Neuropsychopharmacology (2017) 42, 1082–1092

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Repeated 7-Day Treatment with the 5-HT_{2C} Agonist Lorcaserin or the 5-HT_{2A} Antagonist Pimavanserin Alone or in Combination Fails to Reduce Cocaine *vs* Food Choice in Male Rhesus Monkeys

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Cocaine use disorder is a global public health problem for which there are no Food and Drug Administration-approved pharmacotherapies. Emerging preclinical evidence has implicated both serotonin (5-HT) 2C and 2A receptors as potential mechanisms for mediating serotonergic attenuation of cocaine abuse-related neurochemical and behavioral effects. Therefore, the present study aim was to determine whether repeated 7-day treatment with the 5-HT_{2C} agonist lorcaserin (0.1–1.0 mg/kg per day, intramuscular; 0.032–0.1 mg/kg/h, intravenous) or the 5-HT_{2A} inverse agonist/antagonist pimavanserin (0.32–10 mg/kg per day, intramuscular) attenuated cocaine reinforcement under a concurrent 'choice' schedule of cocaine and food availability in rhesus monkeys. During saline treatment, cocaine maintained a dose-dependent increase in cocaine *vs* food choice. Repeated pimavanserin (3.2 mg/kg per day) treatments significantly increased small unit cocaine dose choice. Larger lorcaserin (1.0 mg/kg per day and 0.1 mg/kg/h) and pimavanserin (10 mg/kg per day) doses primarily decreased rates of operant behavior. Coadministration of ineffective lorcaserin (0.1 mg/kg per day) and pimavanserin (0.32 mg/kg per day) doses also failed to significantly alter cocaine choice. These results suggest that neither 5-HT_{2C} receptor activation nor 5-HT_{2A} receptor blockade are sufficient to produce a therapeutic-like decrease in cocaine choice and a complementary increase in food choice. Overall, these results do not support the clinical utility of 5-HT_{2C} agonists and 5-HT_{2A} inverse agonists/antagonists alone or in combination as candidate anti-cocaine use disorder pharmacotherapies.
Neuropsychopharmacology (2017) **42,** 1082–1092; doi:10.1038/npp.2016.259; published online 14 December 2016

INTRODUCTION

Cocaine use disorder is a worldwide public health problem for which there are no approved pharmacotherapies (Acri and Skolnick, 2013; Czoty *et al*, 2016) Serotonin (5-HT) 5-HT_{2C} and 5-HT_{2A} receptors modulate mesolimbic dopamine neurotransmission that mediates the abuse-related effects of cocaine, and as a result, these receptors have emerged as pharmacological targets for candidate cocaine use disorder medications (Alex and Pehek, 2007; Howell and Cunningham, 2015). Both 5-HT_{2C} and 5-HT_{2A} receptors are excitatory G_q/G_{11}-protein coupled receptors (Hannon and Hoyer, 2008), but their distinct anatomical locations within the mesolimbic dopamine system result in distinct effects on dopaminergic neurotransmission. 5-HT_{2C} receptors are located primarily on GABA-ergic neurons that inhibit dopamine neurons, and as a result, stimulation of 5-HT_{2C} receptors excites GABA neurons, subsequently inhibits dopamine neurons, and attenuates abuse-related effects of cocaine. For example, acute pretreatment with the 5-HT_{2C} agonist RO 60-0175 attenuated cocaine-induced extracellular nucleus accumbens (NAc) dopamine increases in both rats (Cathala *et al*, 2015; Navailles *et al*, 2008) and monkeys (Manvich *et al*, 2012). Consistent with this neurochemical evidence, acute pretreatments with RO 60-0175 or the 5-HT_{2C} agonist lorcaserin in rats and monkeys attenuated cocaine discrimination (Callahan and Cunningham, 1995; Collins *et al*, 2016), cocaine self-administration (Collins *et al*, 2016; Cunningham *et al*, 2011; Fletcher *et al*, 2008; Gerak *et al*, 2016; Grottick *et al*, 2000; Harvey-Lewis *et al*, 2016; Manvich *et al*, 2012) and cocaine-induced reinstatement of extinguished cocaine self-administration (Cunningham *et al*, 2011; Gerak *et al*, 2016; Harvey-Lewis *et al*, 2016; Manvich *et al*, 2012; Rüedi-Bettschen *et al*, 2015). Additionally, lorcaserin-induced decreases in cocaine self-administration were sustained during chronic lorcaserin treatment in monkeys (Collins *et al*, 2016; Gerak *et al*, 2016). These results have been interpreted to suggest that 5-HT_{2C} agonists might have utility as candidate cocaine use disorder pharmacotherapies, but it

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Received 28 September 2016; revised 27 October 2016; accepted 14 November 2016; accepted article preview online 18 November 2016

should be noted that lorcaserin treatments that decreased cocaine self-administration also decreased food-maintained responding in monkeys. Poor selectivity of treatment effects on cocaine- *vs* food-maintained responding in preclinical studies is often associated with poor treatment outcomes in clinical trials (Mello and Negus, 1996).

In contrast to 5-HT$_{2C}$ receptors, 5-HT$_{2A}$ receptors are located primarily on dopamine neurons, and as a result, attenuation of dopamine neuronal activity can theoretically be achieved not by stimulating 5-HT$_{2A}$ receptors, but by inhibiting them. Consistent with this possibility, intra-accumbens pretreatment with the 5-HT$_{2A}$ antagonist M100,907 attenuated cocaine-induced NAc extracellular dopamine increases in the rat (Zayara *et al*, 2011). Systemic M100,907 failed to attenuate cocaine-induced NAc extracellular dopamine increases, but did attenuate cocaine-induced striatal dopamine increases in monkeys (Murnane *et al*, 2013). Furthermore, pretreatment with M100,907 (Fletcher *et al*, 2002; McMahon and Cunningham, 2001; Murnane *et al*, 2013) or another 5-HT$_{2A}$ antagonist ketanserin (Munzar *et al*, 2002) attenuated the discriminative stimulus and reinstating effects of cocaine in both rats and monkeys. Although acute 5-HT$_{2A}$ antagonist pretreatments have failed to attenuate cocaine self-administration in both rats (Filip, 2005; Fletcher *et al*, 2002; Nic Dhonnchadha *et al*, 2009) and monkeys (Fantegrossi *et al*, 2002; Murnane *et al*, 2013), repeated 5-HT$_{2A}$ antagonist treatment effects on cocaine self-administration are unknown.

The study goal was to further evaluate the potential of 5-HT$_2$ receptor ligands as candidate medications for cocaine use disorder. Specifically, this study examined repeated 7-day treatment effects with the 5-HT$_{2C}$ agonist lorcaserin or the 5-HT$_{2A}$ inverse agonist/antagonist pimavanserin, administered alone or in combination, on cocaine self-administration by rhesus monkeys in the context of a cocaine-*vs*-food choice procedure that has been used previously to examine effects of other candidate medications (Banks *et al*, 2015). Lorcaserin was investigated because it is more selective for 5-HT$_{2C}$ *vs* 5-HT$_{2A}$ than RO 60-0175 (Bentley *et al*, 2004; Thomsen *et al*, 2008) and because it has been approved by the U.S. Food and Drug Administration (FDA) for obesity treatment (Shukla *et al*, 2015). Pimavanserin was investigated because it is a 5-HT$_{2A}$ antagonist/inverse agonist (Vanover *et al*, 2006) that has received FDA approval for Parkinson's disease-induced psychosis treatment (Walsh, 2016). The combination was evaluated because recent evidence suggests a potential for synergism in 5-HT$_{2C}$ agonist and 5-HT$_{2A}$ antagonist effects (Cunningham *et al*, 2013). Repeated treatment effects were determined because pharmacotherapies for substance use disorders are typically administered chronically in the clinic, and repeated treatment regimens enhance preclinical-to-clinical translation (Comer *et al*, 2008; Czoty *et al*, 2016; Haney and Spealman, 2008; Mello and Negus, 1996). A cocaine *vs* food choice procedure was used for two reasons. First, choice procedures provide a measure of behavioral allocation that permits dissociation of treatment effects on the relative reinforcing effectiveness of cocaine from nonselective effects on operant responding (Banks and Negus, 2012). Second, preclinical choice procedures promote preclinical-to-clinical translation of results, both because human laboratory studies also commonly use choice procedures to assess candidate medication effects on cocaine self-administration, and because a clinical goal of treatment is both to reduce cocaine use and to increase more adaptive behaviors maintained by nondrug reinforcers (Comer *et al*, 2008; Haney and Spealman, 2008; Vocci, 2007). On the basis of the preclinical neurochemical and behavioral evidence cited above, we hypothesized that repeated lorcaserin and pimavanserin treatment would attenuate cocaine choice and produce a complementary increase in food choice.

MATERIALS AND METHODS

Subjects

Studies were conducted in a total of eight adult male rhesus monkeys (*Macaca mulatta*) of either Indian or Chinese origin. Three monkeys were used in studies of schedule-controlled responding for food delivery, and five monkeys were surgically implanted with a double-lumen venous catheter (STI Components, Raleigh, NC or Reiss Manufacturing, Blackstone, VA) for studies of cocaine *vs* food choice. Of these five catheterized monkeys, three had prior cocaine self-administration histories, and two had prior methamphetamine discrimination histories. Monkeys could earn 1 g banana-flavored pellets (Grain-based Precision Primate Tablets; Test Diets, Richmond, IL) during daily experimental sessions (see below). The monkeys diet consisted of food biscuits (Lab Diet High Fiber Monkey Biscuits; PMI Feeds, St Louis, MO) and fresh fruit delivered in the afternoons after behavioral sessions to minimize the effects of biscuit availability and consumption on food-maintained operant responding. Water was continuously available in each monkey's home chamber, which also served as the experimental chamber. A 12 h light/dark cycle was in effect (lights on from 0600 to 1800 h). Environmental enrichment, which consisted of movies displayed on a monitor in the housing room and foraging boards loaded with nuts, seeds, or diced vegetables was also provided after behavioral sessions. Facilities were licensed by the United States Department of Agriculture and accredited by the Association for Assessment and Accreditation of Laboratory Animal Care. The Institutional Animal Care and Use Committee approved all experimental and enrichment protocols. Animal research and husbandry were conducted according to the eighth edition of the Guide for the Care and Use of Laboratory Animals.

Assay of Schedule-Controlled Responding

Behavioral procedure. To provide an initial assessment of the potency and time course of intramuscular (IM) lorcaserin and pimavanserin in rhesus monkeys, experiments were conducted in a food-maintained schedule-controlled responding procedure. As described previously (Banks *et al*, 2010), each home chamber was equipped with a customized operant response panel, which had a response key that could be transilluminated red, and a pellet dispenser (Med Associates, ENV-203–1000, St. Albans, VT) that delivered food pellets to a receptacle below the operant panel. The panel was controlled by a MED-PC interface and an IBM compatible computer programmed in MEDSTATE Notation (Med Associates). Experimental sessions were 150 min in

duration and consisted of five 30 min cycles. Each cycle consisted of two components: a 25 min time-out period followed by a 5 min response period. During the time-out period, no stimulus lights were illuminated, and responding had no scheduled consequences. During the response period, the right key was transilluminated red and subjects could respond for up to 10 food pellets under a fixed-ratio 30 (FR30) schedule of reinforcement. If all 10 food pellets were earned before 5 min had elapsed, the lights were turned off and responding had no scheduled consequences for the remainder of that response period. All monkeys were trained until they responded at relatively stable rates $\geq$ 1.0 response per second during all five cycles for 10 consecutive days (data not shown).

Behavioral sessions were conducted 5 days a week. Test sessions were usually conducted on Tuesdays and Fridays, and training sessions were conducted on Mondays, Wednesdays, and Thursdays. In addition, test sessions were conducted only after a training session during which the monkeys responded at rates $\geq$ 1.0 response per second for all five cycles. During training sessions, monkeys received either no injection or saline injections at the beginning of each cycle. During time course test sessions, either saline, lorcaserin (0.1–1.0 mg/kg, IM) or pimavanserin (1.0–10.0 mg/kg, IM) was administered, and 5 min response periods were initiated 10, 30, 100, 130, 300 min, and 24 h after administration.

Data analysis. Raw response rates from each test cycle were converted to percent of control using the average rate from the previous training day in that monkey as the control value. data were analyzed (JMP Pro 12.2.0, SAS, Cary, NC) using a two-way repeated-measures ANOVA with drug dose and time as the main factors. In the presence of a significant main effect of drug dose or drug dose × time interaction, post *hoc* analyses were conducted using the Dunnett post *hoc* test for comparisons with saline within a given time point. The criterion for significance was set *a priori* at the 95% confidence level ($P < 0.05$).

Assay of Cocaine *vs* Food Choice

Behavioral procedure. As described previously (Banks *et al*, 2011), each housing chamber was equipped with a customized operant response panel, which had two response keys that could be transilluminated red or green, and a pellet dispenser (Med Associates, ENV-203–1000) that delivered food pellets to a receptacle below the operant panel. The externalized portion of the intravenous (IV) catheter was routed through a custom jacket and tether system connected to a dual-channel fluid swivel (Lomir Biomedical, Malone, NY) on the chamber top and then to two safety syringe pumps (Med Associates, PHM-108), one for each lumen of the double-lumen catheter. One pump was used to deliver contingent cocaine injections through one lumen of the double-lumen catheter. The second pump was used to deliver noncontingent saline or lorcaserin (0.032-0.1 mg/kg/h) injections through the second lumen at a programmed rate of 0.1 ml injections every 20 min from 1200 h each day until 1100 h the next morning. Catheter patency was periodically evaluated with IV ketamine (Vedco, St Joseph, MO) administration and after any treatment that produced a rightward shift in the cocaine choice dose-effect function. The catheter was considered patent if IV ketamine administration produced muscle tone loss within 10 s.

Daily experimental sessions were conducted from 0900 to 1100 h in each monkey's home chamber as described previously (Banks *et al*, 2011). The terminal choice schedule consisted of five 20 min components separated by 5 min inter-component intervals, during which responding had no scheduled consequences. During each component, the left, food-associated key was transilluminated red, and completion of the FR requirement (FR100) resulted in food pellet delivery. In addition, the right, cocaine-associated key was transilluminated green, and completion of the FR requirement (FR10) resulted in delivery of the IV unit cocaine dose available during that component. The unit cocaine doses available during each of the five successive components were 0, 0.0032, 0.01, 0.032, and 0.1 mg/kg per injection, respectively. Stimulus lights on the cocaine-associated key were flashed on and off in 3 s cycles, and longer flashes were associated with higher cocaine doses. Ratio requirement completion initiated a 3 s timeout, during which all stimulus lights were turned off, and responding had no scheduled consequences. Experimental parameters used in this study were based on extensive parametric manipulations (Banks *et al*, 2013b; Negus, 2003) and permitted detection of both leftward and rightward shifts in the cocaine choice dose-effect function. Choice behavior was considered to be stable when the lowest unit cocaine dose maintaining at least 80% cocaine *vs* food choice varied by $\leq$ 0.5 log units for 3 consecutive days. The data from these 3 days were subsequently used as the 'baseline' for statistical and graphical comparisons with each pharmacological treatment.

Once cocaine *vs* food choice was stable, experimental test periods were conducted to determine lorcaserin or pimavanserin treatment effects on cocaine *vs* food choice. Each dose of lorcaserin (0.1–1.0 mg/kg per day IM) or pimavanserin (0.32–10 mg/kg per day IM) was tested by repeated administration for seven consecutive days. IM lorcaserin doses were administered between 0840 and 0850 h, and IM pimavanserin doses were administered between 0755 and 0805 h, before the start of the 0900 h behavioral choice session. At the conclusion of each 7-day treatment period, treatments were terminated for at least 4 days and until cocaine *vs* food choice had returned to pretest levels. Each drug treatment was evaluated in a cohort of four monkeys, and three monkeys received both drugs alone and the combination. The dose order within each drug was counterbalanced across subjects, and in those monkeys that received both lorcaserin and pimavanserin, pimavanserin was tested first. The largest pimavanserin dose (10 mg/kg per day) produced large decreases in food-maintained responding, biscuit consumption, or body weights so this dose was tested in only two monkeys. A follow-up study evaluated effects of combined treatment with the largest inactive doses of repeated lorcaserin (0.1 mg/kg) and pimavanserin (0.32 mg/kg) in four monkeys.

Data analysis. The primary-dependent measures for each component were percent cocaine choice, defined as (number of ratio requirements, or 'choices', completed on the cocaine-associated key/total number of ratio requirements completed

on both the cocaine- and food-associated keys) × 100 and rates of operant responding in responses per second. Mean data from the 3 days preceding each pharmacological treatment were averaged for each individual monkey and then averaged across monkeys to yield the group mean 'baseline' data. Mean data from the last 3 days of each 7-day lorcaserin, pimavanserin, or lorcaserin+pimavanserin treatment were averaged for each individual monkey and then averaged across monkeys to yield the group mean data. Percent cocaine choice was then plotted as a function of the unit cocaine dose and analyzed using a mixed-model analysis (JMP Pro 12, SAS) with treatment drug-dose and unit cocaine dose as the fixed main effects and subject as the random effect. A Dunnett's test was performed to compare treatment effects with baseline within a unit cocaine dose. Additional dependent measures collected during each behavioral session included the numbers of food, cocaine, and total choices summed across all components, and these data were analyzed using one- or two-way repeated-measures ANOVA and a Dunnett's test as appropriate. The criterion for significance was set *a priori* at the 95% confidence level ($P < 0.05$).

Drugs

(−)-Cocaine HCl, lorcaserin HCl, and pimavanserin L-tartrate were provided by the National Institute on Drug Abuse Drug Supply Program (Bethesda, MD). All drugs were dissolved in sterile water, and all solutions were passed through a 0.22 micron sterile filter (Millipore, Billerica, MA) before either intravenous or intramuscular administration. Drug doses were calculated and expressed using the salt forms listed above.

RESULTS

Lorcaserin and Pimavanserin Effects on Schedule-Controlled Responding

The average ± SEM control rate of responding throughout the study was 2.44 ± 0.24 responses/s. Both lorcaserin (dose: $F_{3,40} = 31.3$, $P < 0.0001$; interaction: $F_{11,40} = 4.0$, $P = 0.006$) and pimavanserin (dose: $F_{1.03,2.07} = 66.4$, $P = 0.0133$) significantly decreased rates of operant responding (Figure 1). For lorcaserin, both 0.32 and 1.0 mg/kg significantly decreased response rates, and the time course of these lorcaserin effects were dose dependent and dissipated by 5 h (Figure 1a). Pimavanserin had a slow onset of action, and a significant decrease in response rates was not observed until 24 h after 10 mg/kg pimavanserin (Figure 1b). Response rates were not evaluated again until 72 h after pimavanserin treatment, and by this time, rates recovered to baseline levels (data not shown). On basis of these behavioral results and human pimavanserin neuroimaging and pharmacokinetic data (Nordstrom *et al*, 2008), lorcaserin was administered as a 15 min pretreatment and pimavanserin was administered as a 60 min pretreatment for the cocaine *vs* food choice experiments.

Because the IM lorcaserin time course effects on food-maintained responding were dissipating by the 135 min time point, a time point that corresponded with fourth and fifth components of the cocaine *vs* food choice session where cocaine was primarily chosen over food, a follow-up study was conducted evaluating 7-day treatment effects of lorcaserin (0.032–0.1 mg/kg/h) using a continuous intravenous delivery procedure previously described by our laboratory (Banks *et al*, 2013a; Negus, 2004). Due to limited lorcaserin supply, 0.1 mg/kg/h lorcaserin was tested in four monkeys and 0.032 mg/kg/h lorcaserin was tested in two monkeys. At the conclusion of each 7-day treatment period, saline treatment conditions were instituted for at least 4 days and until cocaine *vs* food choice had returned to pretest levels. Lorcaserin doses were evaluated in descending order. Pimavanserin was not evaluated under continuous intravenous delivery conditions due to the long and protracted time course of effects in the assay of schedule-controlled responding.

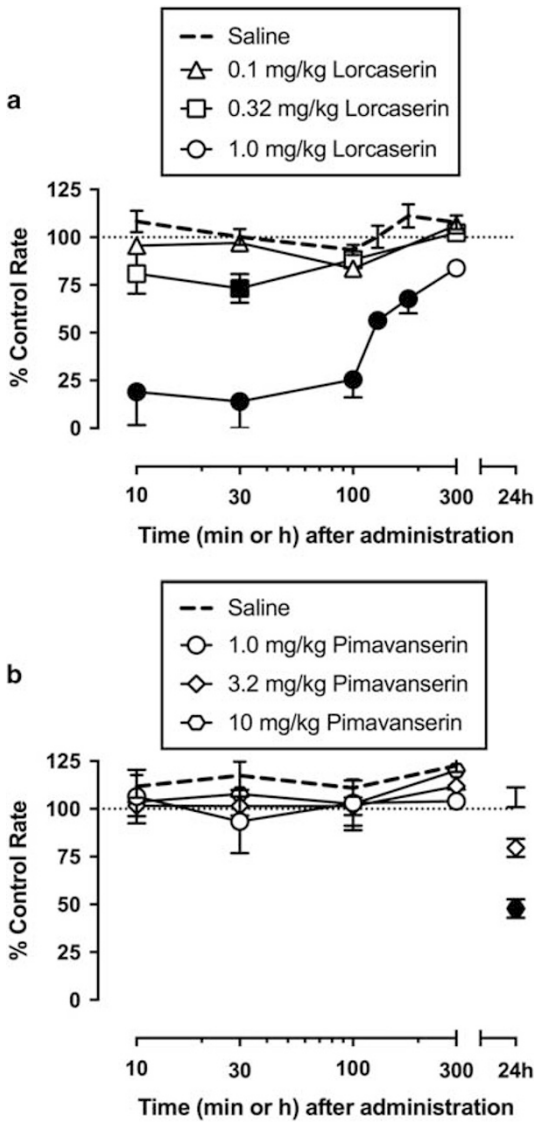

Figure 1 Potency and time course of acute (a) lorcaserin (0.1–1.0 mg/kg, intramuscular) and (b) pimavanserin (1.0–10.0 mg/kg, intramuscular) effects in a schedule-controlled responding procedure in rhesus monkeys ($n = 3$). Abscissae: time in minutes (min) or hours (h) after drug administration. Ordinates: percent control rate of responding. All points represent mean ± SEM. Filled symbols denote significantly different from saline ($p < 0.05$).

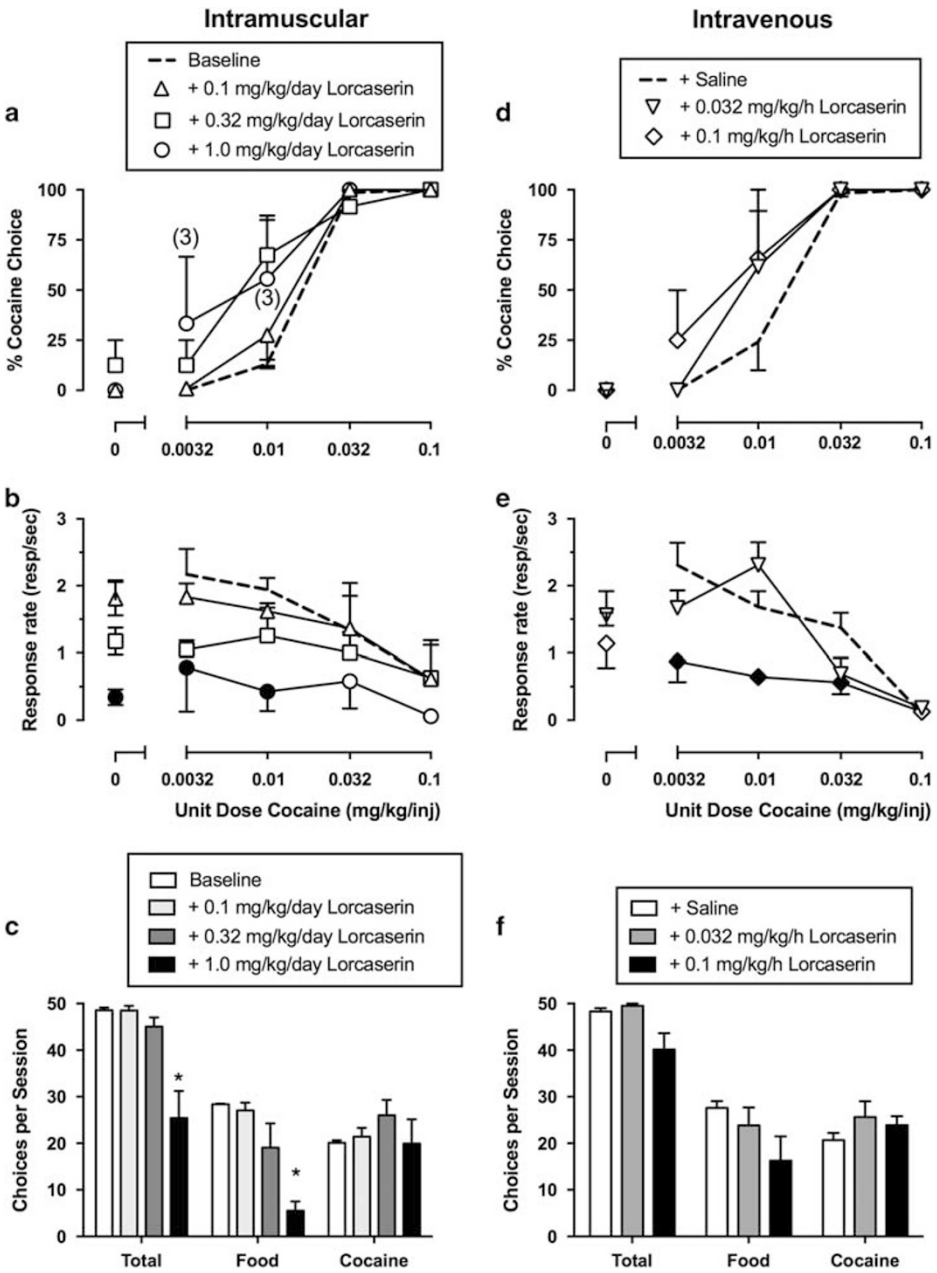

Figure 2 Effects of 7-day intramuscular (0.1–1.0 mg/kg per day, IM; a–c) or intravenous (0.032–0.1 mg/kg/h, IV; d–f) lorcaserin treatment on choice between cocaine and food in rhesus monkeys. Intramuscular (IM) lorcaserin was administered daily 15 min before the behavioral session. Top and middle abscissae: unit dose cocaine in mg/kg per injection. Top ordinate: percent cocaine choice. Middle ordinate: rates of operant responding per component in responses per second. Bottom abscissa: dependent measure. Bottom ordinate: number of choices per session. All points and bars represent mean ± SEM obtained during days 5–7 of each 7-day treatment period. Filled symbols in top panels, and * in the bottom panel, denote significantly different from baseline ($p < 0.05$). IM lorcaserin and 0.1 mg/kg/h IV lorcaserin were evaluated in 4 monkeys. 0.032 mg/kg/h IV lorcaserin was evaluated in 2 monkeys.

Lorcaserin Effects on Cocaine Choice

Under baseline conditions, monkeys primarily chose food when cocaine was not available (0 mg/kg per injection) or the unit cocaine dose was small (0.0032–0.01 mg/kg per injection) and almost exclusively reallocated their behavior to cocaine choice during availability of larger unit cocaine doses (0.032–0.1 mg/kg per injection) (Figures 2,3,4; dashed lines). Figure 2 shows 7-day repeated lorcaserin (0.1–1.0 mg/kg per day) and (0.032–0.1 mg/kg/h) treatment effects on cocaine choice (A, D), rates of operant responding per component (B, E), and numbers of total, food, and cocaine choices per session (C, F), respectively. Because 0.032 mg/kg/h lorcaserin was only tested in two monkeys, statistical analyses were only conducted on the 0.1 mg/kg/h lorcaserin data. Repeated IM or IV lorcaserin treatment did not significantly alter percent cocaine choice. Both 1.0 mg/kg per day (lorcaserin: $F_{3,9} = 13.2$, $p = 0.0012$) and 0.1 mg/kg/h (lorcaserin: $F_{1,3} = 17.7$, $p = 0.0245$; interaction: $F_{3,9} = 5.0$, $p = 0.0267$) lorcaserin significantly decreased rates of operant responding. 1.0 mg/kg per day lorcaserin also significantly

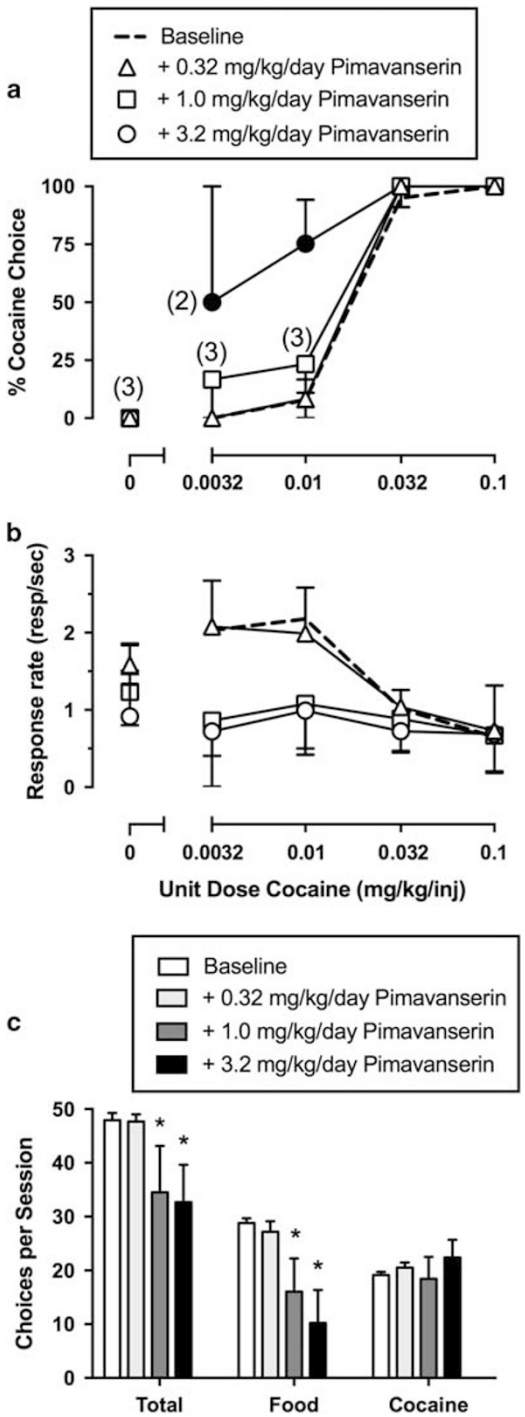

Figure 3 Effects of 7-day intramuscular pimavanserin (0.32–3.2 mg/kg per day, IM) treatment on choice between cocaine and food in rhesus monkeys ($n=4$). IM pimavanserin was administered daily 60 min before the behavioral session. Top and middle abscissae: unit dose cocaine in mg/kg per sinjection. Top ordinate (a): percent cocaine choice. Middle ordinate (b): rates of responding per component in responses per second. Bottom abscissa: dependent measure. Bottom ordinate (c): number of choices per session. All points and bars represent mean ± SEM obtained during days 5–7 of each 7-day treatment period. Numbers in parentheses indicate the number of monkeys contributing to that data point if fewer than the total number ($n=4$) of monkeys tested and denote a component of the behavioral procedure in which one or more monkeys failed to complete at least one response requirement. Filled symbols in top panel, or * in the bottom panel, denote significantly different from baseline ($p<0.05$).

decreased both total and food choices per session (2C; dependent measure: $F_{2,24}=74.7$, $p<0.0001$; lorcaserin dose: $F_{3,12}=12.7$, $p=0.0005$; interaction: $F_{6,24}=4.9$, $p=0.002$).

Pimavanserin Effects on Cocaine Choice

Figure 3 shows 7-day repeated pimavanserin treatment effects on cocaine choice (A), rates of operant responding per component (B), and the overall numbers of total, food, and cocaine choices for the entire session (C). Pimavanserin produced a dose-dependent increase in cocaine choice and a decrease in the numbers of total and food choices per session. Repeated 3.2 mg/kg per day pimavanserin significantly increased preference for smaller unit cocaine doses (0.0032–0.01 mg/kg/injection) (cocaine: $F_{3,41}=36.2$, $p<0.0001$; pimavanserin: $F_{3,41.6}=4.0$, $p=0.013$; interaction: $F_{9,41.2}=3.0$, $p=0.0071$). Furthermore, repeated 1.0 and 3.2 mg/kg per day pimavanserin significantly decreased the numbers of both total and food choices per session (dependent measure: $F_{2,6}=149.7$, $p<0.0001$; interaction: $F_{6,18}=3.0$, $p=0.0324$). Repeated 10 mg/kg per day pimavanserin eliminated food-maintained responding during concurrent cocaine availability such that both monkeys exclusively chose cocaine over food when they responded (Figure 4).

Pimavanserin and Lorcaserin Coadministration Effects on Cocaine Choice

Figure 5 shows 7-day repeated 0.32 mg/kg per day pimavanserin+0.1 mg/kg per day lorcaserin coadministration treatment effects on cocaine choice (A), rates of operant responding per component (B), and numbers of total food, and cocaine choices per session (C). This combination of pimavanserin and lorcaserin doses did not significantly alter any experimental dependent measure.

DISCUSSION

The present study examined repeated 7-day treatment effects with either the 5-HT$_{2C}$ agonist lorcaserin or the 5-HT$_{2A}$ inverse agonist/antagonist pimavanserin, administered alone or in combination, on cocaine *vs* food choice in rhesus monkeys. There were three main findings. First, both acute and repeated lorcaserin and pimavanserin treatment dose-dependently decreased rates of operant responding in monkeys. Second, both lorcaserin and pimavanserin failed to decrease cocaine *vs* food choice at doses at or below those that decreased overall rates of operant responding and reinforcement. Finally, a single combination of ineffective lorcaserin and pimavanserin doses failed to alter cocaine choice, rates of responding, or rates of reinforcement. Overall, the present results do not support the clinical utility of either 5-HT$_{2C}$ agonists or 5-HT$_{2A}$ inverse agonists/antagonists alone or in combination as candidate anti-cocaine use disorder pharmacotherapies.

Lorcaserin Effects on Cocaine Choice

5-HT$_{2C}$ agonists in general, and lorcaserin in particular, have recently emerged as intriguing candidate medications for cocaine use disorder treatment. Enthusiasm for 5-HT$_{2C}$

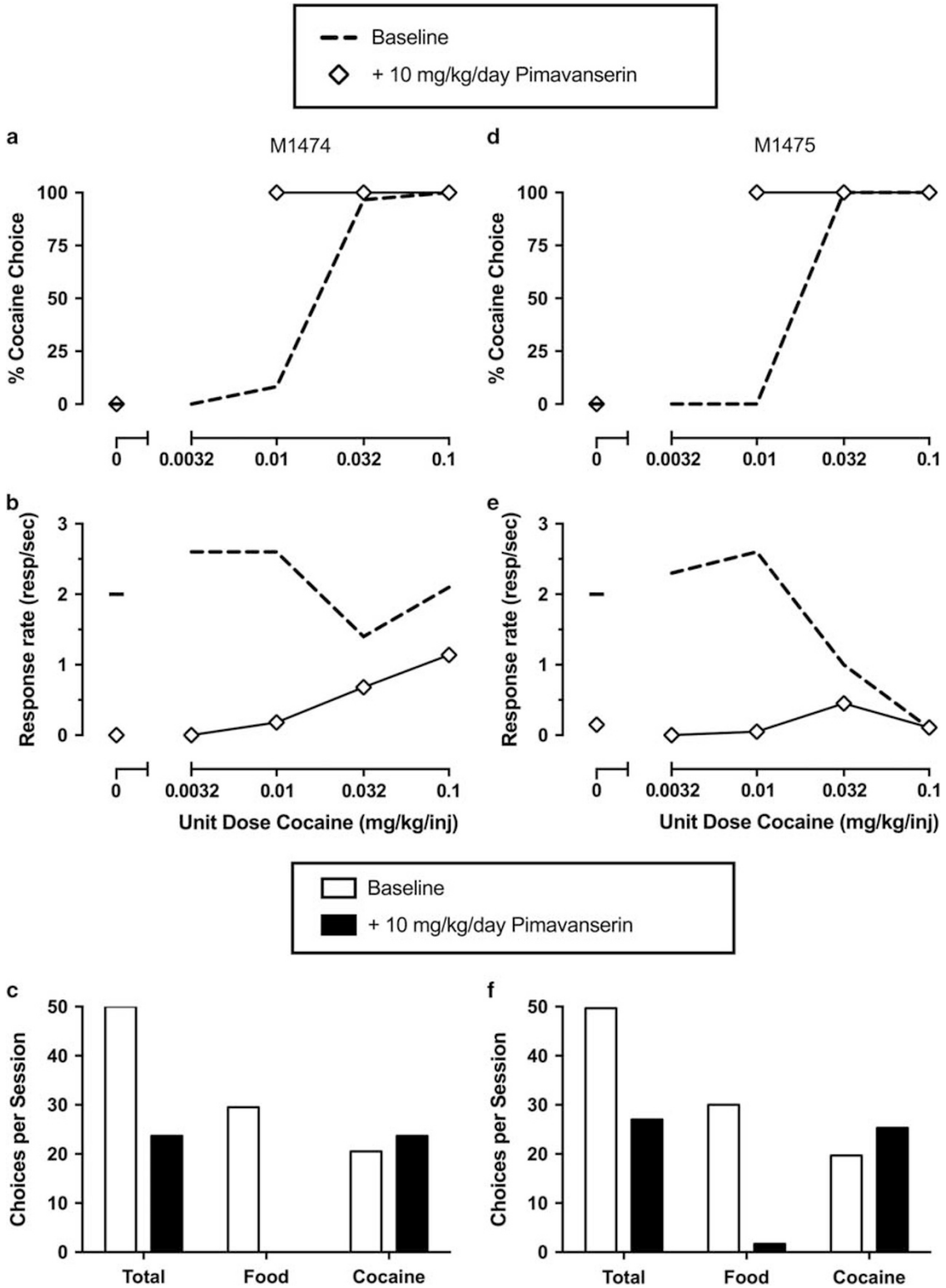

Figure 4 Effects of 7-day pimavanserin (10 mg/kg per day, IM) treatment on choice between cocaine and food in individual rhesus monkeys. IM pimavanserin was administered daily 60 min before the behavioral session. Top and middle abscissae: unit dose cocaine in mg/kg/injection. Top ordinates (a, d): percent cocaine choice. Middle ordinates (b, e): rates of operant responding per component in responses per second. Bottom abscissae: dependent measure. Bottom ordinates (c, f): number of choices per session. All points represent mean data obtained during days 5–7 of each 7-day treatment period. Error bars are not shown due to individual subject data.

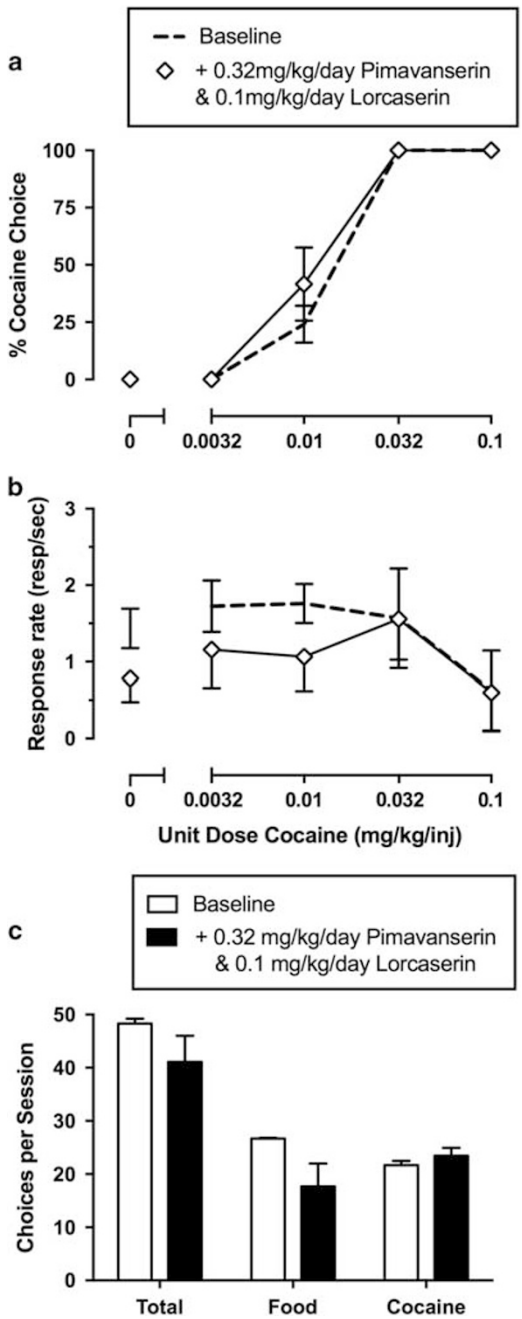

Figure 5 Effects of 7-day combined intramuscular pimavanserin (0.32 mg/kg, IM)+lorcaserin (0.1 mg/kg, IM) treatment on choice between cocaine and food in rhesus monkeys ($n=4$). IM pimavanserin and lorcaserin were administered daily 60 min and 15 min, respectively before the behavioral session.Top and middle abscissae: unit dose cocaine in mg/kg per injection. Top ordinate (a): percent cocaine choice. Middle ordinate (b): rates of operant responding per component in responses per second. Bottom abscissa: dependent measure. Bottom ordinate (c): number of choices per session. All points and bars represent mean ± SEM obtained during days 5–7 of each 7-day treatment period.

agonists stems in part from evidence in rats (Cunningham *et al*, 2011; Fletcher *et al*, 2008; Grottick *et al*, 2000; Harvey-Lewis *et al*, 2016) and nonhuman primates (Collins *et al*, 2016; Gerak *et al*, 2016; Manvich *et al*, 2012) that 5-HT$_{2C}$ agonists produce dose-dependent decreases in cocaine self-administration after acute treatment and sustained decreases in cocaine self-administration during repeated treatment for periods up to 14 days. A caveat to these results has been that 5-HT$_{2C}$ agonist doses that decrease cocaine self-administration also usually decrease responding maintained by other reinforcers. For example, RO 60-0175 was equipotent to decrease responding maintained by 0.25 mg/injection cocaine and 45 mg food pellets in rats (Grottick *et al*, 2000), and lorcaserin was equipotent to decrease responding maintained by 0.032 mg/kg per injection cocaine and 300 mg food pellets in rhesus monkeys (Collins *et al*, 2016). In squirrel monkeys, RO 60-0175 was slightly (<3-fold) more potent to decrease self-administration maintained by a range of cocaine doses than by termination of a stimulus associated with shock delivery; however, another 5-HT$_{2C}$ agonist, mCPP, did not display this selectivity, and in rats, the 5-HT$_{2C}$ agonist WAY 163909 was actually less potent to decrease cocaine self-administration than sucrose-maintained responding (Cunningham *et al*, 2011; Manvich *et al*, 2012). Taken together, these results suggest that 5-HT$_{2C}$ agonists do not selectively decrease the reinforcing effectiveness of cocaine, but rather produce nonselective decreases in operant responding maintained by a broad range of reinforcers.

In agreement with these previous studies, the present study found that lorcaserin produced a dose-dependent, but nonselective, decrease in responding maintained by cocaine and food. Additionally, the failure of lorcaserin to decrease measures of cocaine-*vs*-food choice provides additional evidence to suggest that lorcaserin did not decrease the relative reinforcing efficacy of cocaine in comparison with food. This profile of nonselective decreases in operant responding and failure to decrease cocaine-*vs*-food choice in preclinical studies has generally predicted poor outcomes in clinical trials (Banks *et al*, 2015; Czoty *et al*, 2016; Mello and Negus, 1996). As a result, we interpret the present and previous results as evidence against the hypothesis that 5-HT$_{2C}$ agonists will have utility for cocaine use disorder treatment.

Insofar as behavioral selectivity to decrease cocaine self-administration and cocaine choice is a desirable attribute of candidate medications, it important to note that expression of behavioral selectivity can be influenced by factors independent of the mediction, such as the unit cocaine dose and the type and magnitude of the alternative reinforcer. Regarding cocaine dose, for example, lorcaserin was equipotent (ie, nonselective) to decrease responding maintained by 0.032 mg/kg per injection cocaine and 300 mg food pellets in rhesus monkeys, but even the highest lorcaserin-doses tested in that study failed to decrease self-administration of higher cocaine doses (0.1–0.32 mg/kg per injection) (Collins *et al*, 2016; Gerak *et al*, 2016). More generally, the behavioral selectivity of candidate medications or other treatments to decrease cocaine self-administration or cocaine choice is often inversely related to the unit cocaine dose, with greater selectivity at lower cocaine doses (Banks *et al*, 2013b; Mello and Negus, 1996; Stafford *et al*, 2000). Medications that display behavioral selectivity to decrease large- as well as small-dose cocaine self-administration might be optimal, in part, because drug abuse typically involves the use of large doses and also because responding maintained by small doses can often be reduced by nonpharmacological

strategies (eg, contingency management) (Donny *et al*, 2003; Lile *et al*, 2016).

Preclinical measures of behavioral selectivity can also be influenced by parameters of the alternative reinforcer. Of particular relevance for this study, lorcaserin is clinically approved as an anorectic medication for treatment of obesity, and it has established effectiveness to reduce food consumption (Shukla *et al*, 2015). This raises the possibility that lorcaserin treatment decreased the relative reinforcing effectiveness of food and cocaine equally, resulting in a net no change in cocaine-*vs*-food choice behavior. An implication of this alternative explanation would be that behavioral selectivity of lorcaserin effects on cocaine self-administration might improve if an alternative reinforcer other than food were used. Some support for this possibility is provided by the comparison of 5-HT$_{2C}$ agonist effects on responding maintained in squirrel monkeys by cocaine and by termination of a stimulus associated with shock delivery (Manvich *et al*, 2012). However, even in this study, effects of one 5-HT$_{2C}$ agonist (mCPP) were nonselective, and effects of the other (RO 60-0175) were only weakly selective. Additionally, the failure of lorcaserin to decrease cocaine-*vs*-food choice in the present study contrasts with the effectiveness of other clinically approved anorectic drugs (eg, d-amphetamine and phendimetrazine) to decrease cocaine-*vs*-food choice under identical conditions (Banks *et al*, 2011; Banks *et al*, 2013a). These results suggest that evidence of poor selectivity for 5-HT$_{2C}$ agonists to decrease cocaine self-administration and cocaine choice cannot be attributed solely to use of food as the alternative reinforcer. More generally, the present results extend the range of conditions under which 5-HT$_{2C}$ agonists fail to produce selective decreases in cocaine self-administration.

Pimavanserin and Lorcaserin+Pimavanserin Effects on Cocaine Choice

Repeated treatment with the 5-HT$_{2A}$ inverse agonist/antagonist pimavanserin also failed to attenuate cocaine choice and produce a complementary increase in food choice up to pimavanserin doses that disrupted rates of responding. The present results confirm and extend previous findings that acute 5-HT$_{2A}$ antagonist pretreatment does not attenuate cocaine self-administration in either rats (Filip, 2005; Fletcher *et al*, 2002; Nic Dhonnchadha *et al*, 2009) or monkeys (Fantegrossi *et al*, 2002; Murnane *et al*, 2013). Thus, repeated pimavanserin treatment in the present study did not reveal a therapeutic-like rightward shift in the cocaine choice dose-effect function. Furthermore, the present results are also consistent with repeated quetiapine (Brutcher and Nader, 2015) and risperidone (Hutsell *et al*, 2016) treatment effects on cocaine choice. These two atypical antipsychotics possess 5-HT$_{2A}$ antagonist properties (Richelson and Souder, 2000), and like pimavanserin, they also failed to decrease cocaine *vs* food choice in rhesus monkeys. Overall, the present results and the extant preclinical literature suggest that 5-HT$_{2A}$ receptors are not necessary for cocaine reinforcement and that 5-HT$_{2A}$ antagonists do not represent a promising class of anti-cocaine use disorder medications.

One potential strategy to reduce undesirable effects and enhance the therapeutic effects of canidate cocaine use disorder medications might be to combine 5-HT$_{2c}$ agonists and 5-HT$_{2A}$ antagonist treatments (Howell and Cunningham, 2015). For example, the combination of ineffective 5-HT$_{2c}$ agonist (WAY163909) and 5-HT$_{2A}$ antagonist (M100,907) doses significantly decreased both cocaine- and cue-primed reinstatement of extinguished cocaine self-administration (Cunningham *et al*, 2013). In contrast, the present study found no evidence of a therapeutic-like treatment effect on cocaine choice by combining lorcaserin and pimavanserin doses that alone did not significantly alter rates of operant responding during repeated administration. Larger-dose combinations were not tested due to nonselective decreases in rates of operant responding as reported above. However, the degree to which repeated treatment with other lorcaserin and pimavanserin dose combinations might alter cocaine choice remains to be empirically determined.

Implications for Anti-Cocaine Addiction Medication Development

Currently, there are two ongoing human-laboratory studies (NCT02680288 and NCT02537873) evaluating acute and repeated lorcaserin treatment effects on cocaine self-administration in humans. Results of these and other related studies will help to clarify both the utility of lorcaserin to treat cocaine use disorder and the profile of preclinical effects in laboratory animals that is most predictive of candidate medication effects in humans. Notably, both studies are evaluating lorcaserin effects on choice between intravenous cocaine doses and monetary alternative reinforcers, and the predominant use of choice procedures in these types of human-laboratory studies is one rationale for the use of choice procedures in preclinical studies such as the one reported here.

Further consideration of lorcaserin and pimavanserin as treatment options for cocaine use disorder will have to await the outcome of human-laboratory studies and clinical trials, but the present results can also be compared with results of other candidate medications that have already progressed through both preclinical and clinical studies. In particular, lorcaserin and pimavanserin were tested here as candidate medications hypothesized to reduce cocaine choice by reducing cocaine effects on mesolimbic dopamine release. In this regard, the effects of these 5-HT2 receptor ligands can be compared with effects of other medications hypothesized to attenuate cocaine-induced stimulation of mesolimbic dopamine transmission, including dopamine receptor antagonists (which block postsynaptic dopamine receptors) and kappa opioid receptor agonists (which activate inhibitory kappa receptors on mesolimbic dopamine neurons to inhibit dopamine release). Like lorcaserin and pimavanserin, both dopamine receptor antagonists (John *et al*, 2015; Negus *et al*, 1996) and selective kappa receptor agonists (Negus, 2004; Negus *et al*, 1997) produce nonselective decreases in cocaine- *vs* food-maintained responding and fail to decrease cocaine-*vs*-food choice in rhesus monkeys. Moreover, both dopamine receptor antagonists and kappa receptor agonists have failed to reduce cocaine use in human-laboratory studies and/or clinical trials (Grabowski *et al*, 2000; Walsh *et al*, 2001; Winhusen *et al*, 2014). Overall, then, the results of the present study with lorcaserin and pimavanserin are

consistent with other evidence from other drug classes that pharmacological inhibition of mesolimbic dopamine transmission is not an effective approach to treatment of cocaine use disorder. Additionally, the poor effectiveness of these compounds contrasts with the effectiveness of some other approaches, such as amphetamine maintenance, to produce sustained and selective decreases in cocaine self-administration and cocaine-*vs*-food choice in rats and rhesus monkeys and to decrease metrics of cocaine use in both human-laboratory studies and clinical trials (Banks *et al*, 2015; Pérez-Mañá *et al*, 2011).

FUNDING AND DISCLOSURE

Research reported in this article was supported by the National Institute on Drug Abuse of the National Institutes of Health under Award Number R01 DA026946. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. Both Banks and Negus declare that NIH has funded their research. The authors declare no conflict of interest.

ACKNOWLEDGMENTS

We acknowledge the technical assistance of Jennifer Gough, Floyd Steele, and Kaycee Faunce. We also acknowledge Kevin Costa for writing the original version of the behavioral programs. Banks and Negus were responsible for study concept and design. Banks performed the data analysis. Banks and Negus drafted the manuscript. Both authors critically reviewed content and approved the final manuscript version for publication.

REFERENCES

Acri J, Skolnick P(2013). Pharmacotherapy of substance use disorders. In: Charney D, Buxbaum J, Sklar P, Nestler EJ (eds). *Neurobiology of Mental Illness,* Oxford University Press: London, UK, 2013, pp 761–771.

Alex KD, Pehek EA (2007). Pharmacologic mechanisms of serotonergic regulation of dopamine neurotransmission. *Pharmacol Ther* **113**: 296–320.

Banks ML, Blough BE, Negus SS (2011). Effects of monoamine releasers with varying selectivity for releasing dopamine/norepinephrine versus serotonin on choice between cocaine and food in rhesus monkeys. *Behav Pharmacol* **22**: 824–836.

Banks ML, Blough BE, Negus SS (2013a). Effects of 14-day treatment with the schedule III anorectic phendimetrazine on choice between cocaine and food in rhesus monkeys. *Drug Alcohol Depend* **131**: 204–213.

Banks ML, Blough BE, Negus SS (2013b). Interaction between behavioral and pharmacological treatment strategies to decrease cocaine choice in rhesus monkeys. *Neuropsychopharmacology* **38**: 395–404.

Banks ML, Hutsell BA, Schwienteck KL, Negus SS (2015). Use of preclinical drug vs. food choice procedures to evaluate candidate medications for cocaine addiction. *Curr Treat Options Psychiatry* **2**: 136–150.

Banks ML, Negus SS (2012). Preclinical determinants of drug choice under concurrent schedules of drug self-administration. *Adv Pharmacol Sci* **2012**: 281768.

Banks ML, Rice KC, Negus SS (2010). Antinociceptive interactions between mu-opioid receptor agonists and the serotonin uptake inhibitor clomipramine in rhesus monkeys: role of mu agonist efficacy. *J Pharmacol Exp Ther* **335**: 497–505.

Bentley JM, Adams DR, Bebbington D, Benwell KR, Bickerdike MJ, Davidson JEP *et al* (2004). Indoline derivatives as 5-HT2C receptor agonists. *Bioorg Med Chem Lett* **14**: 2367–2370.

Brutcher RE, Nader MA (2015). Effects of quetiapine treatment on cocaine self-administration and behavioral indices of sleep in adult rhesus monkeys. *Psychopharmacology* **232**: 411–420.

Callahan PM, Cunningham KA (1995). Modulation of the discriminative stimulus properties of cocaine by 5-HT1B and 5-HT2C receptors. *J Pharmacol Exp Ther* **274**: 1414–1424.

Cathala A, Devroye C, Maitre M, Piazza PV, Abrous DN, Revest J-M *et al* (2015). Serotonin2C receptors modulate dopamine transmission in the nucleus accumbens independently of dopamine release: behavioral, neurochemical and molecular studies with cocaine. *Addict Biol* **20**: 445–457.

Collins GT, Gerak LR, Javors MA, France CP (2016). Lorcaserin reduces the discriminative stimulus and reinforcing effects of cocaine in rhesus monkeys. *J Pharmacol Exp Ther* **356**: 85–95.

Comer SD, Ashworth JB, Foltin RW, Johanson CE, Zacny JP, Walsh SL (2008). The role of human drug self-administration procedures in the development of medications. *Drug Alcohol Depend* **96**: 1–15.

Cunningham KA, Anastasio NC, Fox RG, Stutz SJ, Bubar MJ, Swinford SE *et al* (2013). Synergism between a serotonin 5-HT2A receptor (5-HT2AR) antagonist and 5-HT2CR agonist suggests new pharmacotherapeutics for cocaine addiction. *ACS Chem Neurosci* **4**: 110–121.

Cunningham KA, Fox RG, Anastasio NC, Bubar MJ, Stutz SJ, Moeller FG *et al* (2011). Selective serotonin 5-HT2C receptor activation suppresses the reinforcing efficacy of cocaine and sucrose but differentially affects the incentive-salience value of cocaine- vs. sucrose-associated cues. *Neuropharmacology* **61**: 513–523.

Czoty PW, Stoops WW, Rush CR (2016). Evaluation of the "pipeline" for development of medications for cocaine use disorder: A review of translational preclinical, human laboratory, and clinical trial research. *Pharmacol Rev* **68**: 533–562.

Donny EC, Bigelow GE, Walsh SL (2003). Choosing to take cocaine in the human laboratory: effects of cocaine dose, inter-choice interval, and magnitude of alternative reinforcement. *Drug Alcohol Depend* **69**: 289–301.

Fantegrossi WE, Ullrich T, Rice KC, Woods JH, Winger G (2002). 3,4-Methylenedioxymethamphetamine (MDMA, "ecstasy") and its stereoisomers as reinforcers in rhesus monkeys: serotonergic involvement. *Psychopharmacology* **161**: 356–364.

Filip M (2005). Role of serotonin (5-HT)2 receptors in cocaine self-administration and seeking behavior in rats. *Pharmacol Rep* **57**: 35–46.

Fletcher PJ, Grottick AJ, Higgins GA (2002). Differential effects of the 5-HT2A receptor antagonist M100,907 and the 5-HT2C receptor antagonist SB242,084 on cocaine-induced locomotor activity, cocaine self-administration and cocaine-induced reinstatement of responding. *Neuropsychopharmacology* **27**: 576–586.

Fletcher PJ, Rizos Z, Sinyard J, Tampakeras M, Higgins GA (2008). The 5-HT2C receptor agonist Ro60-0175 reduces cocaine self-administration and reinstatement induced by the stressor yohimbine, and contextual cues. *Neuropsychopharmacology* **33**: 1402–1412.

Gerak LR, Collins GT, France CP (2016). Effects of lorcaserin on cocaine and methamphetamine self-administration and reinstatement of extinguished responding in rhesus monkeys. *J Pharmacol Exp Ther* **359**: 383–391.

Grabowski J, Rhoades H, Silverman P, Schmitz JM, Stotts A, Creson D *et al* (2000). Risperidone for the treatment of cocaine dependence: randomized, double-blind trial. *J Clin Psychopharmacol* **20**: 305–310.

Grottick AJ, Fletcher PJ, Higgins GA (2000). Studies to investigate the role of 5-HT2C receptors on cocaine- and food-maintained behavior. *J Pharmacol Exp Ther* **295**: 1183–1191.

Haney M, Spealman R (2008). Controversies in translational research: drug self-administration. *Psychopharmacology* **199**: 403–419.

Hannon J, Hoyer D (2008). Molecular biology of 5-HT receptors. *Behav Brain Res* **195**: 198–213.

Harvey-Lewis C, Li Z, Higgins GA, Fletcher PJ (2016). The 5-HT2C receptor agonist lorcaserin reduces cocaine self-administration, reinstatement of cocaine-seeking and cocaine induced locomotor activity. *Neuropharmacology* **101**: 237–245.

Howell LL, Cunningham KA (2015). Serotonin 5-HT2 receptor interactions with dopamine function: Implications for therapeutics in cocaine use disorder. *Pharmacol Rev* **67**: 176–197.

Hutsell BA, Negus SS, Banks ML (2016). Effects of 21-day d-amphetamine and risperidone treatment on cocaine vs food choice and extended-access cocaine intake in male rhesus monkeys. *Drug Alcohol Depend* **168**: 36–44.

John WS, Banala AK, Newman AH, Nader MA (2015). Effects of buspirone and the dopamine D3 receptor compound PG619 on cocaine and methamphetamine self-administration in rhesus monkeys using a food-drug choice paradigm. *Psychopharmacology* **232**: 1279–1289.

Lile JA, Stoops WW, Rush CR, Negus SS, Glaser PEA, Hatton KW *et al* (2016). Development of a translational model to screen medications for cocaine use disorder II: choice between intravenous cocaine and money in humans. *Drug Alcohol Depend* **165**: 111–119.

Manvich DF, Kimmel HL, Howell LL (2012). Effects of serotonin 2C receptor agonists on the behavioral and neurochemical effects of cocaine in squirrel monkeys. *J Pharmacol Exp Ther* **341**: 424–434.

McMahon LR, Cunningham KA (2001). Antagonism of 5-Hydroxytryptamine2 A receptors attenuates the behavioral effects of cocaine in rats. *J Pharmacol Exp Ther* **297**: 357–363.

Mello NK, Negus SS (1996). Preclinical evaluation of pharmacotherapies for treatment of cocaine and opioid abuse using drug self-administration procedures. *Neuropsychopharmacology* **14**: 375–424.

Munzar P, Justinova Z, Kutkat SW, Goldberg SR (2002). Differential involvement of 5-HT2A receptors in the discriminative-stimulus effects of cocaine and methamphetamine. *Eur J Pharmacol* **436**: 75–82.

Murnane KS, Winschel J, Schmidt KT, Stewart LM, Rose SJ, Cheng K *et al* (2013). Serotonin 2A receptors differentially contribute to abuse-related effects of cocaine and cocaine-induced nigrostriatal and mesolimbic dopamine overflow in nonhuman primates. *J Neurosci* **33**: 13367–13374.

Navailles S, Moison D, Cunningham KA, Spampinato U (2008). Differential regulation of the mesoaccumbens dopamine circuit by serotonin2C receptors in the ventral tegmental area and the nucleus accumbens: An in vivo microdialysis study with cocaine. *Neuropsychopharmacology* **33**: 237–246.

Negus SS (2003). Rapid assessment of choice between cocaine and food in rhesus monkeys: effects of environmental manipulations and treatment with d-amphetamine and flupenthixol. *Neuropsychopharmacology* **28**: 919–931.

Negus SS (2004). Effects of the kappa opioid agonist U50,488 and the kappa opioid antagonist nor-binaltorphimine on choice between cocaine and food in rhesus monkeys. *Psychopharmacology* **176**: 204–213.

Negus SS, Mello NK, Lamas X, Mendelson JH (1996). Acute and chronic effects of flupenthixol on the discriminative stimulus and reinforcing effects of cocaine in rhesus monkeys. *J Pharmacol Exp Ther* **278**: 879–890.

Negus SS, Mello NK, Portoghese PS, Lin C-E (1997). Effects of kappa opioids on cocaine self-administration by rhesus monkeys. *J Pharmacol Exp Ther* **282**: 44–55.

Nic Dhonnchadha BÁ, Fox RG, Stutz SJ, Rice KC, Cunningham KA (2009). Blockade of the serotonin 5-ht2a receptor suppresses cue-evoked reinstatement of cocaine-seeking behavior in a rat self-administration model. *Behav Neurosci* **123**: 382–396.

Nordstrom A-L, Mansson M, Jovanovic H, Karlsson P, Halldin C, Farde L *et al* (2008). PET analysis of the 5-HT2A receptor inverse agonist ACP-103 in human brain. *Int J Neuropsychopharmacol* **11**: 163.

Pérez-Mañá C, Castells X, Vidal X, Casas M, Capellà D (2011). Efficacy of indirect dopamine agonists for psychostimulant dependence: a systematic review and meta-analysis of randomized controlled trials. *J Subst Abuse Treat* **40**: 109–122.

Richelson E, Souder T (2000). Binding of antipsychotic drugs to human brain receptors: Focus on newer generation compounds. *Life Sci* **68**: 29–39.

Rüedi-Bettschen D, Spealman RD, Platt DM (2015). Attenuation of cocaine-induced reinstatement of drug seeking in squirrel monkeys by direct and indirect activation of 5-HT2C receptors. *Psychopharmacology* **232**: 2959–2968.

Shukla AP, Kumar RB, Aronne LJ (2015). Lorcaserin HCl for the treatment of obesity. *Expert Opin Pharmacother* **16**: 2531–2538.

Stafford D, Rice KC, Lewis DB, Glowa JR (2000). Response requirements and unit dose modify the effects of GBR 12909 on cocaine-maintained behavior. *Exp Clin Psychopharmacol* **8**: 539–548.

Thomsen WJ, Grottick AJ, Menzaghi F, Reyes-Saldana H, Espitia S, Yuskin D *et al* (2008). Lorcaserin, a novel selective human 5-Hydroxytryptamine2C agonist: In vitro and in vivo pharmacological characterization. *J Pharmacol Exp Ther* **325**: 577–587.

Vanover KE, Weiner DM, Makhay M, Veinbergs I, Gardell LR, Lameh J *et al* (2006). Pharmacological and behavioral profile of N-(4-Fluorophenylmethyl)-N-(1-methylpiperidin-4-yl)-N′-(4-(2-methylpropyloxy)phenylmethyl) carbamide (2R,3R)-dihydroxybutanedioate (2:1) (ACP-103), a novel 5-Hydroxytryptamine2A receptor inverse agonist. *J Pharmacol Exp Ther* **317**: 910–918.

Vocci FJ (2007). Can replacement therapy work in the treatment of cocaine dependence? and what are we replacing anyway? *Addiction* **102**: 1888–1889.

Walsh S (2016). FDA approves first drug to treat hallucinations and delusions associated with Parkinson's disease. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm498442.htm (accessed on May 6 2016).

Walsh SL, Geter-Douglas B, Strain EC, Bigelow GE (2001). Enadoline and butorphanol: evaluation of κ-agonists on cocaine pharmacodynamics and cocaine self-administration in humans. *J Pharmacol Exp Ther* **299**: 147–158.

Winhusen TM, Kropp F, Lindblad R, Douaihy A, Haynes L, Hodgkins C *et al* (2014). Multisite, randomized, double-blind, placebo-controlled pilot clinical trial to evaluate the efficacy of buspirone as a relapse-prevention treatment for cocaine dependence. *J Clin Psychiatry* **75**: 757–764.

Zayara AE, McIver G, Valdivia PN, Lominac KD, McCreary AC, Szumlinski KK (2011). Blockade of nucleus accumbens 5-HT2A and 5-HT2C receptors prevents the expression of cocaine-induced behavioral and neurochemical sensitization in rats. *Psychopharmacology* **213**: 321–335.