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RESEARCH ARTICLE

5-HT_{2c} agonist, lorcaserin, reduces aggressive responding in intermittent explosive disorder: A pilot study

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Abstract

Rationale: Impulsive aggressive behavior is associated with reduced central function of serotonin (5-HT). Although selective serotonin reuptake inhibitors can reduce such behaviors, many with history of impulsive aggression do not respond adequately to selective serotonin reuptake inhibitors and may require treatment with a direct 5-HT agonist.

Objectives: To test the hypothesis that pretreatment with the selective 5-HT2c agonist, lorcaserin, can reduce aggressive responding in impulsively aggressive individuals.

Methods: Ten male and female adults were given lorcaserin (20 mg), or a matching placebo, in random order, on 2 days separated by at least 1 week. The Taylor aggression paradigm was used to assess aggressive responding, which was represented by mean shock setting administered to an opponent and by frequency of setting high and extreme shock levels to the opponent.

Results: Compared with placebo, lorcaserin attenuated provoked, but not unprovoked, aggression during the Taylor aggression paradigm. This was manifest by reduction in the frequency of selecting high and extreme levels of shock against the opponent.

Conclusion: Lorcaserin may possess anti-aggressive properties that could prove useful in the treatment of impulsive aggressive behavior in human subjects. These data, thus, provide a rationale for a follow-up randomized clinical trial of lorcaserin in individuals with prominent histories of impulsive aggressive behavior.

KEYWORDS
impulsive aggression, lorcaserin, serotonin, treatment

1 | INTRODUCTION

Human aggression is a verbal and/or physical behavior directed at others (or objects) that results in injury to others (or objects). It is at the core of much human suffering and is quite common (Coccaro, Lee, & McCloskey, 2019). No less than 4% of the US population meets lifetime criteria for a disorder of recurrent, problematic, impulsive aggression that is not premeditated in nature and is dysfunctional in nature (intermittent explosive disorder [IED]). Several factors, particularly biogenetic factors, underlie human aggression. Neurochemical studies have pointed to a modulatory role in human aggression for a variety of central neurotransmitters. Some, such as serotonin (5-HT), play an inhibitory role, whereas others play a facilitatory role in the modulation of aggression (Coccaro et al., 2019).

Although there are no Food and Drug Administration approved medications for the treatment of impulsive aggression in humans, agents that target 5-HT, such as selective serotonin reuptake inhibitors (SSRIs), have been shown to increase synaptic 5-HT

concentrations (Fuller, 1994) and reduce impulsive aggressive behavior in humans (Coccaro & Kavoussi, 1997; Coccaro, Lee, & Kavoussi, 2009a; Fava et al., 1993; George et al., 2011; McDougle et al., 1996; Salzman et al., 1995; Silva et al., 2010). However, SSRIs lead to remission of impulsive aggressive behaviors in no more than half of individuals (Coccaro et al., 2009a; Silva et al., 2010). This may be because SSRIs are indirect agonists that require the presence of a critical number of functional 5-HT transporters (5-HTT) to work (Silva et al., 2010). Because many aggressive individuals also have reduced numbers of 5-HTTs (Coccaro, Lee, & Kavoussi, 2009b) and because anti-aggressive responses to SSRIs are directly correlated with 5-HT receptor sensitivity (Coccaro, Kavoussi, & Hauger, 1997), it is likely that many impulsively aggressive individuals will require treatment with a direct 5-HT agonist. The most recent agent available for human use is loracserin, a direct agonist at 5-HT_{2c} receptors. Although stimulation of post-synaptic 5-HT_{2a} receptors is likely associated with adverse behavioral effects, loracserin's affinity for the 5-HT_{2c} receptor is 100 times greater than that for the 5-HT_{2a} receptor and 18 times greater than that for the 5-HT_{2b} receptor (Thomsen et al., 2008). Further support for testing the anti-aggressive activity of lorcaserin is the observation that the hormonal response to 5-HT stimulation is mediated by stimulation of post-synaptic 5-HT_{1a} (Almeida, Lee, & Coccaro, 2010) and 5-HT_{2c} (Coccaro, Kavoussi, Oakes, Cooper, & Hauger, 1996).

In this study, we administered lorcaserin 20 mg po, a relatively selective 5-HT_{2c} agonist, and matching placebo, to 10 impulsively aggressive individuals with IED and had each complete the Taylor aggression paradigm (TAP; Anderson & Bushman, 1997), an analog laboratory assessment of aggressive responding. Compared with placebo, acute lorcaserin was associated with a reduction in high/extreme levels of aggressive responding.

2 | METHODS

2.1 | Participants

Ten adult males (n = 5) and females (n = 5), with a current Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 (American Psychiatric Association, 2013) diagnosis of IED, and ranging from 22 to 51 (Mean ± *SD*: 33.6 ± 10.9) years of age, received a single oral dose of lorcaserin (20 mg) and a single oral dose of matching placebo, double-blinded, in random order, separated by about 7 days in eight participants and at 36 and 45 days in two participants due to issues related to scheduling (Mean ± *SD* for all participants: 14.1 ± 14.2) days. The study was approved by the Institutional Review Board of the Biological Sciences Division of the University of Chicago, and all participants signed an informed consent document.

2.2 | Diagnostic assessment

Psychiatric diagnoses were made according to DSM-5 criteria using information from (a) the Structured Clinical Interview for DSM diagnoses (First, Williams, & Gibbon, 2014) for syndromal (formally Axis I) disorders and the Structured Interview for the Diagnosis of Personality Disorder (Pfohl, Blum, & Zimmerman, 1997) for personality (formally Axis II) disorders, (b) clinical interview by a research psychiatrist, and (c) review of all other available clinical data. Final diagnoses were assigned by team best-estimate consensus procedures involving research psychiatrists and clinical psychologists (Coccaro, Fanning, Keedy, & Lee, 2016). Study participants with a current history of a substance use disorder or a life history of bipolar disorder, schizophrenia (or other psychotic disorder), or intellectual disability were excluded from study.

2.3 | Psychometric assessment of aggression

Aggression was assessed with the aggression score from the Life History of Aggression assessment (LHA; Coccaro, Berman, & Kavoussi, 1997) and the aggression (Physical and Verbal) subscore from the from the Buss-Perry Aggression questionnaire (BPA; Buss & Perry, 1992). The LHA assesses history of actual aggressive behavior, whereas the BPA assesses the tendency to be aggressive.

2.4 | Protocol overview

Study participants were instructed to fast from midnight before the study sessions. Participants arrived at the laboratory at about 8:00 am and then received an oral dose of lorcaserin 20 mg, or a matching placebo capsule, double-blind, in random order, at 9:00 am. Participants remained at rest for 2 hr when lorcaserin is expected to be at peak levels (Bai & Wang, 2010) and when each participant engaged in the Taylor aggression paradigm.

2.5 | Laboratory assessment of aggression: TAP

The TAP is an analog laboratory task designed to assess physical aggression. More than 40 years of research have provided evidence for the task's validity and robustness to various modifications (Anderson & Bushman, 1997). In the TAP, study participants compete against a fictitious opponent in a reaction time game during which electric shock is administered and received. At the start of each session, participants complete a urine drug test and alcohol breathalyzer test; failing either excludes the participant from study. Fingertip electrodes are then attached to the index and middle fingers of the participant's nondominant hand. The participant is informed by the experimenter that he or she will be competing against another "participant," or a computer simulated person "avatar," ("the opponent") in another part of the building. The experimenter then goes out of the room "to prepare the other participant" for the experiment. After a short delay, an upper shock pain threshold is determined by administering increasingly intense shocks at 100-microamp intervals until the participant reports that the shock was "very unpleasant." The

lower shock setting at which point the participant begins to feel the shock is also determined. To increase the credibility of the experimental situation, this procedure is repeated with the other "participant" (an audiotape of a confederate) and overheard by the participant. After the threshold determination, task instructions are provided via intercom to both "participants," indicating that the purpose of the task was to see which participant can lift a finger off a reaction time key the fastest. Before each reaction time trial, each participant selects a shock from 0 to 10 or 20 by pressing one of 12 buttons on the bottom of the console. The slower person on each trial would receive the shock chosen by his or her opponent before that trial. The 10 shock was equivalent to the shock level judged very unpleasant by the participant and represents a "high" level of aggression. The nine shock was set at 95% of this maximum, eight at 90%, seven at 85%, and so forth. The participant is informed that the 20 shock will administer an "extremely severe" shock, twice the intensity of the 10 (in actuality, in the one instance the fictitious opponent selects the 20 shock setting, the participant does not actually receive the shock because he or she "wins" the trial). Thus, a 20-shock selected by the participant indicated extreme aggression towards the opponent. Participants are told that if they selected a 0, no shock would be administered to their opponent on losing trials (a nonaggressive response option was included to increase the ecological validity of the task). Participants next completed 28 reaction time trials consisting of an initial trial, followed by four, six-trial blocks of increasing provocation by the opponent. The average shock setting by the fictitious opponent across the first three blocks was 2.5, 5.5, and 8.5, respectively. The fourth block differs from the third block only in that a highly aversive "20" shock is ostensibly selected by the opponent on only one trial. Blocks were separated by a trial of intermediate intensity to smooth the transition between blocks. The participant loses (receives the opponent shock) on half the trials, with the frequency of wins and losses preprogrammed by the experimenter. After the TAP, the participant completes a questionnaire to determine if he or she believed that the interaction was with another participant and to ensure that the participant did not know that the true purpose of the task was to examine aggressive behavior. TAP aggressive responding in this study was assessed in three ways: (a) mean number of times study participants set a "high" (Level "10") and "extreme" (Level "20") shock level for the opponent, (b) mean shock setting for the opponent across all trials, and (c) mean shock set by study participant before any provocation during the TAP (Trial 1), which reflects "unprovoked aggression."

2.6 | Statistical analysis

The primary analysis utilized paired *t*-tests to test the hypothesis that a single dose of lorcaserin, compared with placebo, would be associated with reduced frequency of "high" and "extreme" shock setting (i.e., "provoked aggressive responding"). Secondary outcome measures were the mean shock setting over all trials (i.e., also "provoked aggression") and mean shock set by study participant before any provocation (i.e., "unprovoked aggression"). Probability values for these outcomes are reported at the one-tail alpha of .05 level because we hypothesized that lorcaserin would reduce, not increase, TAP aggressive responding, and because this was a pilot study designed to estimate potential effect sizes for the TAP variables.

3 | RESULTS

3.1 | Study participants

All participants met DSM-5 criteria for current IED, and all displayed high scores of aggression on LHA (20.3 ± 4.8) and BPA (47.6 ± 11.5) assessments similar to those reported in the literature (note that nonaggressive participants in our studies have mean LHA (n = 825) and BPA (n = 668), scores of 6.4 ± 4.0 and 30.7 ± 11.2, respectively). All study participants accepted the study conditions as explained by the experimenters, and no participant was excluded due to use of alcohol or other drugs. Study procedures were well tolerated by all study participants, and no reports from participants suggested that they knew which condition they had just completed.

3.2 | Effect of loraserin on high/extreme shock settings

The mean frequency for study participants selecting "high/extreme" shock levels was significantly lower after lorcaserin than after placebo (Mean ± *SD*: PLA = 7.30 ± 7.79 vs. LOR = 2.50 ± 2.51; d = .69; paired t = 2.15, df = 9, p = .030); Figure 1. Participants appeared modestly less aggressive (d = .26) during the second TAP session, regardless of drug or placebo (Session 1 = 6.00 ± 6.25 vs. Session 2 = 3.80 ± 6.16), though this difference was not statistically significant (d = .26; paired t = .83, df = 9, p = .428). However, because 4 of the 10 participants received lorcaserin second, it is possible that this inequality in session order could have accounted for some of the observed effect of lorcaserin on aggressive responding. We reran the analysis counter-

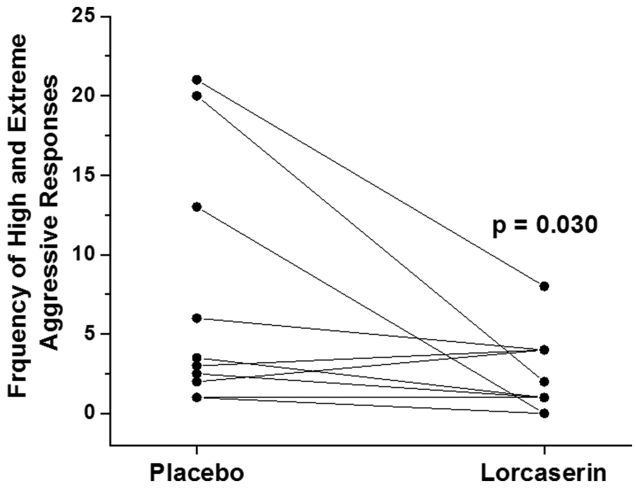

FIGURE 1 Frequency of high and extreme aggressive responses

balancing sessions between placebo (four first session) and lorcaserin (four first session) and found the same result (PLA = 8.50 ± 8.35 vs. 2.50 ± 2.73; d = .81; t = 2.29, df = 7. p = .028).

3.3 | Effect on mean shock setting and other relevant outcome variables

A more modest (d = .24), but nonstatistically significant, effect of lorcaserin was observed in mean shock selected for the opponent over all trials (PLA = 5.91 ± 2.57 vs. LOR = 5.35 ± 2.26, paired t = .69, df = 9, p = .523). Despite this, the correlation between overall mean shock levels and "high/extreme" shock levels selected for the opponent was quite high (PLA: r = .73, df = 8, p = .008; LOR: r = .95, df = 8, p < .001). Notably, there was no difference in mean shock setting for unprovoked aggression (PLA = 3.9 ± 6.1 vs. LOR = 3.3 ± 3.0; d = .08; paired t = .265, df = 9, p = .399). Finally, there was no difference as a function of lorcaserin or placebo on low (paired t = .61, df = 9, p = .555) and high (paired t = .27, df = 9, p = .795) threshold shock settings performed at the beginning of each TAP session.

4 | DISCUSSION

This pilot study suggests that the 5-HT_{2c} receptor agonist, lorcaserin, has anti-aggressive effects in humans with high levels of impulsive aggression (e.g., IED). Selection of both "high" and "extremely high" levels of shock to be delivered to the opponent were lower on lorcaserin compared with placebo. This was not likely due to the modest reduction of highly aggressive TAP responding associated with the second session, regardless of drug condition, because analysis of participants with equal numbers of drug and placebo first or second revealed the same anti-aggressive effect. In addition, note that, in a larger sample of other study participants who completed the TAP twice within three months (n = 39), a similarly sized increase, rather than a decrease, in highly aggressive TAP responding was noted on the second session (manuscript in preparation). If so, this suggests the possibility that the anti-aggressive effect of lorcaserin may be larger than the current data suggest.

The observation that the mean shock level overall selected by participants for opponents was lower on lorcaserin, though not statistically so (but highly correlated with that for high/extreme TAP aggressive responding), is consistent with the fact that mean shock levels overall represent a less sensitive variable for change in aggression responding. This is because the mean shock level variable includes aggressive responding at all levels of aggressive responding, not simply high/extreme TAP aggressive responding (Berman, McCloskey, Fanning, Schumacher, & Coccaro, 2009).

The observation that lorcaserin was not associated with any effect on unprovoked aggression suggests that this effect may only be associated with aggression in response to social threat (aggression by the opponent), rather than premediated/unprovoked aggression, as observed in individuals with DSM-5 IED. Finally, the lack of effect of lorcaserin on threshold levels of shock suggests that lorcaserin has no effect on sensation of pain.

This study has strengths and limitations. Strengths include the study of the well-defined phenotype of DSM-5 IED (Coccaro, 2012) assessed with standardized assessments, the use of a within-subject design allowing subjects to act as their own controls, and the use of a well-studied, valid, laboratory model of human aggressive responding. Limitations include the small sample and its associated risk of type I error and the fact that we did not assess expectancy effects for the drug conditions. Although a sample size of 10 subjects is small, it is in the range of many within-subject studies of drug action, and effect sizes observed were of at least of moderate, if not large, magnitude. Although we did not ask participants about their expectations regarding when they were on placebo or lorcaserin, we did not observe any differences in reports of the experience during the two sessions.

The suggestion that lorcaserin may have anti-aggressive properties is consistent with the serotonin hypothesis of aggression that posits that agents that increase serotonergic activity will reduce impulsively aggressive behavior (Coccaro et al., 1989; Coccaro, Lee, & Kavoussi, 2010). However, what is noteworthy is that, as a receptor agonist, lorcaserin may work when SSRIs are not effective, especially in cases where post-synaptic serotonin (e.g., 5-HT_{2c}) receptors are highly downregulated (Coccaro et al., 1997; Silva et al., 2010).

Future studies could expand the number of study participants to replicate these results. However, we posit that these data provide the rationale to perform a double-blind clinical trial of lorcaserin in impulsively aggressive individuals (e.g., IED) to test the potential anti-aggressive effect of lorcaserin. Such a study would allow for more clinically relevant assessment of the effect of lorcaserin on impulsive aggressive behavior.

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CONFLICT OF INTERESTS

Dr Coccaro reports being a consultant to and being on the Scientific Advisory Boards of Azevan Pharmaceuticals, Inc. and of Avanir Pharmaceuticals, Inc., and being a current recipient of grant awards from NIMH, NIAAA, and the Pritzker-Pucker Family Foundation (PPFF). Dr Lee reports being a recipient of a grant award from Azevan Pharmaceuticals, Inc.

CONFLICT OF INTEREST

The authors have declared that there is no conflict of interest.

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