# 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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Received Nov 20, 2008; revised Jul 9, 2009; accepted Jul 10, 2009.

0006-3223/10/$36.00
doi:10.1016/j.biopsych.2009.07.036

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.

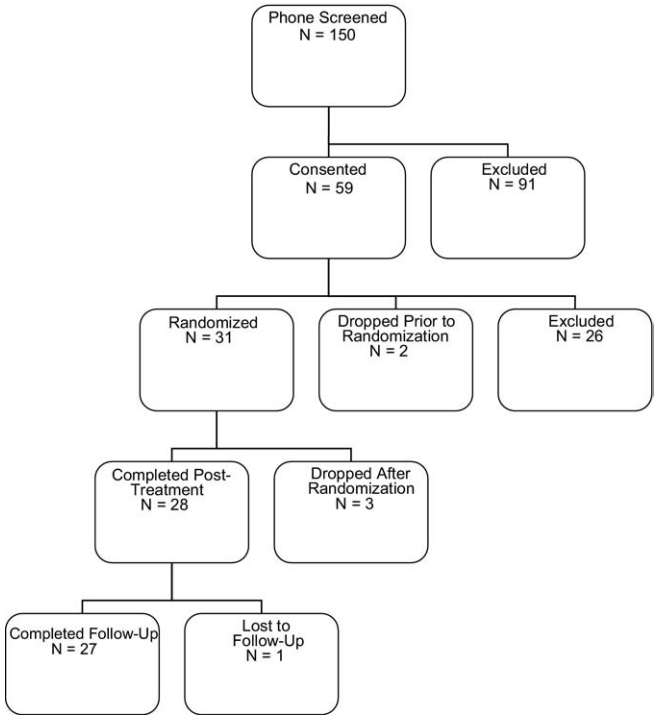


**Figure 1.** Progress of participants in the study.

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

for rating all items on the PDSS and the first author provided training for all raters.

The Clinician Global Impression-Severity scale is a clinician-rated instrument used to assess global severity of symptoms (22). The CGI-S ranges from 1 (normal, not at all ill) to 7 (among the most extremely ill patients), and for panic disorder, our research group has created specific anchor points to delineate the domains of information to be assessed in scoring the CGI-S for patients with panic disorder (25). The following parameters are assessed: number and frequency of panic attacks, intensity of anticipatory anxiety, degree of phobic avoidance, and impairment of function. The CGI-S was used as a secondary continuous outcome measure.

### Cognitive-Behavior Therapy

For this study, we selected a brief version of individual CBT emphasizing interoceptive exposure (exposure to somatic sensations of anxiety, e.g., hyperventilation to induce dizziness, paresthesias, flushes, etc.). The 5-session protocol was a condensed version of an 11-session protocol (26) found to be efficacious in studies (27,28) of the treatment of medication-nonresponsive samples of patients with panic disorder. In the condensed protocol, the first session (60 min) provided patients with a model of panic disorder and its treatment with CBT and included initial monitoring assignments (cognitions around panic attacks). In the second session (60 min), patients were introduced to interoceptive exposure (completed exposure to an initial sensation) and more active experiences evaluating and changing their thoughts associated with anxiety and panic (cognitive restructuring). The next three sessions were devoted to more intensive interoceptive exposure, delivered in a 90-min format and preceded by use of the blinded study medication. Session 3 was devoted to a fuller program of interoceptive exposure conducted in the office. Sessions 4 and 5 continued this program and also included interoceptive exposure practice outside the office (to provide patients with practice with sensations in situations that may motivate agoraphobic avoidance). Home practice assignments were assigned after each session and in latter sessions included instruction in in vivo exposure. Study therapists were doctoral- and graduate-student level providers trained and supervised by the first and second authors (M.W.O., D.F.T.). The consent form provided for in-person or tape-recorded monitoring of the content of sessions for supervision.

### Dosing and Monitoring of Study Medication

At each site, a study physician met individually with study participants, reviewed their medical histories, and provided final approval for them to enter the study. Doses of study drug (50 mg of DCS or matching placebo) were administered by study personnel in a double-blind fashion 1 hour before CBT sessions 3 to 5. Potential adverse effects of the drug were elicited by open questioning by study clinicians.

### Data Analysis

Data were analyzed with SPSS version 15 (SPSS Inc., Chicago, Illinois). Only those patients who completed the 1-month follow-up assessment were included in the analyses. To control for pretreatment variability in symptom severity on the PDSS and CGI-S, we conducted 2 (group: DCS, placebo [PBO]) by 2 (time: posttreatment, follow-up) mixed-factor analyses of covariance (ANCOVAs), with time as the repeated measure and pretreatment scores as the covariate. Effect sizes for the ANCOVA are reported as partial eta-squared ($\eta^2_p$) for which values of .01, .06, and .14 are considered to reflect small, medium, and large effects, respectively (29). A significant omnibus $F$ was further examined using planned between-group $t$ tests.

For the PDSS, we also calculated the proportion of patients in each treatment group meeting criteria for clinically significant change (30). This designation is considered when 1) a score has decreased by a reliable amount exceeding measurement error (reliable change index), and 2) the score is more likely to be representative of a nonclinical population than of a clinical population. These indexes were computed using ClinTools Software for Windows (www.clintools.com). First, a previously established interrater reliability of the PDSS (23) (.71) and the pretreatment standard deviation in the present sample (3.26) were used to calculate a reliable change index of 5. Normative data provided by Shear *et al.* (24) were used to calculate a cutoff score of 5 for the nonclinical range (2 SD below the clinical mean). Thus, for patients to have experienced clinically significant change on the PDSS, their posttreatment total score had to be 1) below 5, and 2) at least 5 points lower than at pretreatment. A 2 (group: DCS, PBO) by 2 (clinically significant change: yes, no) analysis using Fisher's exact test (FET) was used to determine whether the two treatment groups differed in terms of the proportion of patients meeting clinically significant change at posttreatment and 1-month follow up. Alpha level was set at .05.

## Results

### PDSS

The multivariate ANCOVA of PDSS scores at posttreatment and follow-up, controlling for pretreatment PDSS scores (mean 13.8 ± 3.3), yielded a significant main effect of group in favor of DCS, with a large effect size [$F(1,24) = 7.34$, $p = .012$, $\eta^2_p = .234$, d = 1.11]. There was no significant main effect of time [$F(1,24) = .02$, $p = .901$, $\eta^2_p = .001$], nor was there a significant group by time interaction [$F(1,24) = .093$, $p = .763$, $\eta^2_p = .004$], indicating that the stronger response for DCS did not differ by assessment point after pretreatment (Figure 2). Follow-up between group ANCOVAs, controlling for pretreatment scores, indicated that at posttreatment the DCS group showed significantly lower PDSS scores than did the PBO group [$F(1,24) = 8.70$, $p = .007$, $\eta^2_p = .266$]. A similar difference was obtained at follow-up [$F(1,24) = 4.60$, $p = .042$, $\eta^2_p = .161$].

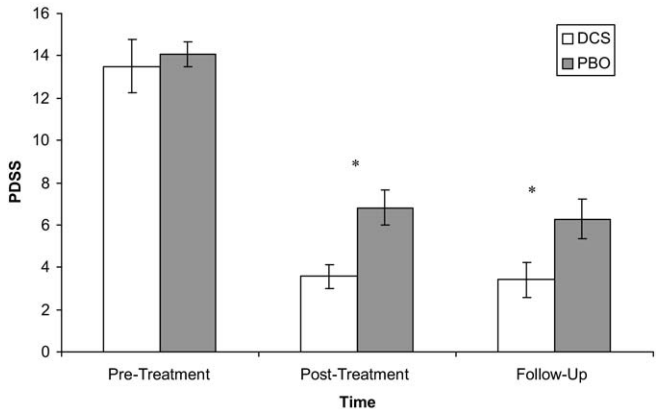


**Figure 2.** Means and standard errors for the Panic Disorder Severity Scale (PDSS) for patients receiving d-cycloserine (DCS) or placebo (PBO) in combination with brief cognitive-behavior therapy for panic disorder. *Groups significantly different, $p < .05$.

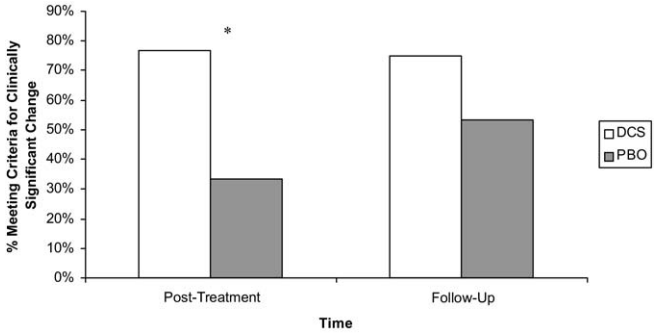


**Figure 3.** Percent meeting criteria for clinically significant change for patients receiving dcycloserine (DCS) or placebo (PBO) in combination with brief cognitive-behavior therapy. *Groups significantly different, $p < .05$.

Because the majority (89.3%) of patients in this trial had failed to respond adequately to pharmacotherapy before randomization, we examined the responsivity of this sample alone (with the exclusion of the five patients who were medication free at randomization). For this subsample, similarly strong effect sizes were obtained (d = .91) relative to the full sample (d = 1.11) for the DCS main effect.

Examination of clinically significant change using Fisher's exact test indicated that at posttreatment, there was a significant difference favoring DCS (FET $p = .030$), with 76.9% of DCS patients versus only 33.3% of PBO patients meeting this criterion (Figure 3). At follow-up, 75.0% of DCS patients versus 53.3% of PBO patients met criteria for clinically significant change; however, this difference was not significant (FET $p = .424$).

### CGI-S

The multivariate ANCOVA of CGI-S scores at posttreatment and follow-up, controlling for pretreatment CGI scores (mean 4.37 + .63), yielded a significant main effect of group in favor of DCS, with a large effect size [$F(1,24) = 7.25$, $p = .013$, $\eta^2_p = .232$]. There was no significant main effect of time [$F(1,24) = 1.08$, $p = .308$, $\eta^2_p = .043$], nor was there a significant group by time interaction effect [$F(1,24) = .12$, $p = .738$, $\eta^2_p = .005$], indicating that the stronger response for DCS did not differ by assessment point after pretreatment. Follow-up between group ANCOVAs, controlling for pretreatment scores, indicated that at posttreatment the DCS group showed significantly lower CGI-S scores than did the PBO group [$F(1,24) = 6.40$, $p = .018$, $\eta^2_p = .211$]. A similar difference was obtained at follow-up [$F(1,24) = 5.52$, $p = .027$, $\eta^2_p = .187$].

### Adverse Effects

No participant reported adverse effects from the study pills.

## Discussion

We found that administration of single doses of DCS, 1 hour before each of three exposure sessions within a five-session protocol, significantly enhanced the efficacy of brief CBT for panic disorder. In addition to significant differences in continuous outcome measures, at posttreatment, 77% of patients who had received DCS, compared with only 33% of patients who had received placebo augmentation, met criteria for clinically significant change. The treatment gains of the DCS group were maintained from posttreatment to follow-up. However, the difference between the DCS and the PBO group in the proportion of patients meeting criteria for clinically significant change was no longer significant at follow-up (75% vs. 53%). The degree of differential improvement on the primary outcome measure, the PDSS, was significant and reflected large effect sizes at both the posttreatment and 1-month follow-up assessments ($\eta^2_p = .266$ at posttreatment, and $\eta^2_p = .161$ at 1-month follow-up). Similar significant effects were evident for CGI-S ratings at these time points.

Consistent with animal and human studies to date (7–17), we believe DCS has its primary effect on consolidating extinction memory over time. With better memory consolidation of the therapeutic learning provided by CBT, DCS may offer more efficient treatment. It is not clear whether faster treatment will translate into more effective treatment outside of the brief protocols where DCS has been tested to date. There is evidence that with additional sessions, patients can catch up to the benefit provided by DCS augmentation (14,15,18). With our brief treatment approach, we did not see an attenuation of the advantage of DCS augmentation across our five-session protocol, but there was limited evidence that some patients who had received placebo had made additional treatment gains over the follow-up period. This effect is not unusual for exposure-based CBT (31), as individuals continue to apply skills learned during the active treatment phase. Hence, DCS may help most patients with panic disorder respond to as little as five sessions of CBT as indicated by this trial. It is unclear whether DCS augmentation will help patients who otherwise would respond poorly to a dozen sessions of CBT achieve a response within this time frame. Studies of the efficacy of DCS augmentation for CBT nonresponders are under way.

To our knowledge, our study represents the first application of DCS to a treatment protocol emphasizing exposure to feared internal sensations (interoceptive exposure). As supported by a range of psychopathology or prevention studies (32), these fears appear to be a core maintaining factor in panic disorder. Our treatment protocol was targeted to using DCS to enhance the retention of in-session interoceptive exposure, with treatment also offering instruction in cognitive interventions and in vivo exposure interventions to help patients extend their treatment gains. In addition, these interventions were targeted to participants who, in most cases (87%), had failed to respond adequately to previous pharmacological interventions. Independent assessment of these patients indicated a strong effect (d = 91) of DCS in this subsample, supporting the use of DCS augmentation in patients who are treatment refractory to traditional antianxiety pharmacotherapy.

We used a particularly brief form of exposure-based CBT for panic disorder. As noted, such brief treatment may provide especially favorable test conditions for DCS effects, where the amount of practice with exposure is limited, hence underscoring the potential value of a drug that enhances consolidation of the therapeutic learning provided by CBT. Nonetheless, our brief treatment approach has the additional advantage of being similar to the brief CBT shown to be especially cost-efficacious in a primary care setting (20). If additional study validates the strength of our findings, brief CBT augmented with DCS may have the particular advantage of an already cost-efficacious approach that can double the number of patients achieving clinically significant benefits. Accordingly, we believe that, if the DCS augmentation effect continues to be replicated, it has the potential of: 1) speeding treatment response to CBT and allowing for more efficient treatment (i.e., fewer CBT sessions), and 2) helping more individuals achieve a beneficial treatment response by aiding the retention of therapeutic learning in individuals who

otherwise may not respond to a finite number of CBT sessions (Supplement 1).

One limitation of our study is the sample size employed. This limitation is shared by other recent pilot studies of DCS augmentation of exposure for other disorders (11,12,14–16), with the exception of a single, moderately sized trial of social anxiety disorder (13). Early analysis of effect sizes of extant clinical trials indicates large effect sizes are common for DCS relative to placebo augmentation for trials outside of OCD (17). Our study indicates that DCS augmentation extends to exposure protocols that focus on fears of internal sensations of anxiety. This finding has promise for extension of DCS augmentation effects to other disorders where exposure to feared internal sensations appears to be an important element of treatment; in particular, exposure to such sensations has been identified as important in novel approaches to treating substance use disorders as well as anxiety disorders (33–35).

There is not yet evidence that DCS augmentation can extend to therapeutic learning in humans outside of clinical exposure paradigms (36). In an initial investigation of the efficacy of DCS for nonemotional and nonextinction based learning in healthy participants, Otto *et al.* (37) found no evidence for DCS augmentation for repeated weekly presentations of verbal and visuospatial memory tasks. Likewise, recent study also showed no consistent benefits for nonemotional verbal memory consolidation in outpatients with schizophrenia when an isolated dose paradigm was used (38). Study is underway to determine if consolidation of more emotional verbal and nonverbal memory tasks are aided by DCS administration.

A number of additional limitations deserve note. Our limited sample size prevented the reliable analysis of site effects, as well as potential moderators of treatment efficacy such as severity of agoraphobic avoidance or anxiety comorbidity. Similar to other trials of panic disorder, we excluded comorbid conditions such as bipolar disorder and severe depression; hence, our trial results can be generalized only to patients without these serious comorbidities. Although we did not have sufficient sample size to directly compare DCS augmentation effects across patients who were and were not taking medications at study entry, our study does indicate that DCS augmentation is effective for patients who have failed to respond adequately to traditional pharmacotherapy for panic disorder.

In summary, our findings encourage further study of DCS augmentation of exposure-based CBT as an additional strategy for the treatment of panic disorder, as well as study of the augmentation of interoceptive exposure interventions for other relevant disorders.

*We thank Dr. Grant Devilly for his statistical assistance; Christen Deveney, Kristen Woodberry, Matthew Monteiro, Gavin Zambruksi, Krista Gray, Danielle Koby, Rebecca Merenda, Traci Cipriano, Jennifer Sparrow, and Jennifer Lefort for serving as study therapists; and Sarah Carlson for serving as a research assistant.*

*Dr. Otto has served, in the last 2 years, as a consultant for Organon (Schering Plough) and Jazz Pharmaceuticals, has received royalties for use of the Structured-Interview Guide for the Hamilton Anxiety Scale, and receives research support from Schering Plough. Dr. David Tolin receives study support from Schering Plough and Indevus.*

*Dr. Krystal has served as a paid scientific consultant to Bristol-Myers Squibb, Cypress Bioscience, Eli Lilly, Forest Laboratories, GlaxoSmithKline, Janssen Research Foundation, Merz Pharmaceuticals, Organon Pharmaceuticals, Pfizer Pharmaceuticals, Shire Pharmaceuticals, Takeda Industries, UCB Pharma, and US Micron. He is also co-sponsor of two pending patents related to the use of glutamatergic agents to treat psychiatric disorders. Dr. Krystal was supported by the Department of Veterans Affairs National Center for PTSD and the National Institute on Alcohol Abuse and Alcoholism.*

*Dr. Simon has served as an investigator on trials sponsored by AstraZeneca, Bristol-Myers Squibb, Cephalon, Forest Laboratories, GlaxoSmithKline, Janssen, Lilly, Pfizer, UCB Pharma, and Sepracor. She has received honoraria support for Forest Laboratories, Janssen, Lilly, Pfizer, UCB Pharma, and Sepracor, and has served as a consultant or an advisory board member for Paramount Biosciences and Solvay.*

*Dr. Hofmann has served as a paid consultant for Organon (Schering Plough) and receives study support from Schering Plough.*

*Dr. Pollack has served on an advisory board or has consulted for AstraZeneca, Brain Cells, Inc., Bristol Myers Squibb, Cephalon, Dov Pharmaceuticals, Forest Laboratories, GlaxoSmithKline, Janssen, Jazz Pharmaceuticals, Eli Lilly and Co, Medavante, Neurocrine, Neurogen, Novartis, Otsuka Pharmaceuticals, Pfizer, Predix, Roche, Laboratories, Sanofi, Sepracor, Solvay, Tikvah Therapeutics, Transcept, Inc., UCB Pharma, and Wyeth; has received research grant support from AstraZeneca, Bristol Myers Squibb, Cephalon, Cyberonics, Forest Laboratories, GlaxoSmithKline, Janssen, Eli Lilly, National Alliance for Research on Schizophrenia and Depression (NARSAD), National Institute on Drug Abuse, National Institute of Mental Health, Pfizer, Roche Laboratories, Sepracor, UCB Pharma, and Wyeth; has served as a speaker for Bristol Myers Squibb, Forest Laboratories, GlaxoSmithKline, Janssen, Lilly, Pfizer, Solvay, and Wyeth; and has equity interest in Medavante and Mensante Corporation.*

*Shawnee Basden and Drs. Pearlson, Basden, Eisenmenger, and Meunier report no biomedical financial interests or potential conflicts of interests.*

*Clinical Trials (Augmenting Exposure Therapy With an N-Methyl-D-Aspartate (NMDA) Agonist for Panic Disorder; http://www.ClinicalTrials.gov/;NCT00131339).*

*Supplementary material cited in this article is available online.*

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