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PERSPECTIVE

Learning from lorcaserin: lessons from the negative clinical trial of lorcaserin to treat cocaine use disorder

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"You can't let your failures define you. You have to let your failures teach you."

(Barack Obama)

The National Institute on Drug Abuse (NIDA) recently completed a Phase 2 clinical trial to evaluate the serotonin 5-HT_{2C} receptor agonist lorcaserin as a pharmacotherapy for cocaine use disorder (CUD), and at present, the only publicly available data are posted on https://clinicaltrials.gov/ct2/show/study/NCT03007394. The results are negative; the study did not show any significant difference between lorcaserin and placebo. The primary outcome measure for this study was the proportion of participants achieving self-reported abstinence confirmed by negative urine samples during the last 3 weeks of the 13-week trial. Only 1 of the 91 lorcaserin-treated participants who completed the trial met the abstinence criterion compared to 4 of 91 completers in the placebo group. Additional analyses are ongoing in subsets of participants and on outcomes of reduced cocaine use as opposed to abstinence, and a more detailed picture of lorcaserin effects on cocaine use will emerge as these analyses are completed and published by NIDA. Nonetheless, the trial was notable for its large size (272 total participants, 182 completers), its execution across 12 sites in 7 states and the District of Columbia, and its strong experimental design, which included not only a placebo control and triple blinding (of participants, care providers, and investigators), but also strategies to monitor and encourage compliance with the treatment regimen. The negative results, together with the withdrawal of lorcaserin as a weight-loss drug due to concerns about increased cancer risk [1, 2], suggest that lorcaserin will not gain approval as a CUD treatment.

Of course, the lorcaserin trial was not intended to fail. Lorcaserin's advancement to a Phase 2 clinical trial capped more than a decade of preclinical research that framed a plausible mechanistic hypothesis supported by a substantial body of preclinical data from laboratory animals [3–5]. These preclinical findings were generally interpreted to predict that lorcaserin maintenance had potential to safely and effectively decrease cocaine use and relapse by humans; hence the clinical trial. However, rather than fulfilling this prediction, the trajectory of translational research with lorcaserin to treat CUD seems destined to resemble the failed translation of other candidate medications for other disorders, e.g., [6]. The question we can begin to ask now is this: what will this failure in translation teach us. This Perspectives article focuses on two lessons and suggests a range of possible future directions.

LESSON 1: "ANTAGONIST" MEDICATIONS HAVE A POOR TRACK RECORD AS CANDIDATE CUD MEDICATIONS

Two major categories of substance use disorder treatments have been described as "antagonist" medications intended to block effects of the abused drug and "agonist" medications intended to mimic effects of the abused drug [7, 8]. In the treatment of opioid use disorder, the mu opioid receptor antagonist naltrexone is the prototype antagonist medication, whereas the high-efficacy mu agonist methadone is the prototype agonist medication. The ascent of lorcaserin as a candidate CUD treatment was founded on behavioral neuroscience studies interpreted to suggest that it might functionally antagonize effects that underlie cocaine's abuse potential [3, 5]. Specifically, the monoamine neurotransmitters dopamine (DA), norepinephrine, and serotonin (5-HT) are cleared from the extracellular space by presynaptic transporter proteins. Cocaine binds to and blocks all three transporters to prevent monoamine uptake and increase extracellular monoamine concentrations, but cocaine-induced increases in DA concentrations at the terminals of mesolimbic DA neurons projecting from ventral tegmental area (VTA) to nucleus accumbens (NAc) are thought to be especially important for cocaine's high abuse potential. Lorcaserin does not bind to monoamine transporters, but instead functions as an agonist at serotonin 5-HT_{2C} receptors. These are G_q-coupled receptors whose activation generally increases neuronal excitability, and among their other locations and functions, they are located on inhibitory gamma aminobutyric acid (GABA) neurons in VTA that innervate and inhibit mesolimbic DA neurons. Both electrophysiological and neurochemical studies have found that 5-HT_{2C} agonists activate these VTA GABA neurons, inhibit mesolimbic DA neurons, and attenuate cocaine-induced increases in NAc DA. This effectiveness of 5-HT_{2C} agonists to attenuate cocaine-induced enhancement of NAc DA signaling suggested that lorcaserin or other 5-HT_{2C} agonists might also be useful to block abuse-related behavioral effects of cocaine and be useful for treating CUD [3, 5].

Although this type of antagonist approach is superficially plausible, lorcaserin is just the latest in a series of antagonist-based strategies to fail in humans as candidate CUD medications. Previous examples include: (1) "DA-sparing cocaine antagonists" (intended to bind DA transporters and have no effect on DA transport themselves while blocking cocaine binding to and inhibition of DA transporters, e.g., [9]), (2) DA receptor antagonists (intended to block effects of cocaine-enhanced extracellular DA at DA receptors [7]), and (3) kappa opioid receptor agonists (intended to bind G_i-coupled kappa receptors on mesolimbic DA neurons to inhibit activity and DA release from those neurons, e.g.,

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[10]). To our knowledge, the concept of a viable DA-sparing cocaine antagonist remains a theoretical possibility that has yet to be realized, and as a result, no drugs in this class have advanced to testing in humans. However, as with lorcaserin, both DA receptor antagonists and kappa receptor agonists advanced at least as far as human laboratory studies and failed to reduce cocaine intake up to medication doses that produced undesirable side effects. Accordingly, one cumulative lesson from decades of CUD medication development would appear to be that antagonist approaches have been consistently ineffective.

A full consideration of the basis for poor performance by candidate CUD antagonist medications is beyond the scope of this commentary, but one contributing factor will be mentioned here: antagonist medications designed to block effects of cocaine-enhanced DA signaling can also impede basal DA signaling in the absence of cocaine. This basal DA signaling in the mesolimbic and nigrostriatal pathways is essential for normal movement, normal mood, and normal reinforcement learning maintained by nondrug reinforcers such as food, sex, and social interaction [11]. CUD itself impairs basal DA signaling [12], and further decreases in DA signaling produced by antagonist medications can exacerbate this hypodopaminergic state to produce dose-limiting side effects. A challenge in developing an effective antagonist medication for treating any substance use disorder is identification of antagonist dosing regimens that block reinforcing effects of the abused drug without blocking essential endogenous neurotransmission involving the receptor to which the abused drug binds. In the case of opioid use disorder, relatively high doses of antagonists like naltrexone can be used because basal signaling in opioid systems is low and opioid receptor blockade has relatively modest effects, but even here, undesirable effects are sufficient to impede compliance with therapeutically effective naltrexone treatment regimens, rendering naltrexone ineffective for most opioid use disorder patients [13, 14]. In the case of CUD, basal DA signaling is higher, interruption of basal DA signaling is more problematic, and medication strategies have yet to be identified that can effectively block effects of cocaine-enhanced DA without also producing problematic disruption of basal DA signaling.

LESSON 2: DRUG-CHOICE PROCEDURES CAN IMPROVE TRANSLATION IN CUD MEDICATION DEVELOPMENT

The promotion of lorcaserin to a multi-site clinical trial depended not only on a plausible mechanistic hypothesis, but also on supportive preclinical data from many types of behavioral procedures routinely used in laboratory animals to assess candidate medications for substance use disorders [4]. A full description of the different types of behavioral procedures is beyond the scope of this commentary (for reviews, see [15–18]), but the most important have been versions of drug self-administration procedures, in which rodents or nonhuman primates responded on a lever or response key to receive intravenous cocaine infusions, and lorcaserin was evaluated for its effectiveness to decrease cocaine-maintained responding. In one study, for example, rhesus monkeys were trained to press a lever under a fixed-ratio 30 schedule of cocaine self-administration (i.e., 30 lever presses for each injection) during daily 90-min sessions [19]. Once responding stabilized, monkeys were treated with a range of intragastric lorcaserin doses administered 90 min before session onset, and each lorcaserin dose was evaluated for 14 consecutive days. Lorcaserin produced a dose-dependent decrease in both rates of responding and in the number of cocaine injections earned per session. This decrease in cocaine self-administration was apparent on the 1st day of treatment and sustained throughout the 14-day treatment period. In addition, in separate groups of monkeys, the lorcaserin dose (3.2 mg/kg) that significantly reduced cocaine self-administration did not significantly decrease overall activity (assessed with accelerometers attached to the monkeys' collars), altered only one of 24 other observed behaviors (an increase in yawning), and produced a significant but small decrease in operant responding maintained by a non-drug reinforcer (food pellets). Overall, the results were interpreted to be "…consistent with the view that [lorcaserin] might have utility in treating cocaine abuse" [19]. Table 1 summarizes results from several other studies interpreted to be supportive of this view.

This preponderance of preclinical data and the interpretations they inspired failed to predict the definitively negative outcome of the clinical trial. However, Table 1 also shows that one preclinical research approach was predictive of clinical results. Specifically, studies in rhesus monkeys and humans that evaluated lorcaserin effects on choice between cocaine and an alternative nondrug reinforcer (food in monkeys, money in humans) found no effect of lorcaserin on cocaine choice [20, 21]. The study in monkeys concluded that results "…do not support the clinical utility of 5-HT_{2C} agonists as candidate anti-cocaine use disorder pharmacotherapies" [20]. The study in humans concluded that results "…do not support a direct therapeutic benefit on drug-reinforced behavior for the currently marketed dose of lorcaserin" [21]. Cocaine-vs.-food choice procedures have also predicted negative results with other candidate antagonist medications, including DA receptor antagonists and kappa opioid receptor agonists [22–26], as well as positive results with amphetamine maintenance (an "agonist" medication [7, 27, 28]) and a host of environmental manipulations that are known to modify clinical drug use and have been incorporated into treatment strategies such as contingency management [23, 29–38]. Taken together, these findings suggest that drug-choice procedures in both laboratory animals and humans may improve preclinical-to-clinical translation of effects with candidate CUD medications by virtue of combining both sensitivity to effective treatments and selectivity for effective vs. ineffective treatments.

Two features of drug-choice procedures may contribute to their utility for translational research on medications development for CUD and other substance use disorders [30, 39, 40]. The first is the primary dependent variable: drug choice. Most of the drug self-administration procedures represented in Table 1 provide access at any given time to only a single reinforcer option (i.e., only cocaine), and the primary dependent variable is a measure of drug self-administration rate. Rates of drug self-administration in these single-option procedures can be decreased by treatments that produce the intended decrease in drug reinforcement, but drug self-administration rates can also be decreased by treatments that produce undesirable impairment of motor function, cognition, or general motivation. In contrast, choice procedures provide simultaneous access to two different reinforcer options (e.g., drug vs. food in laboratory animals, drug vs. money in humans), and the primary dependent variable is a measure of behavioral allocation between those two options. Effective treatments not only decrease drug choice, but also promote behavioral reallocation and increased choice of the nondrug alternative. Choice procedures also measure overall rates of operant behavior as a secondary dependent variable, and these two dependent variables facilitate interpretation of treatment effects. Treatments that produce a desirably selective decrease in reinforcing effects of the abused drug will decrease drug choice and increase choice of the nondrug alternative without decreasing overall behavioral rate. Conversely, treatments that produce motor/cognitive/motivational impairment without altering reinforcing effects of the abused drug will decrease overall rates without altering drug choice. Lorcaserin produced this latter profile of effects in drug-choice procedures [20, 21].

A second feature of choice procedures that promotes translational validity is that human drug abuse occurs in complex environments containing both drug and nondrug reinforcers, and a goal of any drug abuse treatment is not only to reduce drug use,

Table 1. Summary of animal and human laboratory research examining lorcaserin effectiveness to attenuate cocaine self-administration.

Species	Procedure(s)	Dependent measure(s)	Lorcaserin dose(s)/ route	Treatment regimen	Results	Interpreted as effective for CUD (Yes/No)	Ref.
Preclinical studies							
Male and female rhesus monkeys	Cocaine SA (FR) Food-maintained responding (FR)	Rates of responding	1–10 mg/kg, Intragastric (IG)	Acute and repeated 14-day treatment	Acute and chronic decreased cocaine SA Acute decreased food-maintained responding; chronic not tested	Yes	[19]
Male Long-Evans rats	Cocaine SA (FR, PR) Cocaine, cue, and cocaine + cue reinstatement	Rates of responding	0.3–1 mg/kg, SC	Acute pretreatment	Decreased cocaine SA (FR, PR) Decreased cocaine, cue, and cocaine + cue reinstatement	Yes	[71]
Female and male rhesus monkeys	Cocaine SA (PR) Cue, cocaine+cue reinstatement	Rates of responding	0.32–3.2 mg/kg, IG	Acute and 5-day or 14-day repeated treatment	Acute and repeated decreased PR Acute decreased cue and cocaine + cue reinstatement. Repeated decreased cocaine + cue reinstatement	Yes	[49]
Male rhesus monkeys	Cocaine-vs.-food choice (FR)	% cocaine choice Rates of responding	0.1–1 mg/kg/day, IM 0.032–0.1 mg/kg/h, IV	7-day repeated treatment	No effect on cocaine choice Decreased rates of responding	No	[20]
Male Sprague-Dawley rats	Cocaine SA (PR)	Rates of responding	0.32–5.6 mg/kg, IP	Acute pretreatment	Decreased cocaine SA	Yes	[72]
Male and female rhesus monkeys	Cocaine SA (PR)	Rates of responding	0.1–3.2 mg/kg, SC	Acute pretreatment	Decreased cocaine SA	Yes	[73]
Female and male rhesus monkeys	Cocaine + cue reinstatement	Rates of responding	0.1–1 mg/kg, SC	Acute pretreatment	Decreased cocaine + cue reinstatement	Yes	[74]
Male Sprague-Dawley rats	Cocaine SA (FR) Cocaine seeking (cue reinstatement)	Rates of responding	0.25–1 mg/kg, IP	Acute or repeated 10-day treatment during forced abstinence	Acute decreased cocaine SA Acute and repeated decreased cue reinstatement	Yes	[75]
Human laboratory studies							
Humans	Cocaine-vs.-money choice (FR) Subjective effects	Reinforcers earned Score	10 mg, PO	Acute pretreatment	No effect on cocaine choice Increased "High" and "Stimulated" of low-dose cocaine	No	[21]

SA self-administration, *FR* fixed-ratio schedule of reinforcement, *PR* progressive-ratio schedule of reinforcement.

but also to increase more adaptive behaviors maintained by nondrug reinforcers [8]. Choice procedures provide a simplified but powerful tool for investigating medication effects on behavioral allocation in animal or human laboratory settings.

FUTURE DIRECTIONS

Completion of the Phase 2 clinical trial with lorcaserin is only the latest milestone in an ongoing effort to discover safe and effective medications for substance use disorders in general and CUD in particular. This effort will continue, and here we consider four possible future directions. First, one likely direction of future research will be founded on the interpretation that, despite its many strengths, the recently completed clinical trial was not adequate to test lorcaserin as a CUD treatment. Clinical trials can fail for many reasons other than lack of medication efficacy, and possible reasons for failure in this case will certainly be explored. These include (1) inadequate compliance with the intended dosing regimen [41], (2) focus on a rigorous primary outcome measure (abstinence for the final 3 weeks of the trial) that may have missed clinically relevant decreases in cocaine use [42], and (3) clinical testing of a lorcaserin dose (10 mg/kg twice a day; equivalent to 0.35 mg/kg/day in a 70 kg human) lower than that found to be effective in preclinical studies (e.g., 3.2 mg/kg/day for rhesus monkeys in [19]). The first two of these issues can be explored by data mining in the current data set, whereas the third issue would require new clinical trials with higher lorcaserin doses. New studies with higher lorcaserin doses are unlikely given concerns about cancer risk and evidence for emergence of undesirable effects at higher lorcaserin doses in humans [43]; however, lorcaserin was selected for the clinical trial in part because it had been developed and approved independently for a different clinical indication (treatment of obesity) [44, 45]. Other 5-HT_{2C} agonists with higher selectivity for 5-HT_{2C} receptors vs. other targets (e.g., 5-HT_{2A} receptors) are available as alternatives to lorcaserin, and positive allosteric modulators have also been developed [46]. Studies with new 5-HT_{2C} ligands would also require new clinical trials as well as a more general commitment to the ill-fated "antagonist" strategy for CUD treatment.

A second direction of future research will be continued assessment of 5-HT_{2C} agonists as candidate treatments for other substance use disorders. The strongest evidence for lorcaserin effectiveness to treat substance abuse is for tobacco use disorder. Although lorcaserin was ineffective to promote abstinence from cocaine use, a randomized, double-blind, and placebo-controlled clinical trial found that a similar lorcaserin treatment regimen (10 mg/kg BID for 12 weeks) was effective to promote smoking cessation [47]. Effects of lorcaserin or other 5-HT_{2C} agonists on nicotine/tobacco choice have not been examined in animal or human laboratory studies, but lorcaserin did decrease nicotine self-administration in single-option procedures measuring self-administration rates (reviewed in [44]). Lorcaserin has also been evaluated in preclinical assays of opioid, alcohol, and methamphetamine self-administration. Table 2 summarizes lorcaserin effects on opioid self-administration, and as with cocaine, lorcaserin decreased opioid self-administration in single-option procedures measuring self-administration rates in laboratory animals, but it failed to decrease opioid choice in rats, rhesus monkeys, or humans. Insofar as this profile of lorcaserin effects on opioid self-administration and choice is similar to the profile of lorcaserin effects on cocaine self-administration and choice, these results suggest that lorcaserin will not be effective to treat opioid use disorder. Lastly, lorcaserin decreased both alcohol consumption in rats [48] and methamphetamine self-administration in monkeys [49]. Lorcaserin was modestly more potent to decrease ethanol than water or sucrose consumption in rats, and this decrease was sustained over 10 days of treatment. In contrast, methamphetamine self-administration by monkeys was decreased

Table 2. Summary of animal and human laboratory research examining lorcaserin effectiveness to attenuate opioid self-administration.

Species	Procedure(s)	Dependent measure(s)	Lorcaserin dose (s)/route	Treatment regimen	Results	Interpreted as effective for OUD (Yes/No)	Ref.
Preclinical studies							
Male Sprague-Dawley rats	Oxycodone SA (FR) Cue reinstatement	Rates of responding	0.25–1 mg/kg, SC	Acute pretreatment	Decreased oxycodone SA Decreased cue reinstatement	Yes	[76]
Male Sprague-Dawley rats	Remifentanil-vs.-food choice (FR)	% remifentanil choice Rates of responding	0.1–3 mg/kg, IP	Acute pretreatment	No effect on remifentanil choice Decreased rates of responding	No	[64]
Male rhesus monkeys	Heroin SA (FR) Food-maintained responding (FR)	Rates of responding	0.32–1 mg/kg, IM	Acute and repeated (>7 days) treatment	Acute decreased heroin SA Repeated decreased both consumption and demand for small, but not large, heroin dose Acute or repeated did not decrease food-maintained responding	Yes	[77]
Female and male rhesus monkeys	Heroin + cue reinstatement	Rates of responding	0.1–1 mg/kg, SC	Acute pretreatment	Decreased heroin + cue reinstatement	Yes	[74]
Female and male rhesus monkeys	Heroin-vs.-food choice (FR)	% heroin choice Rates of responding	0.032–0.32 mg/kg/h, IV	Repeated 7-day treatment	Increased heroin choice No effect on rate	No	[78]
Human laboratory studies							
Humans	Oxycodone-vs.-money choice (PR) Subjective effects	Reinforcers earned Score	10 mg twice a day, PO	Repeated 14-day treatment	No effect on oxycodone choice Increased "Want" heroin	No	[79]

SA self-administration, *FR* fixed-ratio schedule of reinforcement, *PR* progressive-ratio schedule of reinforcement.

only by high lorcaserin doses that also decreased food-maintained responding, and tolerance developed rapidly to lorcaserin-induced decreases in methamphetamine self-administration. As with CUD, any future studies for other substance use disorders would involve a commitment to an "antagonist" strategy and would likely need to use a different 5-HT_{2C} ligand given the cancer risk associated with lorcaserin.

A third future direction could be to reallocate federally funded research from "antagonist" strategies for CUD treatment to "agonist" strategies or other approaches. Research on treatments for substance use disorders has long favored antagonist approaches, e.g., [50], but as summarized above, this approach has a poor track record for treatment of CUD. "Agonist" approaches have been more controversial but more effective for achieving clinical goals in treatment of opioid abuse (methadone and buprenorphine [51, 52]) and nicotine/tobacco abuse (nicotine formulations, varenicline [53]), and the most effective treatment identified so far for CUD has been amphetamine maintenance [7, 28, 54]. Continued research to understand, implement, and improve agonist-based medications for CUD would seem to be justified [27, 55]. Other approaches are also possible, such as strategies to alleviate or reverse hyperkatifeia induced by drug abuse and withdrawal [56].

In our view, a final direction of future research should be further development and integration of drug-choice procedures into preclinical medications-development research. Drug-choice procedures in rhesus monkeys and humans predicted failure of lorcaserin to produce abstinence from cocaine in the clinical trial. Moreover, drug-vs.-food choice procedures in both rats and rhesus monkeys yielded results consistent with the failure of lorcaserin to modify heroin-vs.-money choice in a human laboratory study. These findings agree with other evidence to suggest that drug-choice procedures in laboratory animals may be useful in reducing false-positive effects in the medications development pipeline of preclinical-to-clinical translational substance use disorder research [16, 30]. For this reason, we propose that drug-choice procedures could play a key role in prioritization of candidate medications for advancement to essential but costly clinical trials.

In addition, the utility of drug-choice procedures could be extended beyond medications development to research on basic mechanisms of drug abuse [55]. Just as single-option self-administration procedures are vulnerable to false-positive effects with candidate medications, so they are also vulnerable to false-positive effects in mechanistic research with commonly used manipulations such as site-specific drug treatments, lesions, or optogenetic/chemogenetic modulation of neural circuits. Preclinical choice procedures could improve translation of results from such studies while also encouraging research on topics inaccessible to single-option procedures, such as vulnerability to drug abuse resulting from impaired sensitivity to alternative reinforcers. Lastly, while drug-choice studies in laboratory animals were initially developed in nonhuman primates using food as the alternative nondrug reinforcer [23, 29, 33, 57–59], technical advances have now enabled development of drug-vs.-food choice procedures in rats [60–69] and development of procedures that use social reinforcement rather than food as the alternative nondrug reinforcer [70]. These advances open new and exciting opportunities in the use of drug-choice procedures for both improving basic knowledge of substance use disorders and developing new medications for their treatment.

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AUTHOR CONTRIBUTIONS

Both authors contributed to the conceptualization and writing of the paper.

ADDITIONAL INFORMATION

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