Efficacy of D-Cycloserine for Enhancing Response to Cognitive-Behavior Therapy for Panic Disorder

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Background: Traditional combination strategies of cognitive-behavior therapy plus pharmacotherapy have met with disappointing results for anxiety disorders. Enhancement of cognitive-behavior therapy with d-cycloserine (DCS) pharmacotherapy represents a novel strategy for improving therapeutic learning from cognitive-behavior therapy that remains untested in panic disorder.

Method: This is a randomized, double-blind, placebo-controlled augmentation trial examining the addition of isolated doses of 50 mg d-cycloserine or pill placebo to brief exposure-based cognitive-behavior therapy. Randomized participants were 31 outpatients meeting DSM-IV criteria for panic disorder with or without agoraphobia, who were offered five sessions of manualized cognitive-behavior therapy emphasizing exposure to feared internal sensations (interoceptive exposure) but also including informational, cognitive, and situational exposure interventions. Doses of study drug were administered 1 hour before cognitive-behavior therapy sessions 3 to 5. The primary outcome measures were the Panic Disorder Severity Scale (PDSS) and Clinicians' Global Impressions of Severity.

Results: Results indicated large effect sizes for the additive benefit of d-cycloserine augmentation of cognitive-behavior therapy for panic disorder. At posttreatment and 1 month follow-up, participants who received d-cycloserine versus placebo had better outcomes on the PDSS and global severity of disorder and were significantly more likely to have achieved clinically significant change status (77% vs. 33%). There were no significant adverse effects associated with DCS administration.

Conclusions: This pilot study extends support for the role of d-cycloserine in enhancing therapeutic learning from exposure-based cognitive-behavior therapy and is the first to do so in a protocol emphasizing exposure to feared internal sensations of anxiety in panic disorder.

Key Words: Cognitive-behavior therapy, d-cycloserine, panic disorder

Converging evidence from comparative treatment trials (1,2) and meta-analytic studies (3,4) indicates that pharmacotherapy and cognitive-behavior therapy (CBT) offer similar levels of acute benefit to patients with panic disorder. There has long been hope that the combination of these two modalities of treatment would lead to an especially powerful intervention. However, studies to date generally have failed to support this hypothesis (5). A recent meta-analysis of 23 randomized comparisons (incorporating data from 1709 patients across 21 trials) indicated that acute combined treatment with antidepressants and CBT was superior to monotherapy with pharmacotherapy or CBT, but the advantage was lost after medication discontinuation (3). Also, for the treatment of panic disorder, the cost-benefit ratio of combination treatment is substantially less favorable than that provided by CBT alone (6).

In the context of these disappointing results, a novel strategy for combining pharmacotherapy and CBT has emerged. Rather than being applied as an anxiolytic in its own right, pharmacotherapy has been applied as a strategy to enhance the retention of the therapeutic learning provided by exposure-based CBT. This approach is an outgrowth of basic research on the brain circuitry underlying fear learning and extinction that identified d-cycloserine (DCS), a partial agonist of the *N*-methyl-D-aspartate (NMDA) receptor, as an agent capable of enhancing extinction learning (7). Following successful validation of this strategy in the animal laboratory (8–10), DCS has been applied in multiple small studies to extinction learning in the context of exposure-based CBT (11–16). In the initial randomized trial, Ressler *et al.* (11) showed that single doses of d-cycloserine given before each of two treatment sessions could enhance outcome from exposure therapy using a virtual reality environment for height-phobic adults.

In response to this finding, we conducted a placebo-controlled, double-blind trial examining the efficacy of 50 mg of DCS for the treatment of social anxiety disorder (12). Study pills (DCS or matched placebo) were administered 1 hour before each of the final four sessions of a five-session CBT protocol emphasizing exposure to public speech situations. Relative to brief CBT with placebo, brief CBT with DCS augmentation was associated with significantly greater benefit at the end of acute treatment and at a 1-month follow-up. This study design and finding were recently replicated by Guastella *et al.* (13), with evidence of significant benefits across an array of outcome measures for DCS versus placebo augmentation of a five-session CBT protocol for social anxiety disorder. Weaker evidence for DCS augmentation effects have been evident in studies of obsessive-compulsive disorder (OCD) (14–17); these studies are noteworthy for more intensive (twice weekly) and/or repeated (10 dose) applications of DCS to a longer program of CBT. The frequency of DCS administration in these studies may be of importance given that animal studies indicate that tolerance to DCS develops rapidly (for review, see Otto *et al.* [18]).

Relative to these applications of DCS to CBT for other anxiety disorders, CBT for panic disorder relies strongly on exposure to feared internal sensations (interoceptive exposure) (1) rather

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than just external cues (e.g., heights in the case of acrophobia and social interactions in the case of social anxiety disorder). Accordingly, the present study provides an initial evaluation of an exposure strategy distinct from the external cue exposure of previous human and animal studies. Similar to the studies by Ressler *et al.* (11), Hofmann *et al.* (12), and Guastella *et al.* (13), in this study we conducted a pilot double-blind, randomized, controlled trial and used an isolated dosing strategy of 50 mg of DCS administered before the last three of five weekly CBT sessions. Consistent with recent studies that have utilized very brief (four to six acute session) protocols of CBT in clinical settings (19,20), for this study we selected a brief protocol of CBT that may be particularly relevant for 1) showing the effects of enhancement of therapeutic learning with DCS and 2) ultimate application to patients in primary care and other settings where access to a longer course of CBT is limited. We hypothesized that augmentation of brief CBT for panic disorder with DCS would lead to significantly better outcome, as assessed by broad measures of panic disorder and global severity, than augmentation with placebo at both posttreatment and at a 1-month follow-up evaluation.

Methods and Materials

Participant Selection

Identical study protocols were approved by the Institutional Review Board at each of three study sites. Participants were first screened by phone, followed by in-person diagnostic and severity evaluations with masters or doctoral level clinicians. After a complete description of the study, participants provided written informed consent. Participants then underwent diagnostic evaluation using the Structured Clinical Interview for DSM-IV (SCID-IV) (21) and severity rating using the Clinician Global Impression-Severity scale (CGI-S) (22) specific to panic disorder, as guided by the Massachusetts General Hospital (MGH) CGI-S rating guide for panic disorder.

Included were adults aged 18 to 65 with a current DSM-IV diagnosis of panic disorder (with or without agoraphobia) designated by the patient as the most important source of current distress and with panic disorder severity of at least 4 (moderate severity) on the CGI-S; mild severity was allowed for patients taking a stable dose of medications (this criterion was met by only one patient, 3% of the sample). Diagnostic exclusions included a history of bipolar disorder, psychosis or delusional disorders, or substance abuse or dependence (other than nicotine) in the last 3 months; current posttraumatic stress disorder (other comorbid anxiety disorders were allowed as long as they were not a primary source of distress); current major depression with severity greater than mild to moderate (as indicated by the presence of seven or more DSM-IV major depressive episode symptom criteria or meeting criteria for psychomotor retardation or suicide items on the SCID-IV); or severe agoraphobia that prevented regular attendance of sessions without being accompanied by another. Medical exclusion factors included pregnancy or lactation, as well as women of child-bearing potential not using a medically acceptable means of birth control; individuals with severe unstable medical illness; a history of seizures other than febrile seizure; clinically significant laboratory findings; or serious medical illness for which hospitalization was deemed likely within the next 3 months.

Participant flow throughout the study is summarized in Figure 1. Of potential participants providing informed consent, 33 outpatients with a principal DSM-IV diagnosis of panic disorder with or without agoraphobia met inclusion criteria and entered the study. Enrolled patients were recruited at the Center for Anxiety and Related Disorders at Boston University (n = 6), the Institute of Living in Hartford, Connecticut (n = 16), and MGH in Boston (n = 11). Five patients discontinued participation (two before randomization at week 3 of the protocol, three after randomization), leaving 28 treatment completers. One treatment-completing patient was subsequently lost to follow-up.

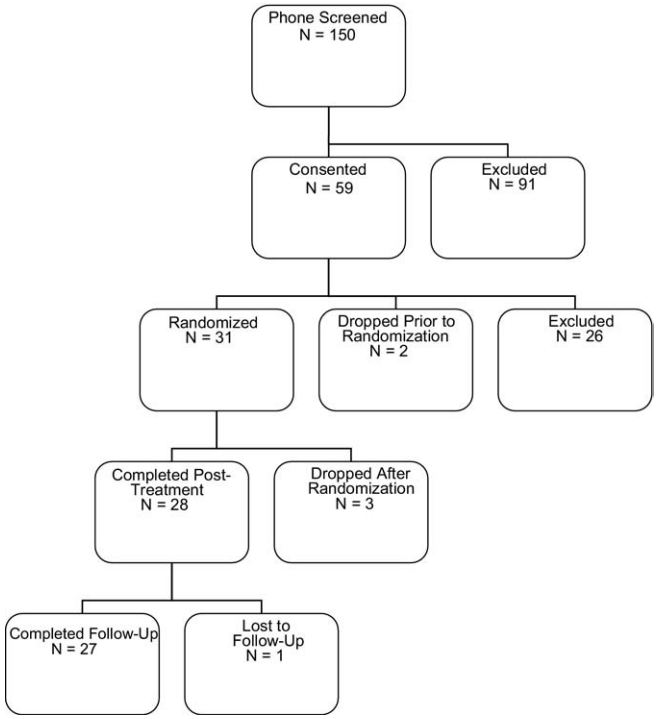

Figure 1. Progress of participants in the study.

Of the 28 participants who completed acute treatment, 14 were women (50.0%). The mean age of this sample was 35.0 (SD = 11.0) years. All the participants were white, and two participants endorsed Hispanic ethnicity. Most patients (25 of 28; 89.3%) were taking psychiatric medication at the time of entry into the trial; of these 25, 12 (48.0%) were taking a combination of antidepressant and benzodiazepine medication, 7 (28.0%) were taking an antidepressant alone, 3 (12.0%) were taking a benzodiazepine alone (1 taking as needed [p.r.n.] only), and 1 (4.0%) was taking gabapentin and atomoxetine. All participants had been stable on this dose of medication for a minimum of 2 months before entering the trial and agreed to maintain this stable dose of medication throughout the trial (the one patient taking p.r.n. benzodiazepines discontinued this use).

Measures

Outcome measures were assessed at baseline and at 1 week (posttreatment) and 1 month (follow-up) following the cessation of treatment sessions. The primary continuous outcome measure was the Panic Disorder Severity Scale (PDSS) (23). The clinician-rated PDSS includes seven items assessing dimensions of panic disorder severity: 1) frequency of panic attacks, 2) distress during panic attacks, 3) anticipatory anxiety, 4) agoraphobic fear and avoidance, 5) interoceptive fear and avoidance, 6) impairment of work functioning, and 7) impairment of social functioning. Shear *et al.* (23,24) have demonstrated interrater reliability ranging from .71 to .87. Prior to study, the sites reviewed decision rules