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Effects of lorcaserin (Belviq®) on nicotine- and food-maintained responding in non-human primates

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Abstract

Background—Accumulating evidence suggests that the FDA-approved serotonin 5HT_{2C} receptor agonist, lorcaserin (Belviq®), may be a promising candidate for the management of substance use disorders, including nicotine addiction. The present study was conducted to determine the efficacy and selectivity of acute or continuous lorcaserin treatment for decreasing the reinforcing effects of nicotine in a primate species.

Methods—Adult rhesus monkeys ($n=4$) with a history of nicotine self-administration (>2 years) responded for injections of nicotine (0.32–100 $\mu\text{g/kg}$ IV) or food pellets under a fixed-ratio schedule of reinforcement during daily 100-min sessions. When responding was stable, lorcaserin was administered either as an acute pretreatment (0.1–1.0 mg/kg, IM) or by continuous infusion (0.1 mg/kg/hr, SC for 3–5 days). Daily activity patterns were also monitored immediately following experimental sessions.

Results—Results indicate that acute lorcaserin pretreatment produced significant and dose-dependent decreases in nicotine-maintained responding across a >100 -fold range of self-administered nicotine doses. Continuous lorcaserin treatment decreased intake of 10 $\mu\text{g/kg/inj}$ nicotine to about 50% of baseline values. Food-maintained responding was only moderately decreased in 3 of 4 subjects after acute administration and unaffected in all subjects during

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Author Disclosures

Contributors

DSJ designed study, performed research, performed data analysis, wrote the manuscript. CEB performed research. MRK assisted with data analysis. JB designed study and assisted with manuscript preparation. SJK designed study, performed research, performed data analysis, wrote and edited the manuscript. All authors approve of the final version of the manuscript.

Conflict of Interest

No conflicts declared.

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continuous treatment. Daily activity also was significantly decreased—to 50% of control values—following experimental sessions in which acute lorcaserin was administered.

Conclusions—These data indicate that lorcaserin reduces IV self-administration of nicotine at a dose that decreases motoric activity but less consistently disrupts food-maintained responding. Further research into lorcaserin's potential utility for the management of nicotine dependence is warranted.

Keywords

serotonin; nicotine; lorcaserin; self-administration; pharmacotherapy; smoking cessation

1. Introduction

Nicotine use disorder continues to be one of the most prominent forms of substance use in the United States (American Society for Addiction Medicine, 2008). Nicotine use via tobacco products accounts for over 5 million deaths annually and billions of dollars in economic cost to society (World Health Organization, 2008). Though several pharmacotherapies have been FDA-approved for the management of nicotine use disorder (e.g., varenicline, bupropion, nicotine replacement therapy (NRT)), these medications are not effective for all smoking populations (Dhalaria et al., 2012; Hajek et al., 2009) and new medication approaches with novel mechanisms of action are urgently needed (Cahill et al., 2016; Yilmazel Ucar et al., 2014 for review).

Medication approaches for the development of smoking cessation aids have primarily, though not exclusively, aimed to modulate the direct actions of nicotine through nicotinic acetylcholine receptors (e.g., mecamylamine, varenicline, NRT). Another approach that has received less attention involves the modulation of neural systems that more generally mediate reward processes and, thereby, the reinforcing effects of nicotine. Although previous research has focused predominantly on the role of dopaminergic (DA) neurotransmission in the ventral striatum and other brain reward pathways (Brazell et al., 1990; Di Chiara, 2000; Hernandez and Hoebel, 1988; Ritz et al., 1987; Volkow et al., 2002a; 2002b), considerable evidence now shows that the serotonergic system (5-HT) and, more specifically, the 5-HT_{2C} receptor subtype, plays a key role in mediating dopamine release in the mesolimbic system (Bubar and Cunningham, 2008). For example, selective 5-HT_{2C} agonists such as Ro 60-0175 have been shown to attenuate the behavioral and neurochemical effects of drugs of abuse (Manvich et al., 2012; Howell and Cunningham, 2015), including cocaine-induced increases in locomotor activity in rodents (Fletcher et al., 2004) and dopamine efflux in the nucleus accumbens in rats and squirrel monkeys (Navailles et al., 2007; Manvich et al., 2012). Taken together, these data suggest that the 5-HT_{2C} receptor may be a potential target for the development of smoking cessation aids (Fletcher et al., 2012; Higgins et al., 2013).

Lorcaserin (Belviq®) is a 5-HT_{2C} receptor agonist ($K_i=15$ nM), with lesser affinity for 5-HT_{2A} and 5-HT_{2B} receptors ($K_i=112$ nM and 174 nM, respectively; Thomsen et al., 2008), and is approved by the FDA for clinical use as a weight-loss medication. Clinical studies have indicated that lorcaserin is well-tolerated (Smith et al., 2008; 2010) and, in a study with recreational drug users, therapeutic doses of lorcaserin primarily elicited subjective ratings

of “drug like/dislike” that did not differ from placebo (Shram et al., 2011). Further, subjects reported significant increases in ratings of “dislike” following supratherapeutic doses of lorcaserin, suggesting low abuse liability (Shram et al., 2011). In preclinical studies in rats, lorcaserin, like other 5-HT_{2C} agonists, has been shown to dose-dependently decrease responding for intravenous (IV) nicotine after acute administration or during a 10-day treatment regimen (Levin et al., 2011). Additionally, lorcaserin reduced cue-induced reinstatement of extinguished IV nicotine self-administration in rats (Higgins et al., 2012), suggesting potential utility for the reduction of relapse to smoking behavior. These findings have prompted recent Phase II clinical trials with lorcaserin as a stand-alone aid for smoking cessation (Shanahan et al., 2016) or as adjunct pharmacotherapy in combination with the nicotine patch (www.clinicaltrials.gov: NCT02906644).

Notwithstanding previous studies of lorcaserin in laboratory animals, its effectiveness in reducing IV nicotine self-administration has not yet been explored in non-human primates. In addition to observed differences in the serotonergic system between primates and rodents (see Weerts et al., 2007 for review), such studies are valuable because they provide the opportunity to analyze the effectiveness of candidate medications in subjects with long histories of IV drug self-administration. In this regard, unsuccessful smoking cessation attempts have been positively associated with amount of daily tobacco use (Breslau and Johnson, 2000; Hymowitz et al., 1997) and previous laboratory studies similarly have shown that the reinforcing effects and intake of nicotine in non-human primates may increase with long-term nicotine self-administration (Kohut and Bergman, 2016). Thus, determination of the effects of lorcaserin in subjects with extended histories of nicotine self-administration can improve the evaluation of its potential clinical value. With this in mind, the present study was conducted to assess the extent to which acute or continuous lorcaserin treatment may attenuate the reinforcing effects of IV nicotine in rhesus monkeys with an extensive history of IV nicotine self-administration (i.e., >2 years). As lorcaserin has been reported to also alter other types of behavior (e.g., food consumption and activity; Collins et al., 2016; Higgins et al., 2012), we also assessed its effects on food-maintained behavior and daily activity levels. Results indicate that doses of lorcaserin that markedly decreased IV nicotine self-administration produced less pronounced effects on food-maintained responding, providing preclinical support for the continued evaluation of lorcaserin’s pharmacotherapeutic utility in smoking cessation programs.

2. Methods

2.1 Subjects

Four adult rhesus macaques (*Macaca mulatta*; 3 male and 1 female), weighing between 5 and 9 kg, served as subjects. Monkeys were housed within a temperature- and humidity-controlled vivarium in well-ventilated stainless-steel chambers (64 × 64 × 79 cm) with olfactory, auditory, and visual exposure to conspecifics. All subjects had self-administered nicotine for two to three years prior to the initiation of the present studies (Kohut and Bergman, 2016) with a range of 254–344 mg/kg of cumulative self-administered nicotine at the start of the study (see Table 1). Monkeys were provided with a high protein chow (Purina Monkey Chow 5045, Brentwood, MO), fresh fruit and vegetables, and the opportunity to

earn food pellets during daily operant sessions; water was freely available. A 12-hr light-dark cycle was in effect (lights on 0700 – 1900 hours) throughout the study. Animal maintenance and husbandry were conducted in accordance with the guidelines issued by the Institute of Laboratory Animal Resources (ILAR-NRC, 2010) and the NIH Office of Laboratory Animal Welfare (OLAW). All protocols used in these studies were fully approved by the Institutional Animal Care and Use Committee at McLean Hospital.

2.2 Apparatus

Each subject was prepared with a chronic indwelling catheter under aseptic conditions that connected to an intravenous access port (Access Technologies, Skokie, IL) placed subcutaneously (SC) in the mid-lumbar region. In acute studies, subject also wore a custom-designed primate jacket (Lomir, Quebec, Canada) that protected the port and housed a commercially available 3-way accelerometer (FitBit Zip, FitBit, San Francisco, CA). The accelerometer has been shown to produce reliable activity data in human studies and was used here to measure daily activity counts (Imboden et al., 2017). During daily experimental sessions, the subject sat in a standard primate chair (Primate Products, Immokalee, FL or PLAS Lab Model 515-SASR, Lansing, MI) within a custom-built sound-attenuating chamber and faced an operant response panel containing response keys and lights that could be illuminated to serve as visual stimuli (SuperBright LEDs, Fairchild Semiconductor, San Jose, CA). Each chamber also was equipped with an external pellet dispenser (Gerbrands Model G5210, Arlington, MA) for delivery of 1-g banana-flavored food pellets (1-g; Formula 4TUR, Purina Mills Test Diet, Richmond, IN) and a syringe pump (Harvard Apparatus, Braintree, MA) for intravenous drug delivery. The response panel and food receptacle were mounted at a height and position that was easily within reach of the seated subject. All experimental events were programmed on a desktop PC connected to the chambers via a Med Associates interface (Georgia, VT).

2.3 Self-Administration Procedures

2.3.1 Self-Administration Training—Monkeys responded during daily 100-min sessions that began at hour 0900-1000 and consisted of components of food and nicotine availability. Monkeys were promptly returned to the home-cage after experimental sessions (hour 1100–1200). During the first component (food-maintained responding), red lights illuminated the center response key, signaling the availability of 1-g banana-flavored food pellets for 10-min. During the second component (IV self-administration), green lights illuminated the center response key, signaling the availability of IV injections of nicotine or saline for 90-min. Initially, both food pellets and IV injections of 10 µg/kg/inj were available under a fixed ratio (FR) 1; time-out (TO) 10-s schedule of reinforcement. The response requirement was then increased over several sessions to 3 in one subject (FR3; TO 10-s) and to 5 in three subjects (FR5; TO 10-s). These schedule parameters were selected to maximize responding for nicotine in individual subjects. Completion of the response requirement triggered reinforcer delivery and the concurrent 1-sec illumination of a light below the response key and initiated the 10-s TO period. During TO periods, all lights were extinguished and responding had no scheduled consequences. To limit the influence of satiety, no more than 50 food pellets could be earned during the session (see also Kohut and Bergman, 2016); the number of nicotine injections was not similarly restricted. If the

maximum number of food pellets was obtained prior to the end of the food component, all lights were extinguished and responding had no programmed consequences for the remainder of the component.

2.3.2 Nicotine Dose-Effect Determinations—Test sessions began when responding for nicotine (10 µg/kg/inj) was stable across sessions. Stability was achieved when the number of drug injections/session was within 20% of the mean for at least two of three consecutive days. Initially, saline or each of several doses of nicotine was available for IV self-administration in 2–3 consecutive sessions or until responding was stable (maximum 5 consecutive sessions at a single dose). Doses of nicotine were presented in an irregular order that varied across subjects; complete dose–effect curves for self-administration of IV nicotine were determined in all subjects. Subsequently, monkeys were returned to the maintenance-dose condition, and the effects of lorcaserin treatment were evaluated.

2.3.3 Lorcaserin Pretreatment—Dose-ranging studies were initially conducted to determine the dose of lorcaserin (0.1–1.0 mg/kg) that decreased self-administration of the maintenance dose of nicotine (10 µg/kg/inj) to at least 50% of control values. Results indicated that 1.0 mg/kg of lorcaserin produced substantive decreases in IV nicotine self-administration without decreasing food-maintained behavior to similar levels. Consequently, acute pretreatment with 1.0 mg/kg lorcaserin was studied further by varying the unit dose of self-administered nicotine in an irregular manner in each subject. In this manner, the acute effects of 1.0 mg/kg lorcaserin on the full range of self-administered doses of nicotine (0.32–100 µg/kg/inj) were determined in each subject. Test sessions with lorcaserin typically occurred on the second or third day of access to a given dose of nicotine to ensure stable levels of nicotine self-administration. All test data with lorcaserin pretreatment reflect single determinations in each individual.

2.3.4 Continuous Lorcaserin—In studies of continuous treatment with lorcaserin, all subjects responded for nicotine and food pellets under an FR1; TO 10-s schedule. After nicotine self-administration was stable for each subject (i.e., when drug responding was within 20% of the mean for two of three consecutive days), osmotic minipumps were implanted contralateral to vascular ports under ketamine anesthesia (10 mg/kg) and were prepared to deliver 0.1 mg/kg/hr lorcaserin. Pumps were implanted approximately 4-hr after the final baseline nicotine self-administration session and the behavioral session corresponding to Day 1 of continuous treatment began approximately 17-hr later. Subjects continued daily 100-min self-administration sessions with the maintenance dose of 10 µg/kg/inj nicotine for the next 3–5 consecutive days. Mini-pumps were removed under ketamine anesthesia (10 mg/kg) approximately 4-hours after the final chronic treatment session. Subjects then continued to self-administer the maintenance dose of nicotine for at least two more days.

2.4 Data Analysis

The primary dependent variable from each daily session was the number of reinforcement deliveries (nicotine injections and food pellets). Baseline nicotine dose–effect curves were determined using self-administration data from the day prior to lorcaserin tests (i.e., when

saline treatment was administered). Activity data from the corresponding self-administration test sessions described above were downloaded from FitBit servers in one-minute epochs using custom software and processed with scripts written in Python (Version 2.7.11). Data was then organized as total activity counts for 3-hr, 4 – 10-hr, and on the day following lorcaserin test sessions (12 – 36-hr). Control activity data were determined by averaging activity counts from the 2 – 3 sessions nearest to each lorcaserin test during which saline or a given dose of nicotine was available for IV self-administration. Activity data were transformed to a percent of control by comparing counts to saline activity (for nicotine alone control) or to the corresponding nicotine dose (for lorcaserin treatment).

One-way analysis of variance (ANOVA) was used to determine effects of lorcaserin on 10 µg/kg/inj nicotine and food-maintained responding in dose-ranging studies. Two-way ANOVA for repeated measures (RM) with factors of Treatment (saline or 1.0 mg/kg lorcaserin) and Nicotine Dose (1.0 – 100 µg/kg) was used to determine the effects of lorcaserin on the number of IV injections and food pellet deliveries per session. Two-way RM ANOVA with factors of Time (3, 4 – 10-hr, and 12 – 36-hr post-lorcaserin treatment) and Nicotine Dose (0.32 – 100 µg/kg) were used to evaluate changes in daily activity following nicotine self-administration alone or following lorcaserin pretreatment. All statistical analyses were performed using GraphPad Prism for Mac (Version 6, San Diego, CA) with a criterion of significance of $p < .05$ and were followed by post hoc Dunnett or Bonferroni comparisons to control or saline conditions, where appropriate.

2.5 Drugs

(–)-Nicotine hydrogen tartrate was obtained commercially (Wako Pharmaceuticals) and solubilized in sterile water buffered with 1N NaOH to achieve a pH of 5.5–6.0. Each unit dose was delivered at an injection speed of 0.1 ml/sec and volume per injection was adjusted to deliver the range of unit doses of nicotine in accordance with previously published methods (Kohut and Bergman, 2016; Mello et al., 2014). Lorcaserin was obtained from Cayman Chemical (Ann Arbor, MI) and dissolved in saline vehicle. Acute lorcaserin was administered intramuscularly (IM) 15-min before the onset of behavioral sessions. IV nicotine was filtered with a syringe-driven 0.22-micron filter (Millipore Corporation, Billerica, MA). Nicotine doses are expressed as the base and lorcaserin doses are expressed as the salt.

3. Results

3.1 Effects of Acute Lorcaserin on Food- and Nicotine-Maintained Responding

Data are presented as mean $\pm$ SEM for the group. During dose-ranging studies, subjects earned an average of 47 ± 10 nicotine injections (10.0 µg/kg/inj) and 50 ± 0 food pellets. Acute treatment with lorcaserin produced dose-dependent decreases in responding maintained by 10.0 µg/kg/inj nicotine ($F(3,9)=7.01$, $p<.01$) and by food pellets ($F(3,9)=5.30$, $p<.05$; see Figure 1). Doses of 0.1 and 0.32 mg/kg lorcaserin produced no significant effect on nicotine self-administration or food-maintained responding (p 's $>.05$). However, 1.0 mg/kg lorcaserin significantly decreased responding for 10.0 µg/kg/inj nicotine to 35%, and food pellets to 83%, of control values (both p 's $<.05$; Figure 1).

Nicotine self-administration described an inverted U-shaped function across the range of doses studied (0.32 – 100 µg/kg/inj) for each subject with 1.0 µg/kg/inj nicotine producing peak responding at the group level (121 injections $\pm$ 48; see Figure 2). Pretreatment with 1.0 mg/kg lorcaserin shifted the nicotine dose-effect curve downward in all subjects and the ANOVA found significant main effects of Dose ($F(5,15)=5.04$, $p<.01$) and Treatment ($F(1,3)=13.14$, $p=.03$), as well as a significant Dose X Treatment interaction ($F(5,15)=2.963$, $p=.047$). Post-hoc comparisons indicated that self-administration of unit doses of 1.0 and 3.2 µg/kg/inj nicotine, which produced significantly higher levels of responding when compared to saline under baseline conditions ($p's<.05$), was reduced to levels observed during saline availability following pretreatment with 1.0 mg/kg lorcaserin ($p>.05$ from saline, all doses). Food-maintained responding during saline sessions was highly stable (Range: 48–50 pellets per session; Table 2) and grouped data shows that 1.0 mg/kg lorcaserin alone did not significantly decrease food-maintained responding (all $F's<3.5$, $p's>.16$; see Table 2). Inspection of individual data revealed that effects on food-maintained responding varied across subjects: one subject typically responded for fewer than 15 food pellets after lorcaserin treatment whereas three subjects responded for 36–50 food pellets.

3.2 Effects of acute lorcaserin on daily activity

Daily activity data from three subjects were analyzed by transforming raw activity counts to percent of control values and are presented as the group mean $\pm$ SEM in Figure 3. Data from the fourth subject were excluded from analysis due to malfunction of the accelerometer. Nicotine self-administration did not affect daily activity levels at any Dose ($F(6,12)=0.45$, $p=.83$) or Time ($F(1,2)=0.75$, $p=.48$) and there was no significant Dose X Time interaction ($F(6,12)=0.78$, $p=.60$) when compared with IV saline control values; see Table 3. Nicotine data were subsequently collapsed across time points (Overall Mean: 97% of control $\pm$ 16% SEM) to use as the nicotine control value for statistical analysis of the effects of lorcaserin treatment on daily activity. Previous studies have shown that nicotine can dose-dependently impact activity in laboratory subjects (Ksir et al., 1987) and, as such, the effects of lorcaserin on activity were assessed across each of the self-administered nicotine unit doses. However, as shown in Figure 3, pretreatment with 1.0 mg/kg lorcaserin only significantly decreased activity levels with regard to Time ($F(3,6)=32.6$, $p<.001$) with no main effect of nicotine Dose ($F(6,12)=0.63$, $p=.70$) nor a significant Dose X Time interaction ($F(18,36)=1.0$, $p=.48$). That is, significant decreases in activity from lorcaserin treatment were observed in the 3-hr time-period immediately following experimental sessions to 28% of control values across doses (Range: 13–45%; $p<.001$) and, to 66% of control in the 4–10-hr time-period (Range: 37–101%; $p<.05$). Full recovery to 100% of control activity levels (Range: 77–125%; $p=.98$) was observed on the day following test sessions, i.e., 12 – 36-hr post treatment (see Figure 3).

3.3 Effects of continuous lorcaserin delivery on responding maintained by 10 µg/kg/inj nicotine and food-pellet delivery

Individual data from three subjects and group mean ($\pm$ SEM) values are presented in Figure 4. Mean self-administration of 10 µg/kg/inj nicotine in sessions immediately prior to the onset of continuous lorcaserin delivery (88 injections $\pm$ 25 SEM) was not significantly different ($t(2) = 3.87$, $p = .06$) from self-administration during acute testing (61 injections

± 17 SEM). Responding for nicotine was stable at 10 $\mu\text{g/kg/inj}$ for each subject, with mean baseline values of 76, 135, and 55 injections for D002, 8206, and DJ9L, respectively (see Figure 4). Continuous infusion of 0.1 mg/kg/hr lorcaserin via osmotic minipump for 3 – 5 days decreased nicotine self-administration by approximately 40 – 50% overall (from 88 to 41 mean injections per session over the treatment period) with no appreciable effect on food-maintained responding (see Figure 4). The effects of continuous lorcaserin were highly consistent among subjects and, by the last day of treatment, nicotine self-administration was decreased to ~50% or less of control values in each subject. Upon discontinuation of chronic lorcaserin treatment, nicotine self-administration increased to 86% of control values during the two sessions following mini-pump removal in two subjects (Mm D002 and Mm 8206). Self-administration of 10.0 $\mu\text{g/kg}$ nicotine in the third subject (Mm DJ9L) remained at approximately 50% of baseline for the two sessions following mini-pump removal but recovered to control levels after 8 sessions of self-administration of other doses of nicotine (2 session at 100 $\mu\text{g/kg}$ and 6 sessions at 3.2 $\mu\text{g/kg}$; data not shown).

4. Discussion

The present study was designed to evaluate the effects of acute and continuous lorcaserin treatment on nicotine self-administration, food-maintained responding, and general activity in non-human primates with a relatively long history (>2 years) of nicotine self-administration. The main findings were that lorcaserin treatment: 1) consistently decreased nicotine self-administration, evident either as a downward shift in the self-administration dose-effect curve in acute treatment studies or as a persistent decrease in self-administration of an IV dose of nicotine in continuous treatment studies; 2) less consistently altered food-maintained responding; and 3) produced time-limited decreases in levels of general activity. Taken together, the results of the present study provide additional evidence that lorcaserin significantly decreases nicotine intake, supporting its further investigation for the management of nicotine use disorder. However, lorcaserin's apparent non-selective effects on other behaviors indicate the need for careful analysis of its therapeutic utility.

A considerable body of data suggests that agonists acting at serotonin receptor subtypes, e.g., the 5-HT_{2C} receptor, may be promising drugs for the treatment of psychostimulant disorders, including nicotine use disorder (see Howell and Cunningham, 2015; Higgins et al., 2013, Meltzer and Roth, 2013; for review). Previous studies in rodents have demonstrated that lorcaserin and the subtype-selective 5-HT_{2C} receptor agonist Ro 60-0175 may decrease responding for a single dose of nicotine but did not expand those experiments to evaluate their effects across a wider range of self-administered nicotine doses (Fletcher et al., 2012; Grottick et al., 2001; Higgins et al., 2012; Levin et al., 2011). Thus, it has been unclear whether the effects of lorcaserin could be surmounted by increasing the dose of nicotine available for self-administration. In the present study, acute pretreatment with 1.0 mg/kg lorcaserin shifted the entire dose-effect curve, encompassing a >100-fold range of doses, for nicotine self-administration downward, thereby indicating that the effects of lorcaserin could not be surmounted by higher nicotine doses. This finding has clear clinical implications, as it suggests that increased nicotine use appears unlikely to overcome lorcaserin's treatment effects. Moreover, decreases in nicotine-maintained responding were generally consistent over 3 – 5 days of continuous treatment with lorcaserin and these

findings are consistent with previous reports showing that orally-administered lorcaserin reliably decreased cocaine self-administration over a 14-day treatment period in rhesus monkeys (Collins et al., 2016) and suggest that tolerance does not develop rapidly to the desired treatment effects of lorcaserin. However, studies in which high daily dosages of lorcaserin are administered over extended time periods (e.g., months) are necessary for a full evaluation of whether and at what rate tolerance may develop to lorcaserin's effects.

The marked effects of lorcaserin on nicotine self-administration during acute and continuous administration protocols are in contrast to its effects on food-maintained responding. Acute lorcaserin pretreatment significantly decreased responding maintained by a food reinforcer less consistently than that of nicotine, whereas continuous lorcaserin treatment did not disrupt food-maintained responding in any subject. It is unclear whether the different effects of lorcaserin on food-maintained behavior in the two experiments were due to differences in dosing regimen (acute bolus dose vs. continuous accumulating dosage) or differences in response requirement (FR5 vs. FR1 in, respectively, acute and continuous dosing studies). Some reduction in food-maintained responding is perhaps not surprising in view of lorcaserin's FDA-approval as a weight loss medication and, as well, previous reports of decreases in feeding or food-reinforced behavior in rats (Higgins et al., 2012; Thomsen et al., 2008) and monkeys (Collins et al., 2016). Indeed, more pronounced effects of lorcaserin on food-maintained responding might have been expected in the present experiments. However, it is important to note that food-maintained responding in the present study was used only as a marker for non-selective effects of lorcaserin and subjects were limited to a 10-min component of food-maintained responding with access only to a modest quantity of food pellets (50 g) to limit the influence of satiety on responding. It is likely that under other conditions, e.g., models of binge-eating, the effects of lorcaserin would be magnified. It is nevertheless possible that lorcaserin's effects on food-maintained responding in the present report, though limited, are related to its projected clinical utility, e.g., for preventing weight gain in smoking cessation programs (e.g., Shanahan et al., 2016).

In the present study, general activity was decreased after acute lorcaserin administration to below 50% of control levels during the 3-hr period immediately following the session, recovered at least partially within 4 – 10-hr after treatment, and returned to control levels within 12 – 36-hr. The time-course of decreased activity is in line with the reported plasma half-life of about 11-hr for lorcaserin in humans (Eisai Inc., 2016). Previous studies in rhesus monkeys and rodents also have demonstrated that doses of lorcaserin that effectively decrease drug self-administration (i.e., cocaine, nicotine) also generally decrease activity (Collins et al., 2016; Higgins et al., 2012; Levin et al., 2011). Such decreased activity does not appear to reflect sedation or non-specific motoric disruption that prevents subjects from engaging in operant behavior. Visual inspection of cumulative records following 1.0 mg/kg lorcaserin pretreatment in the present study shows that responding for nicotine was more spaced with less "loading" during the first 30-min of the session but that the regularity of food-maintained responding was largely maintained throughout the session (data not shown). These observations raise the possibility that motivational value plays an important role in the effects of lorcaserin or other 5-HT_{2C} agonists on the behavior in question. In this regard, lorcaserin is known to decrease extracellular dopamine in reward-related brain regions, and a previous study in rats showed that lorcaserin administration increases

intracranial self-stimulation threshold intensity—an effect opposite to that produced by reinforcing drugs like nicotine or cocaine (Zeeb et al., 2015). Taken together, these findings suggest that lorcaserin's ability to attenuate dopamine in the mesolimbic system may ultimately impact several motivated behaviors. The relevance of this consideration to treatment tolerability and compliance are unknown and require further investigation.

Lorcaserin's effects are believed to be mediated through its action as a 5-HT_{2C} receptor agonist (Collins et al., 2016; Smith et al., 2008) as pharmacological blockade of this receptor reduces the suppressant effects of lorcaserin on both nicotine and cocaine self-administration, intracranial self-stimulation, food-maintained responding, and locomotor activity (Harvey-Lewis et al., 2016; Higgins et al., 2012; Zeeb et al., 2015). It is of note, however, that lorcaserin also has activity at other 5-HT receptors. In this regard, a recent drug discrimination study found that the 5-HT_{1A} agonist, 8-OH-DPAT, and the selective 5-HT_{2A} agonist, DOM, engendered lorcaserin-like responding in rats trained to discriminate lorcaserin suggesting a role of 5-HT_{1A} and 5-HT_{2A} receptors in the behavioral effects of lorcaserin (Serafine et al., 2016). These results suggest that the role of various 5-HT receptor subtypes in lorcaserin's therapeutic effects require further examination and highlight the importance of receptor-subtype selective pharmacological manipulations that might lead to medications with better safety and selectivity.

5. Conclusions

Generally, there is a high concordance between medications that decrease drug self-administration in non-human primates and in humans (Mello and Negus, 1996; Mello, 2005). The present studies further illustrate the value of self-administration methodology for identifying novel treatment medications for substance abuse, and strongly support the continued assessment of lorcaserin as a potential novel treatment for nicotine use disorder. Lorcaserin's unique mechanism of action and existing FDA approval makes it an especially promising medication candidate, as it can be rapidly assessed in clinical studies and compared to the most commonly prescribed smoking cessation aids. However, lorcaserin's range of behavioral effects indicates the need to identify the particular 5-HT receptor-subtype mechanisms that mediate its therapeutic and behavioral effects; in turn, this effort may lead to more efficacious therapeutics for smoking cessation.

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Highlights

- Treatment with lorcaserin decreased nicotine self-administration.
- Lorcaserin had a modest decrease or no effect on responding for food reinforcement.
- Home-cage activity was decreased after acute treatment with lorcaserin.
- Further characterization of lorcaserin as a smoking cessation is warranted.

Figure 1.

Dose-ranging studies with lorcaserin (0.1 – 1.0 mg/kg I.M.) on responding for nicotine (10 $\mu\text{g/kg/inj}$, I.V. circles) and food (1-g banana-flavored pellets, squares). Abscissae: Dose of lorcaserin (mg/kg). Ordinates: Percent of control responding for 10 $\mu\text{g/kg/inj}$ nicotine. Data are presented as mean $\pm$ SEM for the group. Control values were the average number of reinforcers earned from the session immediately preceding pretreatment tests. * $p<.05$, ** $p<0.01$ from saline; $n=4$ all cases.

Effects of Acute 1.0 mg/kg Lorcaserin on Individual and Group Nicotine Self-Administration

Figure 2.

Effects of 1.0 mg/kg lorcaserin on drug-maintained responding over a 100-fold range of nicotine doses (0.32 – 100 µg/kg). Data are presented for individual subjects (left four panels) as well as for the group as mean $\pm$ SEM (right panels). Abscissae: Dose of nicotine available (µg/kg/inj). Ordinates: Total injections earned/90-min session. White circles indicate the single preceding session where saline pretreatment was administered, while black circles indicate lorcaserin pretreatment tests. Other details as in Fig. 1. * $p<.05$, ** $p<.01$ from saline self-administration. $n=3$ for 0.32 µg/kg nicotine dose, else $n=4$.

Figure 3.

Effects of 1.0 mg/kg lorcaserin pretreatment on patterns of daily activity following nicotine self-administration (0.32 – 100 $\mu\text{g/kg}$) sessions shown in Figure 2. Data are presented as mean percent of control activity counts ($\pm$ SEM) at different time-points after varying nicotine doses were self-administered (symbols). Dashed Line represents overall mean percent of control for all nicotine control days. Abscissae: Time after self-administration session in hours. Ordinates: Percent of control activity. * $p < .05$, ** $p < .01$ time period vs. nicotine control; $n=3$ all cases.

Effects of Continuous Lorcaserin Treatment on Nicotine (10.0 $\mu\text{g/kg/inj}$)- and Food-Maintained Responding

Figure 4.

Effects of continuous lorcaserin administration (0.1 mg/kg/hr, S.C.) on food- and 10.0 $\mu\text{g/kg/inj}$ nicotine-maintained responding. White symbols indicate baseline sessions which immediately preceded sessions with lorcaserin treatment (black symbols). Abscissae: Day of treatment; P1, P2=post lorcaserin treatment sessions 1 and 2, respectively. Top Ordinates: Total nicotine reinforcers earned. Bottom Ordinates: Total food pellets earned. Data are presented for individual monkeys and as mean $\pm$ SEM for the group ($n=3$). Mini-pumps were implanted approximately 17-hours prior to the self-administration session on Day 1 of continuous treatment and removed 4-hours after the last continuous treatment session. See text for additional details.

Table 1

Sex, weight, age, and lifetime self-administered nicotine (mg/kg) for each subject at the start of the study.

Subject	Sex	Weight (kg)	Age (years)	Lifetime Nicotine Intake at Start of Study (mg/kg)
Mm D002	M	8.0		254.18
Mm DJ9L	F	5.8		344.92
Mm 462	M	7.8		321.09
Mm 8206	M	8.2		316.77

Effects of 1.0 mg/kg lorcaserin alone on food-maintained responding. Numbers reflect mean $\pm$ SEM for number of 1-g banana pellets earned. No significant main effects were observed. Nicotine self-administration sessions occurred after food components.

Table 2

Nicotine Dose (μ g/kg)	0.0	0.32	1.0	3.2	10.0	32.0	100
Treatment Condition							
Saline	48 ($\pm$ 1)	49 ($\pm$ 1) ^a	50 ($\pm$ 0)	50 ($\pm$ 0)	50 ($\pm$ 0)	50 ($\pm$ 0)	48 ($\pm$ 2)
1.0 mg/kg Lorcaserin	35 ($\pm$ 12)	32 ($\pm$ 8) ^a	31 ($\pm$ 6)	34 ($\pm$ 9)	41 ($\pm$ 4)	32 ($\pm$ 11)	34 ($\pm$ 10)

^a $n = 3$, else $n = 4$.

Effects of Nicotine Self-administration on Daily Activity. Numbers reflect mean $\pm$ SEM for the percent of saline self-administration activity when several nicotine doses were available for self-administration. No significant differences were observed. ($n=3$)

Table 3

Nicotine Dose (mg/kg)	0.0	0.00032	0.0001	0.0032	0.01	0.032	0.1
<i>Activity (% of Saline)</i>							
3-hour	87 (± 4)	156 (± 78)	140 (± 51)	98 (± 27)	89 (± 31)	102 (± 28)	128 (± 49)
10-hour	95 (± 10)	58 (± 16)	89 (± 17)	84 (± 14)	70 (± 17)	80 (± 11)	88 (± 16)