The serotonin-2C agonist Lorcaserin delays intravenous choice and modifies the subjective and cardiovascular effects of cocaine: A randomized, controlled human laboratory study

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ABSTRACT

Background: Lorcaserin is a modestly selective agonist for 2C serotonin receptors (5-HT$_{2C}$R) approved for weight-loss therapy. This class can attenuate cue-induced responding and drug taking in preclinical studies, but effects in humans have not been reported.

Methods and participants: We evaluated effects of single 10 mg doses of lorcaserin on the subjective and reinforcing effects of cocaine, using a randomized, double-blind, within-subject, cross-over design. Male, non-treatment-seeking, regular cocaine users received either single doses of oral placebo ($n = 9$) or lorcaserin ($n = 9$), followed by low- or high- doses of intravenous cocaine (0.23 or 0.46 mg/kg-injection). They were then allowed to self-administer the lower dose of cocaine.

Results: Cocaine was well tolerated after lorcaserin pretreatment. Oral lorcaserin did not modify the number of cocaine injections self-administered. However, it prolonged the time over which participants made intravenous choices relative to the duration of monetary (cash) decisions. Lorcaserin increased ratings of 'high' and 'stimulated' after low-dose cocaine or vehicle, but decreased craving for cocaine after intravenous vehicle. It also caused small but significant increases in heart rate following noncontingent injections of intravenous placebo or cocaine. When active cocaine was self-administered, lorcaserin decreased heart rate after selection of a monetary choice, but increased it following an intravenous choice.

Conclusions: Combined treatment with cocaine and lorcaserin was safe in a limited number of subjects, but did not diminish cocaine-motivated behavior or drug-induced 'high'. Some positive subjective effects of cocaine were enhanced by lorcaserin, and it delayed intravenous choices and decreased craving under some conditions. Effects on heart rate depended on the type of reinforcer being self-administered.

Trial registration: clinicaltrials.gov Identifier, NCT02680288.

1. Introduction

Cocaine use disorders are an important health problem in the United States, causing significant medical, mental health, and social problems (Center for Behavioral Health Statistics and Quality, 2015). Although a wide variety of different potential therapeutic classes have been evaluated, no drugs are currently approved for relapse prevention after cocaine abuse or dependence. Serotonin (5-HT or 5-hydroxytryptamine) is one of three monoamine neurotransmitters that play important roles in affect and goal-directed behaviors. Type 2C serotonin receptors (5-HT$_{2C}$R) exert complex actions on limbic neurons, playing a role in both dopamine release and drug-motivated behaviors.

Lorcaserin is a modestly selective agonist for 5-HT$_{2C}$R receptors approved by the FDA for weight-loss therapy (Chan et al., 2013). This class can attenuate cue-induced responding and drug taking in preclinical studies (Collins et al., 2018), but effects in humans have not been reported. Lorcaserin is marketed at a dose of 10 mg twice daily in patients with a medical indication for weight loss, such as diabetes or heart disease. Supratherapeutic doses are associated with both 'high' and negative subjective effects in liability testing, leading it to be

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Table 1
Overview of the study design.

Overnight day	Oral treatment	Intravenous treatment	Objective
1	Placebo	None	First 24-hour washout, to ensure elimination of any medications that may have been taken prior to admission.
2	Placebo	Cocaine/Placebo[a]	Test if intravenous dosing tolerated.
3	Lorcaserin/Placebo[b]	Cocaine/Placebo[b]	First double-blind oral and intravenous dosing
4	Placebo	Cocaine/Placebo[b]	Second 24-hour washout, to ensure elimination of Day 3 oral treatment.
5	Lorcaserin/Placebo[b]	Cocaine/Placebo[b]	Second double-blind oral and intravenous dosing

[a] To facilitate the evaluation of adverse events and the subjective effects of cocaine, study personnel but not participants were aware of cocaine dose.

[b] Double-blind treatment.

classified as Drug Enforcement Administration schedule IV (Shram et al., 2011).

Given that lorcaserin is currently clinically available, well-tolerated in humans, and can modify psychostimulant-motivated behavior in animals (Collins et al., 2015; Gerak et al., 2016); its potential as a treatment for cocaine use is of interest. Although lorcaserin is currently approved for chronic use in patients with a medical indication for weight loss, supratherapeutic single doses can cause euphoria, hallucinations, and dissociation reactions in humans (Shram et al., 2011). There is no data currently available on the potential interaction of lorcaserin and cocaine in humans. Because both agents potentiate serotonergic function, combined dosing may cause the serotonin syndrome. In addition, there may be unanticipated effects of combined dosing. To mitigate potential toxicity, single rather than multiple daily doses of lorcaserin were evaluated in the current study for their effects on cocaine-reinforced behavior, with comparison to monetary-reinforced responding. This approach is also justified by observations that single and multiple doses of lorcaserin have similar effects on cocaine-reinforced behavior in rhesus monkeys (Collins et al., 2015). Based on findings of attenuated cocaine self-administration and reinstatement in rodents (Harvey-Lewis et al., 2015) and non-human primates (Collins et al., 2018), our hypothesis was that pretreatment with lorcaserin would decrease cocaine self-administration and craving in humans.

2. Materials and methods

2.1. Participants

The protocol was performed under US Food and Drug Administration IND 117,990, Lorcaserin Treatment of Cocaine Abuse after approval by the Institutional Review Board of the Kansas City Veterans Affairs Medical Center. Subjects were recruited through word-of-mouth and advertisements posted in the community or on the internet. Those interested could receive a $20 stipend for each participant who was referred, for up to 10 potential subjects who met preliminary screening criteria. They were required to be current users of cocaine by rapid route (smoking or intravenous injection) and to supply a cocaine-positive urine collected within six weeks prior to dosing. Although women were not excluded, overnight arrangements were only sometimes available for females. All participants were not seeking medical treatment for cocaine abuse, did not have an active psychiatric condition, and had no clinically significant findings on physical exam. None of the participants had a history of asthma, cardiac disease, seizure disorders, or other medical condition that might make participation hazardous. Screening labs included blood counts, routine chemistry measures, urinalyses, and 12-lead electrocardiograms.

2.2. Study design

A randomized, double-blind, double-dummy, placebo-controlled,

within-subject, cross-over design was used to evaluate the safety of intravenous cocaine in participants receiving oral lorcaserin, as well as its effects on the subjective and reinforcing actions of cocaine in a laboratory setting. To prevent unauthorized drug use and allow better monitoring of adverse events, participants were observed during overnight admissions of 5 days duration. They received a stipend of $1506 for completing the entire protocol.

2.3. Cocaine and the study medication

The study design is outlined in Table 1. Oral placebo was administered on Overnight Days 1, 2, and 4. These doses were known to be oral placebo to study personnel but not participants. To allow one day of observation and ensure washout of any potential illicit substances, intravenous treatments were initiated on Overnight Day 2. In order to be randomized to double-blind oral treatment, participants were required to report at least 20 mm of cocaine-induced 'high' and to self-administer at least two cocaine injections on Overnight Day 2. This ensured a baseline response to cocaine that could be reduced by treatment with the study medication. Double-blind lorcaserin (marketed as Belviq, 10 mg single oral doses) was administered on either Overnight Day 3 or 5 (only one active dose per subject). This design allowed participants to become experienced with laboratory procedures prior to receiving active oral treatment. Lorcaserin tablets were enclosed within size 00 capsules filled with microcrystalline cellulose, administered at approximately 9:00 AM, 20 min prior to the start of intravenous dosing. After dosing, electrocardiogram signals were continuously monitored, with blood pressure and heart rate checked at frequent intervals (1, 2, 4, 6, 8, 10, 15, 20, 30, 40, 50 min after intravenous dosing). Safety labs were repeated 7 h after double-blind oral treatments, and included blood counts, routine chemistry measures, urinalyses, and 12-lead electrocardiograms. Participants returned three days after their final overnight day for a health status check.

2.4. Intravenous self-administration

The National Institute of Drug Abuse (Bethesda, MD) supplied cocaine hydrochloride which was delivered intravenously at a dose of 0.23 mg/kg in approximately 2.4 ml of saline over one minute using an Alaris 8015 interface and patient-controlled analgesia (PCA) module. A two-fold higher noncontingent dose was administered one hour later, by two activations of the PCA module. Participants were then offered six choices for additional injections of the lower dose or a monetary amount at 20-min intervals. Active cocaine was administered in either the morning or afternoon, with this order reversed each day. Identical dosing with double-blind intravenous vehicle was administered at alternate times of day, with each different dose paired with a color that was unique across four days of intravenous dosing. This procedure allowed double-blind evaluation of injections that were noncontingent (0.00, 0.23, or 0.46 mg/kg of cocaine) or self-administered (0.00 or

0.23 mg/kg of cocaine) within one day. Although participants were required to distinguish between different sampling doses of cocaine, each was associated with a distinct color that was presented alongside questionnaires, allowing it to be readily identified. Individuals meeting inclusion criteria for the present study routinely described taking multiple consecutive doses of cocaine. Overall, repeated dosing in a laboratory setting allows a more efficient evaluation of cocaine dose and likely resembles its use in a recreational setting. Our design also facilitated more direct comparisons between oral treatments.

Responding on a computer mouse was used to select between intravenous and monetary choices, with five additional mouse clicks required to obtain either reinforcer. If no selection was completed within 2 min, the choice was withdrawn with neither reinforcer administered. In preliminary studies, we observed that drug-reinforced responding can be facilitated by limiting the availability of monetary reinforcement according to the amount of cocaine self-administered. Accordingly, amounts of cash offered were adjusted according the number of injections of a given dose that had been self-administered: $0.00 for 0 or 1 injections, $0.05 for 2, $0.50 for 3, $1 for 4, and $2 for 5 earned injections (corresponding to $0.20 to $2 if participants made at least 2 intravenous choices). To ensure participant safety, intravenous dosing was stopped after tachycardia exceeding 130 beats per minute (bpm) or blood pressure > 165 mmHg systolic or 100 mmHg diastolic.

2.5. Assessments

2.5.1. Subjective drug effects

Visual analogue scale (VAS) responses were recorded on a 100 mm scroll bar marked from 0 ('not at all') to 100 ('extremely') at baseline, 3, 6, 10, 15, and 20 min after intravenous dosing. Participants were asked to indicate 'Do you feel ANY IV drug effects', 'Does the IV drug have any GOOD effects?', 'Does the IV drug have any BAD effects?', 'Do you feel STIMULATED from the IV drug?' 'How HIGH are you from the IV drug?' Craving was assessed by asking participants to indicate 'How much do you WANT TO USE cocaine?' The Addiction Research Center Inventory (ARCI) was completed 20 min after each noncontingent dose, with responses subdivided into scales of 1.) Psychostimulant effects, the Amphetamine and Benzedrine Groups (BG); 2.) Euphoria, the Morphine-Benzedrine Group (MBG), 3.) Sedation, the Pentobarbital-Chlorpromazine-Alcohol Group (PCAG), and 4.) Somatic-dysphoric effects, the lysergic acid diethylamide (LSD) scale.

2.5.2. Cocaine crossover value

At 18 min after noncontingent doses, participants completed the Multiple Choice Questionnaire (MCQ), which involves a series of hypothetical choices between receiving a second intravenous dose or a series of monetary alternatives of increasing value (Griffiths et al., 1993). The dollar amount at which participants switch from selecting drug to money is the *crossover point*. Values of $0.5, 1, 2, 4, 6, 10, 15, 20, 25, and 50 were offered.

2.6. Data analysis

Based on preliminary studies, participants were expected to make approximately 5 out of 6 potential cocaine choices during self-administration sessions, with a standard deviation of 1.56 choices (31.2%) (Walsh et al., 2001). Accordingly, including approximately eight participants per group would be sufficient to provide > 72% power to detect a reduction in cocaine self-administration of 50% or more. Participants were randomized by block allocation to four different schedules (lorcaserin on day 3 and oral placebo on day 5 with cocaine in the morning or afternoon for both of these sessions [AA or AB, respectively], or lorcaserin on day 5 and oral placebo on day 3 with cocaine at the same time of day for both sessions [BA or BB, respectively]). A study pharmacist randomly assigned participants to different blocks and concealed the assignment from those recording clinical outcomes.

Primary measures were the number of cocaine injections self-administered, the magnitude of cocaine-induced 'high' measured by VAS, and the tolerability of combined lorcaserin and cocaine. Statistical analyses were performed by Systat Inc. software, using the Shapiro-Wilk test to evaluate for normality. Comparisons were made by analysis of variance (ANOVA), with oral dose (placebo or 10 mg of lorcaserin), and intravenous dose (0.0, 0.23, and 0.46 mg/kg of cocaine), and time (if available) as factors. Post hoc comparisons by a single factor were performed by ANOVA simple main effects. Otherwise, post hoc comparisons were performed by Bonferroni t-tests. Using the correction by Sidak (Sankoh et al., 1997) for a 40% correlation between interrelated areas, a type I error (alpha) value of 0.026 was applied in these instances. A value of $p < 0.05$ was used as a criterion for the significance of comparisons by ANOVA. Data on adverse events are presented descriptively.

To compare changes in cardiovascular measures during self-administration of cocaine, all responding in individual participants was averaged for a given category of oral

dose (placebo or lorcaserin), intravenous dose (placebo or cocaine), and choice (intravenous or monetary). Comparisons were then made across group means of the averaged data, using oral dose, intravenous dose, and reinforcer type as factors.

3. Results

3.1. Participant characteristics

During the initial lead-in intravenous dosing, two subjects were excluded because of elevated blood pressure values following cocaine that exceeded stopping criteria, one because of heart rate greater than stopping criteria, and two because they failed to self-administer at least two cocaine injections. An additional subject failed to tolerate cocaine due to nausea and lightheadedness during the lead-in and did not participate further.

As outlined in Table 2, nine male, cocaine-dependent volunteers between and 34 and 49 years of age provided written informed consent and completed the study. One additional participant failed to receive lorcaserin because of a pharmacy error, and another subject left early because of a family problem at home. In total, nine doses of oral placebo and nine doses of lorcaserin were administered under double-blind conditions. All of the nine participants who received lorcaserin met the DSM-V criteria for Cocaine Use Disorder and had ASI values indicating clinically-significant disorders.

3.2. Tolerability of the study medication

After receiving oral placebo and cocaine during his second double-blind session, subject 250 became agitated and asked to discontinue participation. Following reassurance, he completed all remaining procedures without incident. Participant 262 reported self-limited

Table 2
Participant recruitment and demographics. The upper flow chart shows results of multi-stage screening of potential subjects using telephone interviews, in-person exams, and intravenous dosing. Demographics of the nine male subjects who received both oral treatments are shown below. '?' describes subjects who received cocaine without purchasing. The randomly assigned order of oral dosing with placebo and lorcaserin is shown in the last column.
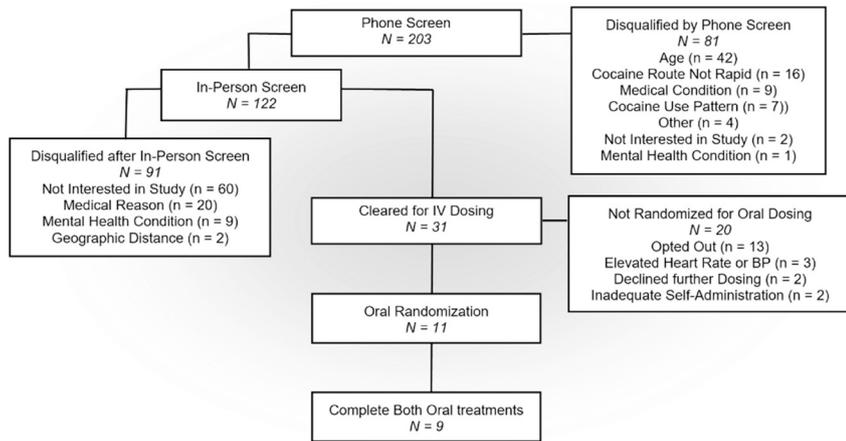
Number	Race[a]	Age (years)	Education (years)	Cocaine use days[b]	Years since first use	Cocaine ($/week)	Cigarettes (packs/ week)	Drug[c]	Mental healthl[c]	Family[c]	Oral dose (mg)[e]
242	W	48	13	20	15	?[d]	4	0.269	0.091	0.329	10, 0
250	AA	42	10	16	20	1600	20	0.058	0.000	0.282	10, 0
255	AA	37	13	15	9	600	2	0.241	0.000	0.000	0, 10
262	AA	37	12	10	6	?[d]	1	0.031	0.000	0.025	10, 0
264	AA	45	12	15	8	100	3	0.131	0.000	0.000	0, 10
282	AA	34	10	20	10	150	7	0.092	0.023	0.225	0, 10
287	AA	41	14	12	6	100	2	0.021	0.000	0.000	10, 0
289	AA	37	14	20	15	200	6	0.182	0.000	0.000	0, 10
290	W	49	20	20	29	2000	7	0.128	0.148	0.147	0, 10
2-W7-AA	2-W7-AA	41.1 ± 1.67	13.1 ± 0.94	16.4 ± 1.20	13.1 ± 1.98	679 ± 224	5.78 ± 1.59	0.128 ± 0.029	0.029 ± 0.017	0.112 ± 0.043	

[a] Race: AA (African American), W (Caucasian).
[b] Days of drug use over the last 30 days.
[c] Addiction Severity Index composite rating.
[d] Not purchasing cocaine.
[e] Randomization order is shown left to right.

gastrointestinal distress with an increased frequency of bowel movements on the evening after receiving oral placebo and cocaine. After receiving lorcaserin and low-dose cocaine, participant 282 had a brief period of mild chest discomfort and eructation.

3.3. Cocaine self-administration

Numbers of injections chosen during self-administration are shown in Table 3. When intravenous cocaine was available, participants self-administered a greater number of drug injections but fewer monetary reinforcers [$F_{(1, 32)} = 11.4$ & 9.47, $p < 0.02$ for either]. Lorcaserin treatment did not modify either cocaine- or monetary- reinforcement [$F_{(1, 32)} = 0.27$ & 0.46, $p > 0.05$ for either].

Participants responded more slowly on their first mouse click which initiated either an intravenous or monetary choice, with response rate increasing over subsequent responding (Fig. 1). When an intravenous choice was made, overall latency and latency for the first mouse click varied significantly with oral dose ($F_{(1, 22)} = 6.61$ & 8.80, $p < 0.02$ for either), but not intravenous dose or the interaction of lorcaserin and cocaine doses. In contrast, latency across monetary choices did not vary significantly with oral dose, intravenous dose, or their interaction. When collapsed across intravenous treatments, active lorcaserin

Table 3
Cocaine self-administration during double-blind sessions. Group means and standard error are show for 9 participants who self-administered intravenous placebo and cocaine after both oral placebo and lorcaserin.

Intravenous treatment	Oral treatment	Number or reinforcers self-administered	
		Intravenous	Money
Placebo	Placebo	2.00 (0.70)	3.67 (0.72)
	Lorcaserin	1.78 (0.73)	4.11 (0.71)
Cocaine	Placebo	4.67 (0.59)*	1.33 (0.59)*
	Lorcaserin	4.11 (0.76)	1.89 (0.76)

* Indicates a significant effect of cocaine compared to intravenous placebo, $p < 0.01$.

increased overall response latency and latency for the first mouse click when participants were responding for intravenous but not monetary choices. Latency for an initial click to choose intravenous reinforcement was $5.40 ± 0.45$ and $9.63 ± 1.38$ s following oral placebo and lorcaserin, respectively. This corresponded to a prolongation of greater than four seconds after active oral treatment.
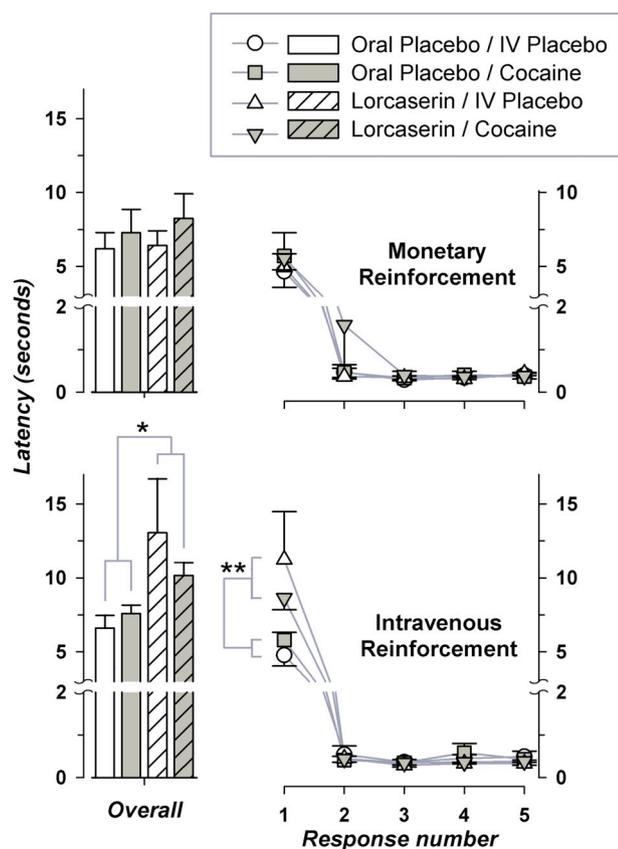
Fig. 1. Response Latency during Cocaine Self-Administration. Latency is shown on vertical axes both as overall values to complete five clicks on a computer mouse, and values associated with each individual mouse click, plotted horizontally. Responding during monetary and intravenous reinforcement is shown on the upper and lower graphs, respectively. Group means with standard error are shown for 5 to 9 participants per condition. * indicates a significant simple main effect of lorcaserin, with one and two symbols corresponding to $p < 0.03$ and $p < 0.01$, respectively.

3.4. Subjective effects

Effects of cocaine and lorcaserin on different VAS items are shown in Fig. 2. Cocaine produced dose-related increases in 'High', 'Stimulated', and 'Good Drug' ratings [$F_{(2, 396)} = 53.8, 56.3, \& 40.0; p < 0.001$ for all]. Each of these measures varied significantly with oral treatment [$F_{(1, 396)} = 16.9, 10.3, \& 12.5; p < 0.01$ for all]. Treatment with lorcaserin increased all three ratings in participants receiving intravenous placebo, with values for 'High' and 'Stimulated' also increased by approximately two-fold after low-dose cocaine. In contrast, lorcaserin treatment decreased craving following intravenous placebo [$F_{(1, 214)} = 15.8, p < 0.001$] but not either dose of cocaine.

Injection value measured by the Multiple Choice Questionnaire as well as ratings of 'Any' and 'Bad' drug effects by VAS varied significantly with dose of cocaine [$F_{(2, 66)} = 17.3, p \leq 0.001; F_{(2, 396)} = 54.3 \& 4.47; p \leq 0.02$ for either] but not lorcaserin. As we have previously reported (Grasing et al., 2010), cocaine produced dose-related increases the ARCI morphine-benzedrine subscale [$F_{(2, 66)} = 4.39, p \leq 0.02$]. However, there is no effect of lorcaserin on this measure. For most VAS measures, ANOVA showed significant main effects of time.

3.5. Cardiovascular measures

ANOVA revealed significant effects of lorcaserin treatment on heart rate and systolic blood pressure [$F_{(1, 594)} = 14.4 \& 27.9; p < 0.001$ for either] (Fig. 3). Treatment with lorcaserin potentiated cocaine-induced increases in systolic blood pressure, and also caused small but significant increases in heart rate after noncontingent intravenous placebo or cocaine.

During self-administration, both systolic and diastolic blood pressure varied significantly with cocaine dose and its interaction with lorcaserin treatment [$F_{(1, 315)} = 7.00 \& 5.12, p < 0.03$ for either]. Treatment with lorcaserin increased both measures during self-administration of cocaine but not intravenous placebo (data not shown).

As shown in Fig. 4, heart rate during self-administration varied significantly with cocaine dose (0 or 0.23 mg/kg-injection) and its interaction with lorcaserin dose and type of reinforcement [$F_{(1, 315)} = 4.91, p < 0.03$]. Effects of lorcaserin on heart rate depended on the type of reinforcer chosen and whether active or placebo cocaine was being self-administered. Lorcaserin treatment decreased heart rate after a monetary choice when active cocaine was being self-administered, but increased it after participants selected either intravenous placebo or cocaine. No participant met stopping criteria because of increased blood pressure or heart rate.

4. Discussion

In the present study, active oral treatment with lorcaserin did not decrease either cocaine self-administration or drug-induced 'high'. Given its negative effects on primary measures, secondary outcome variables were analyzed. We found that lorcaserin treatment delayed early decisions to choose intravenous but not alternative reinforcers, while decreasing craving after intravenous placebo. Delayed responding occurred as participants evaluated a specific color previously paired with noncontingent injections. Lorcaserin did not modify subsequent responding as subjects completed the required four additional mouse clicks. That responding was made rapidly, apparently with minimal further consideration. Previous work has shown that non-intuitive decisions which require greater effort and deliberate reasoning are more prolonged (Kahneman, 2003; Kahneman, 2011). Because lorcaserin potentiated the positive subjective properties of low-dose cocaine and intravenous placebo, motivation for drug may have declined as drug craving was satiated. If so, this may have slowed responding for drug injections as respondents required more effort to evaluate their internal state. Even so, the overall number of cocaine injections chosen by participants was not altered by lorcaserin pretreatment.

Activation of 5-HT$_{2C}$Rs appears to biphasically modulate release of dopamine in brain reward regions. Cocaine-induced dopamine release in the nucleus accumbens shell is increased by delivery of a 5-HT$_{2C}$R agonist to that brain region at a low dose (Navailles et al., 2008), but attenuated after a higher dose; with opposite effects after treatment with a 5-HT$_{2C}$R antagonist (De et al., 2004). Although systemic delivery of 5-HT$_{2C}$R agonists decreases extracellular dopamine in the nucleus accumbens (Browne et al., 2017), microinjection to the medial prefrontal cortex augments accumbal dopamine (Leggio et al., 2009). Biphasic effects of 5-HT$_{2C}$Rs on dopaminergic tone may underlie different effects of lorcaserin in humans and animals. Lorcaserin administered in the present study at a relatively low, clinically relevant-dose on the order of 0.14 mg/kg may have modestly increased accumbal dopaminergic tone, augmenting the positive subjective effects of vehicle or
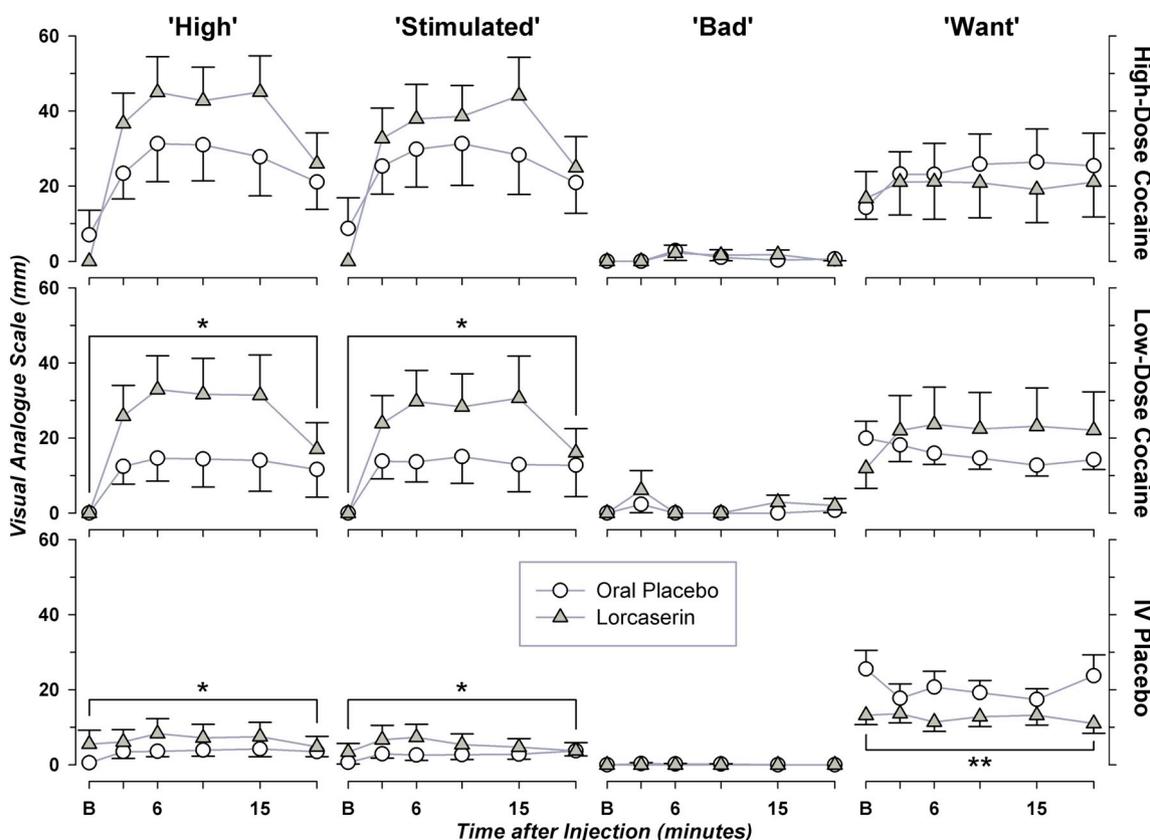
Fig. 2. Lorcaserin modifies Visual-Analogue Measures. Participants used a computer mouse to endorse cocaine-induced 'High' or other subjective effects, shown on vertical axes. Time after intravenous injection is plotted horizontally. Group means with standard error are shown after treatment with oral placebo ($n = 9$) or 10 mg of lorcaserin ($n = 9$). For either oral treatment, each participant received two injections of intravenous placebo and a single injection of low- and high- dose cocaine. * indicates a significant effect of lorcaserin, with 1 and 2 symbols corresponding to $p < 0.05$ and $p < 0.001$ by simple main effects.

low-dose cocaine. This is consistent with a previous report of dose-related increases drug-induced 'High' after supratherapeutic doses of lorcaserin (Shram et al., 2011). Although we did not observe an increase in self-administration, this may occur after a lower, otherwise ineffective dose of cocaine.

Preclinical studies have shown that lorcaserin doses of 0.6 mg/kg or more decrease cocaine self-administration in rats (Harvey-Lewis et al., 2015) or monkeys (Collins et al., 2015; Banks and Negus, 2017; Gannon et al., 2017), with 0.3 mg/kg or greater attenuating cue- or drug- induced reinstatement (Harvey-Lewis et al., 2015). These relatively high doses of lorcaserin likely diminish dopaminergic tone in reward regions (Browne et al., 2017). When rhesus monkeys responded under a progressive-ratio schedule, intragastric lorcaserin also attenuated self-administration of 0.010 to 0.100 mg/kg-injection of cocaine, but not 0.320 mg/kg-injection (Gerak et al., 2016). Given these results, a relatively low 0.23 mg/kg-injection dose of cocaine was chosen for the present study. Because the subjective effects of cocaine doses < 0.23 mg/kg-injection are not easily identified by most participants, lower doses were not evaluated. We also found that lorcaserin decreased craving after intravenous vehicle, with no effect on this measure following different doses of cocaine. It is unclear how this finding relates lorcaserin's actions in preclinical models of reinstatement, but it would appear more closely linked to cue- rather than drug- induced responding.

We found that lorcaserin caused small but significant increases in the heart rate of participants receiving noncontingent injections of intravenous placebo or cocaine, while augmenting cocaine-induced increases in systolic blood pressure. No significant effects on diastolic blood pressure were observed. In patients using lorcaserin for management of obesity, decreased blood pressure has been reported, with no effect on heart rate (Chan et al., 2013). Therefore, effects on cardiovascular measures in the present study may be due to specific characteristics of our subjects, such as expectations of stimulant reward. Consistent with this, lorcaserin increased heart rate after intravenous self-administration of vehicle or cocaine, but caused decreases following selection of a monetary choice while participants were self-administering active cocaine.

Combined treatment with cocaine and lorcaserin appears to be safe, based on evaluation of a limited number of subjects. Because of nonselective decreases in operant responding and its failure to decrease cocaine-versus-food choice in rhesus monkeys, Banks et al. (Banks and Negus, 2017) suggested that lorcaserin is unlikely to have clinical utility for treatment of cocaine use disorders. Studies in rodents have shown that lorcaserin diminished opioid self-administration only at doses well above those used clinically (Panlilio et al., 2017). Our own findings also do not support a direct therapeutic benefit on drug-reinforced behavior for the currently marketed dose of lorcaserin. Even so, this dose did selectively slow responding that preceded intravenous choices, implying that greater effort was expended during drug-taking decisions. Decreased craving in participants receiving intravenous placebo could also translate into a therapeutic benefit in abstinent individuals. On the other hand, lorcaserin increased the positive subjective effects of cocaine on some VAS measures.

Cocaine produces robust cardiovascular and subjective effects that can be readily detected in relatively small panels of participants in a
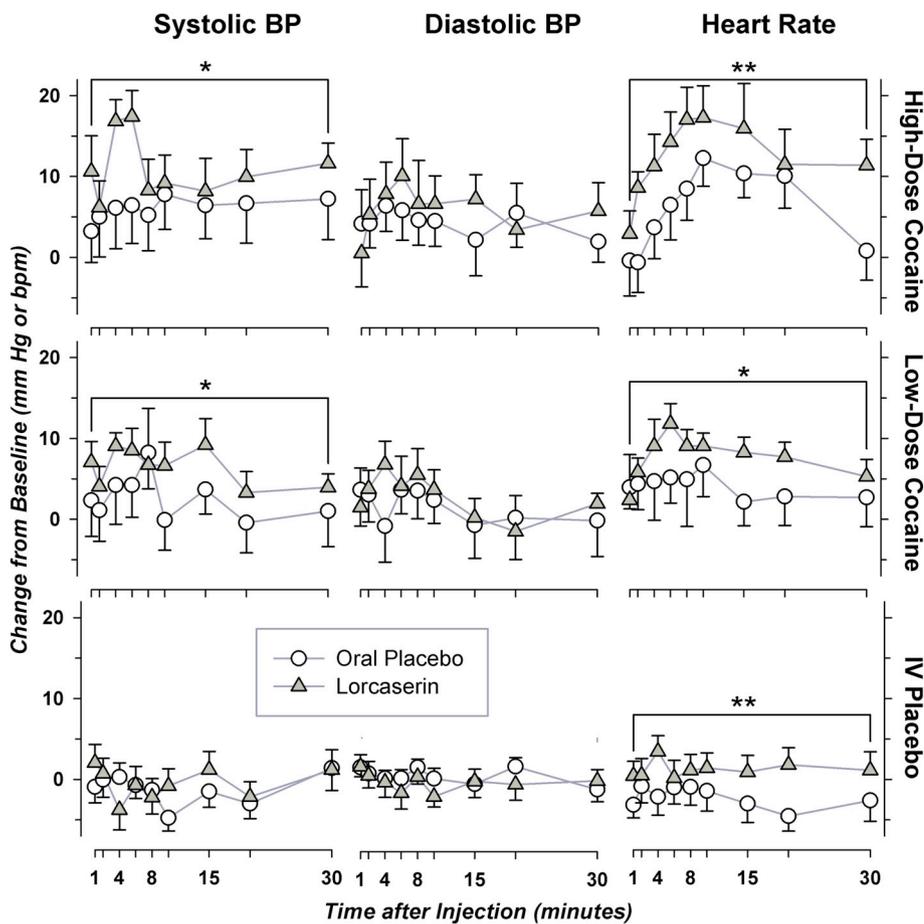
Fig. 3. Cardiovascular Measures after Treatment with Noncontingent Cocaine and Lorcaserin. Group means with standard error for absolute change in blood pressure (mm Hg) and heart rate (beats per minute) after noncontingent cocaine are shown following treatment with oral placebo ($n = 9$) or lorcaserin ($n = 9$). * indicates a significant effect of lorcaserin, with 1 and 2 symbols corresponding to $p < 0.05$ and $p < 0.001$ by simple main effects.
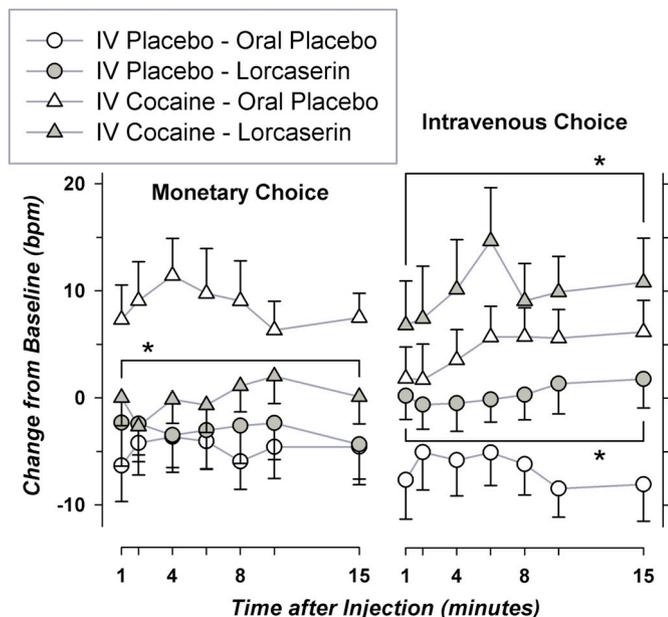

Fig. 4. Effects of Lorcaserin and Cocaine on Heart during Self-Administration. Values after monetary and intravenous choices are shown on the left- and right-graphs, respectively. Group means with standard error for absolute change in heart rate (beats per minute) after cocaine self-administration are shown for 5 to 9 participants per condition. * indicates a significant effect of lorcaserin corresponding to $p < 0.001$.

laboratory setting (Lukas et al., 2001; Hart et al., 2008). Based on an initial power analysis outlined above, sample size for the present study was adequate. Nonetheless, relatively few participants were evaluated with a large number of measures included. Only males were included, with most participants being of African American race. Lorcaserin is rapidly absorbed, reaching peak plasma concentrations within 2 h of dosing (Arena Pharmaceuticals, 2012). Initial measures following injections of low-dose cocaine in the present study preceded peak concentrations of lorcaserin. Nonetheless, lorcaserin clearly modified the subjective and cardiovascular effects of low-dose cocaine within 30 min of oral dosing, consistent with its rapid effects after supratherapeutic doses in a previous study (Shram et al., 2011). Lorcaserin accumulates to approximately 30% higher plasma concentrations after chronic dosing (Smith et al., 2009), which may have decreased its effects in the present single-dose study relative to chronic dosing. Because our participants were non-treatment seeking, we cannot exclude a therapeutic value on drug taking in patients who are motivated to avoid cocaine use. Further study is needed to determine whether effects of lorcaserin treatment will translate into a clinical benefit in cocaine use disorders.

5. Conclusions

Double-blind treatment with oral lorcaserin did not decrease primary measures of drug taking and cocaine-induced 'high'. Changes in secondary outcomes after active treatment included a prolongation of operant responding for intravenous reinforcement and increases in drug-induced 'high' and 'stimulated' after low-dose cocaine. Pretreatment with lorcaserin augmented cocaine-induced elevations of

systolic blood pressure and had complex context-dependent effects on heart rate.

Conflict of interest

All authors declare that they have no conflict of interest pertaining to this manuscript.

Compliance with ethical standards

This protocol followed all applicable regulations for protection of human subjects as outlined by the United States Department of Health & Human Services, including the Food and Drug Administration; and was approved by our local Institutional Review Board.

Contributors

Kenneth Grasing, Principal Investigator, designed and conducted the study, organized and analyzed the data, and wrote the majority of the manuscript; Melissa Hickman and Jimmie Pirtle contributed to analyses and writing; Varun Boinpelly assisted with data analyses; Kamalakar Surineni and Hemant Thakur assisted with writing; All authors approved the final manuscript before submission.

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