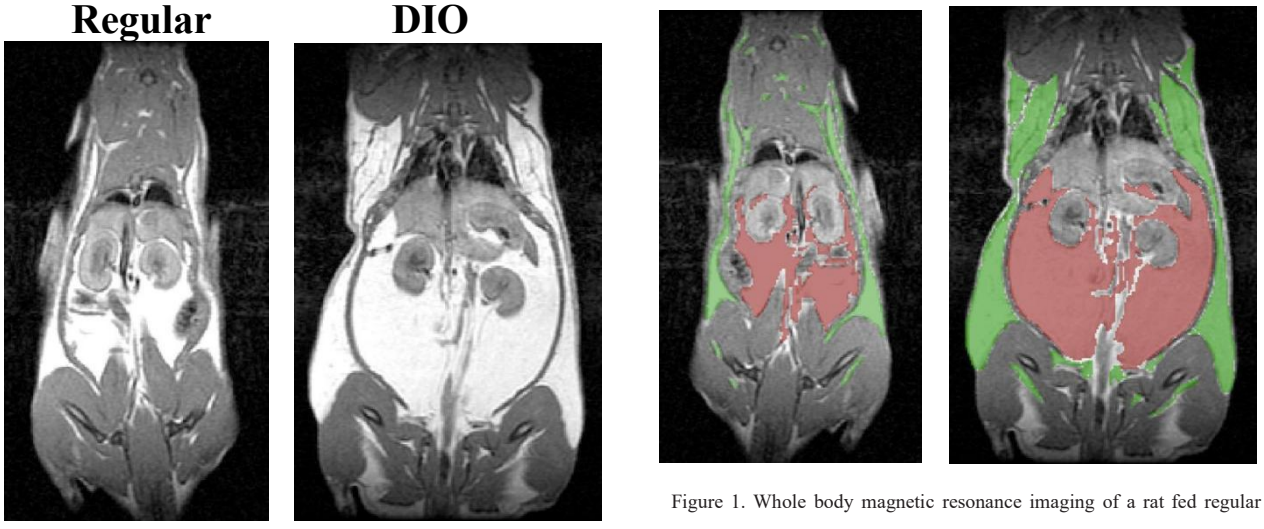


Figure 1. Whole body magnetic resonance imaging of a rat fed regular

diet for 12 weeks and a rat fed high-fat diet (DIO) for the equivalent period. The lower figures show the segmentation of these images between the subcutaneous (green) and visceral (red) fat compartments.

acquired from a 1 cm 9 1 cm 9 1 cm voxel in the liver using a standard PRESS sequence.

### Quantitative magnetic resonance imaging

Subjects were restrained in a Plexiglas tube which was inserted into the magnet bore (Echo MRI-B; Echo Medical Systems, Houston, TX). Data were collected over a 110-sec scan time, and the animals remained fully conscious throughout this period. The average of two such readings were taken for each rat. The maximal size of rat that could be accommodated within the restraining tube, the diameter of which was constrained by the magnet bore was approximately 1 kg. Quantitative magnetic resonance (QMR) uses similar technology to conventional MRI, but rather than an image it provides quantitative body composition data. The QMR technique has been validated in rats against chemical carcass composition (Johnson et al. 2009). It provides estimates of fat and lean mass and free and total body water mass, but unlike Dual energy x-ray absorbtiometry (DEXA), it does not provide data regarding bone mass.

### Echocardiography

General anesthesia was induced and maintained with gaseous isoflurane in oxygen. The left chest wall was close clipped and coupling medium (Aquasonic Ultrasound Gel; CDMV, Montreal, QC) applied. An ultrasound machine (MyLab Alpha, Esaote Canada, Georgetown, ON) with a 7/3 MHz phased array transducer was used for echocardiographic evaluation. A left parasternal approach was used and long- and short-axis views of the heart were captured. Color flow and pulsed Doppler interrogation of the aortic and mitral valves was performed. Images were reviewed off line for evidence of aortic and mitral valve regurgitation.

### Initial characterization of the DIO model

The initial part of this study involved a characterization of the DIO model and the primary endpoints that were integral to the treatment phase of the study. A total of 26 rats were fed a high-fat diet (Research Diets D12492) for 3 months, while a further 10 rats were fed regular diet (LabDiet 5001) for the equivalent period. The 10 ad-lib regular diet rats, served as controls to characterize the DIO model, otherwise data from these animals are not reported in the current study. Body weights and food/ water intakes were measured weekly. At 6 and 12 weeks, additional measures of body composition (QMR), and blood lipid content was measured, and an oral glucose tolerance test (OGTT) was conducted. Because QMR only provided a measure of total fat content, MRI of a single representative rat from each of the two diet groups was conducted at 12 weeks to examine the distribution of fat between the visceral and subcutaneous compartments and to measure fat content of the liver.

### Treatment phase

Following characterization of the DIO rats, all 26 rats fed the high-fat diet for 3 months were allocated into 3 groups balanced for equivalent body weight, food/water intake, and fat mass. Designated groups were vehicle SC
b.i.d ($n$ = 10 rats), lorcaserin 1 mg/kg SC b.i.d ($n$ = 8), and lorcaserin 2 mg/kg SC b.i.d ($n$ = 8). Lorcaserin
hydrochloride (Hangzhou Trylead Chemical Technology Co., Hangzhou, China) was dissolved in saline and administered in a dose volume of 1 ml/kg, Lorcaserin dose was expressed as that of the base.

Initially over a 3-day period, all rats received twice daily SC saline injections for familiarization purposes. Next the 28-day treatment phase began. During this period all rats were allowed ad-lib access to high-fat diet and water. Body weight and food/water intakes were measured daily at approximately 14:00 h. Treatments were administered at approximately 08:00 h and 17:00 h, that is, just prior to dark phase onset. At the completion of the 28-day treatment phase the animals were reassessed for body composition through QMR, and blood was collected for measurement of lipid content, clinical chemistry, and glucose response to an oral glucose load. These studies were completed over 5 days immediately following cessation of drug treatment. At 7 and 14 days post cessation of drug treatment both food/water intake and body weight was recorded to determine these measures at washout.

### Safety phase

Blood was collected for clinical chemistry and cell counts. On day 21 and 22 post cessation of drug treatment, all rats underwent echocardiography. At the completion of the 22 day washout phase, the rats were sacrificed and organ weights were checked for gross appearance and weighed. Cardiac tissue was also taken for histology purposes. The tissue was flushed with saline and suspended in a solution of 10% neutral-buffered formalin. Formalin-fixed hearts were sectioned longitudinally in a plane from the base of the aorta through the apex, and the ventral hemisections were processed and paraffin embedded for light microscopy. Three 4 lm sections taken at 100 lm intervals were stained with hematoxylin and eosin. Additional sections at 100 lm intervals were examined in those cases where original sections did not capture aortic and right and left atrioventricular valves. Histologic examination was carried out by a single board certified pathologist (JDeL), and valves were scored individually on the basis of location and composition of valvular thickenings or other abnormalities.

In a parallel study, a cohort of Sprague–Dawley rats were treated once daily with 5-HT creatinine

sulfate (4 days 75 mg/kg i.p. 9 1 daily, followed by 24 days
60 mg/kg i.p. 9 1 daily) or saline control. This treat-
ment schedule was adopted based on the experimental evidence that it would elicit a cardiac valvulopathy (Gustafsson et al. 2005; Elangbam et al. 2008), that is, a control for the lorcaserin study. At the completion of this treatment phase, all rats underwent echocardiography, followed by sacrifice and removal of cardiac tissue for histol-

percentage lean and fat mass was in the range
80.9 0.4% (lean mass) and 7.6 0.3% (fat mass).

After 6 weeks on the study diets, the DIO group had a significantly greater body weight, fat content (measured either as % fat or g fat), blood cholesterol, and an elevated response to an oral glucose load compared to rats fed regular diet (see Table 1). Since lean mass was not increased, the gain in body weight was essentially due to increased adiposity. Actual food and water consumption was lower compared to rats fed a regular diet. At this stage, there were no group differences in blood glucose (fasted and unfasted) or triglyceride levels.

After 12 weeks, the DIO group showed similar changes to that seen at 6 weeks although with slightly increased magnitude and significance. The only qualitative differ- ence from 6 weeks, was a significant elevation in unfasted blood glucose levels (see Table 1). Some variability was evident across the rats fed the high-fat diet, consistent with individual rats showing differences in susceptibility to obesity (Ghibaudi et al. 2002). For example fat content ranged from 11.6% to 24.0% across all DIO rats, com- pared to 8.4–13.5% in rats fed regular diet. Whole body MRI images were taken of a representative DIO rat and a regular diet control rat after 12 weeks on diet to deter- mine the fat content between the visceral and subcutane- ous compartments (see Fig. 1). Measurement of fat volumes from the visceral compartment were 38,104 $mm^3$ versus 180,470 $mm^3$, and from the subcutaneous com- partment were 116,430 $mm^3$ versus 254,490 $mm^3$ (regular vs. DIO). This translated to a difference in relative fat distributions with the DIO rat having 41.5% fat in the visceral compartment compared to 24.7% in the rat fed regular diet. The MRS data demonstrated a liver fat content of 19.7% and 3.8% between the DIO and regular diet groups respectively.

## Effect of 28-day lorcaserin treatment in the DIO model – efficacy

At baseline, over the 4 pretreatment days prior to the onset of drug treatment, all 3 groups fed the high-fat diet had equivalent body weights ($F_{2,23} = 0.03$, NS), daily food, and water intakes ($F_{2,21} \leq 0.4$, NS) (see "baseline" on Fig. 2A, B, E, and F).

Over the 28 days of treatment, vehicle-treated rats gained approximately 70 g (10.6 0.4%) of body weight (see Fig. 2A and B). Lorcaserin (1–2 mg/kg b.i.d)-treated rats showed a dose-related reduction in body weight gain relative to vehicle-treated controls, such that percentage weight gain in the 1 mg/kg b.i.d group was 7.6 1.2%, and in the 2 mg/kg b.i.d group was 5.4 0.6%. Overall
analysis of the 28 days of treatment revealed a significant treatment 9 days interaction both on body weight ($F_{54,644} = 6.2$, $P < 0.01$) and percentage body weight change ($F_{54,644} = 6.4$, $P < 0.01$). By treatment day 12, the percentage body weight change was significantly different between VEH and 2 mg/kg LOR groups and remained so for the duration of this treatment. On no days were any significant group differences evident between Veh and 1 mg/kg LOR groups (see Fig. 2A and B).

Daily food intake was reduced by lorcaserin treatment, although the magnitude of this effect was small and essentially confined to the 2 mg/kg dose (see Fig. 2E). The effect of lorcaserin on cumulative food intake was affected in a time-dependent manner over the 28-day treatment period (treatment: $F_{2,23} = 4.1$; $P < 0.05$; treatment 9 day: $F_{56,644} = 2.7$; $P < 0.01$). To examine the time dependency, a separate analysis was conducted to examine average intake by week (Fig. 2E inset). A main effect of week ($F_{3,69} = 17.7$, $P < 0.01$) was found, although treatment narrowly missed significance ($F_{2,23} = 2.8$; $P = 0.08$). The clearest effect of lorcaserin on food intake was evident during the first week, and confining the analysis to week 1 revealed a main effect of lorcas- erin ($F_{2,23} = 5.4$, $P = 0.01$) (see Fig. 2E inset). Analysis of weeks 2, 3, or 4 failed to show a main effect of lorcaserin ($F_{2,23} \leq 1.9$, NS). Equivalent analyses on water intake identified no main effect of treatment ($F_{2,23} = 1.8$, NS) although a significant treatment x day interaction was found ($F_{56,644} = 1.6$, $P < 0.01$). Again this seemed to reflect a predominant effect of lorcaserin treatment to reduce intake during week 1 (see Fig. 2F).

On body composition, lorcaserin produced a significant decrease in fat mass measured either in grams ($F_{2,23} = 5.6$; $P = 0.01$), or as percent change ($F_{2,23} = 5.0$; $P < 0.05$) (see Fig. 2C and D). In each case only the 2 mg/kg LOR group was significantly different to vehicle. In contrast there was no effect of lorcaserin on lean mass (grams: $F_{2,23} = 0.2$, NS; % change: $F_{2,23} = 0.2$, NS). Total mass was also reduced (grams: $F_{2,23} = 4.5$, $P < 0.05$; % change: $F_{2,23} = 4.7$, $P = 0.01$) (see Fig. 2C and D).

Lorcaserin modestly affected plasma lipid levels (see Table 2). Although there was no main effect of treatment on either blood cholesterol, triglyceride, or glucose (fasted) levels including pre- versus posttreatment as a factor (treatment: $F_{2,23} < 0.5$, NS; treatment 9 time: $F_{2,23} < 1.8$, NS), restricting comparisons to day 28 identified a significant lowering of cholesterol by lorcaserin compared to vehicle pretreatment (see Table 2). All
groups had equivalent cholesterol levels at baseline.

## Effect of 28-day lorcaserin treatment in the DIO model – safety

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At the completion of 28-day treatment with lorcaserin at 1 and 2 mg/kg, blood was collected for analysis of total

Figure 2. (A) Effect of vehicle or lorcaserin (1–2 mg/kg SC b.i.d.) on body weight measured over 3 days baseline (BL), 28-day treatment, and 2 weeks washout phase (WO). (B) represents the conversion of body weight, to percent change compared to pretreatment baseline. This conversion shows that at 2 mg/kg b.i.d., lorcaserin reduced % body weight by approximately 5.2% compared to vehicle controls. (C) Measurement of body composition, that is, fat or lean mass, was made using QMR and a difference value was determined between a reading made 6 days before treatment phase, and 1 day after the treatment phase. (D) represents the conversion of body composition, to percent change compared to pretreatment baseline. (E) Cumulative food, and (F) water intake, measured over the baseline, 28-day treatment and, washout phase. In figure (E) and (F) the inset shows the daily intakes averaged for each animal by week. $N$ = 8–10 rats per group, all rats fed high-fat diet (Research Diet D12492; 5.24 kcal/g). $*P < 0.05$ versus vehicle.

Characterization of lorcaserin pharmacokinetics in the DIO model

There were no lor-caserin levels in the blood plasma that could be detected before the trial began. Table 4 and Figure 4 show that the medication Cmax and AUC0-8h increased proportionally with dosage after acute administration of lor-caserin (1-2 mg/kg SC). On DAY 1, the levels of Cmin and Cmax were determined to be 13-160 ng/mL (1 mg/kg) and 34-264 ng/mL (2 mg/kg), respectively. These values were consistent across the AM and PM doses.

The pharmacokinetic parameters showed no significant change after 7 days of dosing. For instance, there was no change in the lorcaserin AUC0-8 h measured AM or PM between day 1 and day 7 (refer to Table 4 and Fig. 4), suggesting that there was no evidence of drug accumulation or autoinduction during the 7-day treatment period. So, during the course of a week of therapy, the drug exposure at both lorcaserin dosages was stable.

Discussion

The polygenic and heterogeneous causal nature of obesity is better reflected by obesity models like the DIO rat, which have been found to have advantages over monogenetic models for the study of medications to treat obesity (Halford et al., 2010; Vickers et al., 2011; Nilsson et al., 2012; Fellman et al., 2013). According to previous studies (Ghibaudi et al., 2002; Buettner et al., 2006), male Sprague-Dawley rats were utilized as part of the DIO model in this investigation. The rats were given a high-fat diet (D12492, Research Diet) that included soy-bean oil and lard as fat sources. As a result, animals fed the D12492 diet for 12 weeks gained weight from adiposity, mostly in the visceral fat compartment; dyslipidemia, or high cholesterol; glucose intolerance after oral loading; and probably hepatic steatosis. Taken together, these findings suggest that the DIO technique has promise as a representation of real obesity (Vickers et al. 2011;

emphasised the predictive power of these models by re-evaluating the preclinical model in light of the clinical results of pharmaceutical treatments. Such investigations are clearly valuable in light of the ongoing clinical failure of NCEs caused by insufficient effectiveness prediction (Kola and Landis 2004; Enna and Williams 2009; Hay et al. 2014). The predictive validity of the DIO model was recently brought to light by Vickers et al. (2011), who demonstrated that the magnitude of body weight change generated by anorectic medications of various pharmacological classes in a 28-day DIO model seems to align well with clinical results. This dataset is enhanced by the present investigation. Collectively, these DIO studies demonstrate that lorcaserin causes a small but noticeable change in the body, which is an improvement over orlistat but still lower than the changes seen with topiramate/phentermine (Qnexa®), rimo-nibant, the CB1 antagonist, and sibutramine, the mixed NA/5-HT reuptake inhibitor (Kennett and Clifton 2010; Heal et al. 2013). The current DIO rat research found a lesser impact size of lorcaserin on body weight reduction compared to prior investigations (Smith et al., 2008; Thomsen et al. 2008). However, it is possible that nausea and malaise contributed to the weight shift recorded in the later studies. Specifically at supratherapeutic levels, lorcaserin has been shown to cause nausea and malaise as main adverse effects in clinical trials (Chan et al., 2013; Schram et al., 2011). Predicting the clinical results of an NCE using the DIO model is possible, provided that clinically undesirable factors like sedation and

malaise are adequately considered in relation to the decrease in body weight increase.

Perhaps other 5-HT2C receptor agonists have better tolerability profiles by reducing adverse effects like nausea and malaise (Higgins et al. 2013a, b) or are more functionally selective at the 5-HT2C receptor (Urban et al. 2007), but lorcaserin's 3.2% weight change seems to be the optimal effect size for this drug. With the DIO model's apparent predictive power, this ought to be testable, provided that safety and tolerability concerns are adequately addressed. Finally, it is worth mentioning that the current studies did not aim to determine the behavioral mechanisms behind lorcaserin's anorectic effect. However, it would be beneficial to understand lorcaserin's antiobesity mechanisms in order to identify the populations of obese patients who are most affected by the anorectic effects of 5-HT2C receptor agonists, such as lorcaserin.

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