No Effects of D-Cycloserine Enhancement in Exposure With Response Prevention Therapy in Panic Disorder With Agoraphobia

A Double-Blind, Randomized Controlled Trial

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Abstract:

Purpose/Background: D-cycloserine (DCS) is a partial N-methyl-D-aspartate receptor agonist that potentially augments response to exposure therapy in anxiety disorders by enhancing extinction learning. This randomized, double-blinded, placebo-controlled augmentation trial examined (1) the effectiveness of adding 125 mg of DCS to exposure therapy (before or directly after the first 6 treatment sessions) in patients with panic disorder with agoraphobia and (2) the effectiveness of DCS augmentation preceding exposure relative to DCS augmentation directly postexposure.

Methods/Procedures: Fifty-seven patients were allocated to 1 of 3 medication conditions (placebo and pre-exposure and postexposure DCS) as an addition to 6 exposure sessions within a 12-session exposure and response prevention protocol. The primary outcome measure was the mean score on the "alone" subscale of the Mobility Inventory (MI).

Findings/Results: No differences were found in treatment outcome between DCS and placebo, administered either pre-exposure or postexposure therapy, although at 3-month follow-up, the DCS postexposure group compared with DCS pre-exposure, exhibited greater symptom reduction on the MI-alone subscale. Ancillary analyses in specific subgroups (responders vs nonresponders, early vs late responders, severely vs mildly affected patients) did not reveal any between-group DCS versus placebo differences. Finally, the study did not find an effect of DCS relative to placebo to be specific for successful exposure sessions.

Implications/Conclusions: This study does not find an effect of augmentation with DCS in patients with severe panic disorder and agoraphobia administered either pretreatment or directly posttreatment sessions. Moreover, no preferential effects are revealed in specific subgroups nor in successful exposure sessions. Yet, a small effect of DCS administration postexposure therapy cannot be ruled out, given the relatively small sample size of this study.

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Panic disorder is among the most prevalent anxiety disorders, with a 12-month prevalence rate estimated at approximately 2.7%.[1] Current treatment involves psychological therapy (mostly cognitive behavioral therapy [CBT] or exposure with response prevention therapy [ERP], medication (predominantly selective serotonin reuptake inhibitors [SSRIs] and benzodiazepines), or a combination; the combined treatment demonstrates an advantage over monotherapy.[2–4] Although effect sizes of treatment are moderate to large,[5,6] relapse rates are relatively high,[7,8] and there is still substantial room for improvement, particularly for patients at the more severe and chronic end of the spectrum.[9] Therefore, current research focuses on treatment-enhancing strategies.

One of the pharmacological enhancement targets is the N-methyl-D-aspartate (NMDA) receptor in the amygdala that is involved in the acquisition, consolidation, reconsolidation, and extinction of fear memory.[10] Animal research has indicated that D-cycloserine (DCS), a partial NMDA agonist, can enhance extinction of fear memory by indirectly stimulating glutamatergic transmission at its receptor.[11–13] Because extinction learning is considered to be a core mechanism of ERP,[14,15] this suggests that DCS might be a relevant ERP treatment enhancer.

So far, 18 clinical studies have investigated the potential treatment-enhancing effect of DCS as an addition to ERP in adults with anxiety disorders.[16–33] Whereas initial small placebo-controlled trials have reported large effects in the advantage of DCS enhancement of ERP,[21,22,25,26] more recent larger trials produced smaller effect sizes.[24,29,30,34] This decrease in effect size is confirmed in recent meta-analyses on this topic. The first meta-analysis by Norberg et al[35] combined 10 studies and found a large effect size ($d = 0.6$), Rodrigues et al[36] reported a medium effect size ($d = 0.34$) for 13 studies, and the most recent Cochrane review reported no significant effect of DCS augmentation in 21 clinical trials (adult and children).[37] Moreover, as of yet, only 2 studies on panic disorder with or without agoraphobia have been conducted, demonstrating positive outcomes, either directly or at post hoc investigation of specific subgroups. Otto et al[22] performed a randomized controlled trial (RCT) in which 31 patients with panic disorder with or without agoraphobia received 50 mg of DCS or placebo 1 hour before 3 weekly interoceptive exposure sessions. The DCS group revealed a significantly greater reduction of symptoms directly posttreatment. In a second RCT, conducted by

Siegmund et al,[23] 39 patients with panic disorder with agoraphobia underwent 8 sessions of group CBT, accompanied by 3 individual sessions of in vivo exposure (flooding). The latter 3 individual sessions were augmented with either 50 mg DCS or placebo. Although no additional overall effects of DCS were found, post hoc analyses yielded a trend for DCS to accelerate symptom reduction in patients with severe symptoms. In line with this, a recent study on patients with posttraumatic stress disorder (PTSD) found no overall ERP enhancing effect of DCS; however, subgroup analyses revealed that PTSD patients who needed longer ERP treatment exhibited an enhanced ERP-induced symptom reduction on DCS.[24]

The decreasing effects of recent somewhat larger scale controlled trials on DCS enhancement mentioned previously has led to a shift in the DCS research. Nowadays, DCS research focuses on (1) specific subgroups of patients, (2) the timing of DCS administration, and (3) DCS administration after successful exposure sessions only. The first topic involves identifying subgroups of patients who might specifically benefit from DCS enhancement, such as subgroups at the more severe end of the spectrum. The second topic entails the timing of DCS administration, either before or after ERP therapy. Animal studies suggest that DCS does not only enhance the consolidation fear extinction, but also the consolidation of fear acquisition and, therefore, carries the risk of erroneously enhancing fear acquisition in unsuccessful exposure sessions.[11,38,39] To date, none of the RCTs in humans has directly compared DCS augmentation pre-exposure therapy to postexposure therapy. A comparison of DCS effectiveness between pre- and post-ERP sessions is of clinical importance because—provided that DCS administered directly postsessions is at least as effective as administration before the sessions—this would enable clinicians to augment successful sessions only.[39] The third topic entails administration of DCS associated with those sessions during which significant fear extinction has occurred. There is some evidence that DCS might only augment successful sessions, that is, sessions in which a decrease of anxiety has occurred as operationalized by a decrease of Subjective Units of Distress (SUD) anxiety scores during sessions, or low SUD anxiety scores at the end of sessions. To test whether DCS might only augment sessions during which anxiety reduction has appeared, 2 RCTs have been reanalyzed by Smits et al.[40,41] In the first placebo-controlled study, 29 patients with height phobia received DCS or placebo directly after two 30-minute virtual reality exposure sessions. The treating clinician measured symptom severity at the beginning of the second session with the Clinical Global Impression Scale. In the second study, 145 patients with social phobia received 50 mg of DCS before 5 of 12 group CBT sessions. Although DCS did not indicate an advantage over placebo in this study, DCS was found to enhance exposure therapy in those patients who experienced successful ERP (operationalized as low SUD anxiety scores as a result of ERP, and as predicted using clinician-based outcome assessments at the beginning of the next session). In a third study, de Kleine et al[42] have been unable to replicate these findings in their original sample, using the exact same conceptualization of successful exposure therapy with SUD scores, and the same method of reanalysis of their original data on 67 PTSD subjects who received either DCS or placebo.

To sum up, recent reviews have been contradictory with respect to the potential effects of DCS, with some meta-analyses demonstrating effects between 0.25 and 0.6[35,36] versus a recent Cochrane review indicating no effect.[37] Only 2 earlier small-scale studies have specifically targeted panic disorder and agoraphobia,[22,23] and to the best of our knowledge, no earlier studies have specifically addressed timing of dosing (pre-ERP vs post-ERP sessions) within 1 study design. Therefore, the present study aimed to replicate and extend previous findings of DCS augmentation in ERP in a group of patients with panic disorder and agoraphobia.

The first aim of this study was to compare the addition of DCS and placebo to ERP. The second aim was to investigate differential effects of DCS enhancement in pretreatment and posttreatment. We hypothesized that DCS enhances or accelerates the effect of ERP and will be equally effective when administered either pretreatment or posttreatment. Third, in an attempt to replicate the previously mentioned post hoc effects in specific subgroups, we investigated whether DCS-enhanced ERP would be more effective in specific panic disorder subgroups (ie, early vs late responders, severely vs mildly affected patients) and whether DCS enhances successful exposure sessions, that is, those sessions that demonstrate low end-session SUD anxiety or SUD credibility (of something negative happening) ratings, by examining (fully in line with Smits et al[40,41]) DCS moderating effects on end fear or end credibility (of the feared outcome) preceding outcome measures at the next session.

METHODS

Patients

Patients were recruited between October 2010 and October 2013 at the outpatient clinics in 3 participating Dutch mental health care institutions. This study is registered at www.trialregister.nl (identifier: 6 577) as part of a large multicenter grant. The grant provided was used to conduct 2 different multicenter trials; the study described in the current article and a DCS augmentation study with a similar design of group CBT in patients with obsessive compulsive disorder. Results of that study will be published separately. The local ethics committee approved the current study, and all subjects provided written informed consent to participate. Adult patients with panic disorder with agoraphobia (N = 196) were invited to participate and underwent at baseline a semistructured interview using the Dutch version of the Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders*, *Fourth Edition* Axis I diagnoses (SCID-I)[43,44] was used to determine inclusion and exclusion criteria for the study. Exclusion criteria encompassed severe major depressive disorder, a current bipolar disorder, current psychotic disorder, and dependence and abuse of alcohol or drugs during the past 3 months according to the SCID-I interview. With respect to depression severity, scores greater than 29 as assessed with the Beck Depression Inventory II (BDI)[45] served as an exclusion criterion as well. Other exclusion criteria were intellectual disability (Verbal IQ <80 as assessed by the Dutch Reading Test for adults)[46]; an inability to adequately read or speak Dutch; a history of neurological disease, renal, or liver abnormalities; pregnancy or lactation; a history of severe adverse reactions to penicillin; and an unsuccessful evidence-based behavioral therapy for panic disorder in the preceding 12 months. Moreover, current daily, daytime use of benzodiazepines was an exclusion criterion. Selective serotonin reuptake inhibitors were allowed as long as the dosage was kept stable at least 3 months before the start of the study until the end of the study.

For patient flow chart, see Supplemental Digital Content, Figure 1S (http://links.lww.com/JCP/A458). Twenty-three patients refused to be interviewed and could therefore not be invited to participate, and 18 patients were lost to contact before intake. Hence, 155 patients were interviewed. Ninety-eight patients were excluded because (*a*) they did not fulfill an SCID-I primary diagnosis of panic disorder with agoraphobia (n = 38), (*b*) they refused to participate in the study (n = 40), or (*c*) they met one of the other exclusion

criteria (n = 20). Fifty-seven patients were randomized to either DCS before the exposure session (n = 19), DCS after the exposure session (n = 19), or placebo (n = 19).

Psychometric Assessments

Assessments were taken 1 week preceding the start of therapy (baseline), before session 4 (midstudy medication period), before session 8 (poststudy medication period), after session 12 (post-ERP), and at 3- and 6-month follow-up. The primary outcome measure was the mean score on the "alone" subscale of the Mobility Inventory (MI).[47] This self-report questionnaire has good reliability and validity[48] and contains 27 items (5-point scale per item) that measure agoraphobic avoidance behavior; situations are rated on the amount of avoidance "when alone" and "when accompanied by a significant other." Secondary self-report outcome measures entailed mean scores of the MI "accompanied" subscale, the Beck Anxiety Inventory (BAI)[49] and the Beck Depression Inventory II.[45] One additional outcome measure, the Panic Disorder Severity Scale (PDSS),[50] was assessed by means of interview. These questionnaires are proven to be valid and reliable.[51–54]

In addition, subjective self-reported fear and credibility levels (SUD anxiety and SUD credibility) were measured at the beginning and at the end of each session, with scores ranging between 0 (no anxiety or credibility) and 10 (maximum anxiety or credibility). Finally, during all assessments, the Fawcett side effects checklist[55] was used to monitor possible adverse effects as a result of DCS administration.

Exposure with Response Prevention Therapy

Patients underwent twelve 90-minute individual sessions of ERP using a standardized treatment protocol. This protocol was based on evidence-based CBT manuals for panic disorder with agoraphobia.[56,57] In the first session, psychoeducation was provided, and an idiosyncratic fear hierarchy was constructed. The next 6 sessions, which were augmented with DCS/placebo, all included interoceptive or in vivo exposure as well as elements of psychoeducation and cognitive restructuring. Sessions 8 to 12 (without study medication) included in vivo ERP, cognitive restructuring, and (in the final session) the construction of a relapse prevention plan.

Therapists were licensed psychologists and residents in psychiatry who were well trained in CBT and in the current study protocol. These therapists participated in the monthly supervision sessions during the course of the study. All sessions were audiotaped (unless this was impossible because of ERP performance in an outside setting not allowing for audiotaping), and 5% of the tapes were randomly checked to guarantee treatment integrity.

Design, Dosing, Randomization, Power Calculation, and Monitoring of Study Medication

This study entailed a randomized, double-blinded, placebo-controlled multicentered trial, with DCS as an adjunct to 6 of 12 weekly exposure sessions and with 3 treatment arms. Previous research had shown DCS augmentation to be most effective when administered for a limited number of times, early in treatment.[35] Patients in condition 1 (pre-DCS) received a fixed dose of 125 mg of DCS half an hour before the first 6 exposure sessions, and placebo directly after the first 6 exposure sessions. Patients in condition 2 (post-DCS) received placebo half an hour before the first 6 exposure sessions and DCS directly after the first 6 exposure sessions. Patients in condition 3 (placebo) received placebo both half an hour before and directly after the first 6 exposure sessions.

The sample size was calculated using G-power and based on 2 groups (DCS vs placebo), a 0.05-significance level (two-tailed), and a power of 80%. Calculations were based on the only available enhancement study using DCS before exposure therapy in panic disorder at the time of the sample size calculation,[22] which yielded an effect size of 1.1 on DCS enhancement. To establish an effect size (Cohen's *d*) of 1, a per-protocol sample size requires 20 patients per condition, with a two-sided α set at 0.05 and a β of 0.20.

The medication used in the study was prepared by the Utrecht University Medical Centre Pharmacy Department, which also performed the randomization procedure. The randomization sequence was guarded by the pharmacy until the last follow-up data have been collected. Thus, both researchers and patients were blind to the allocation sequence. Furthermore, the therapists distributed the study's medication.

Statistical Analysis

Data were analysed using SPSS version 19 (SPSS Inc, Chicago, Ill). Between-group differences in baseline characteristics were compared using two-tailed χ^2 statistics for categorical variables and 1-way analysis of variance statistics for continuous variables.

Because we anticipated that patients would drop out of the study, and because we expected that this dropout would be nonrandom, we concluded that we would obtain biased results if we would limit our analysis to the complete cases only. Therefore, we estimated linear mixed-effects modeling (LMM) for repeated measures data, which include all available data of all patients in the analyses, and we evaluated the differences in effect between DCS and placebo based on predicted means from the LMM and not on observed means. The LMM was fitted, regressing the main outcome variable MI "alone" on the exposure group indicator (DCS vs placebo), 5 time indicators (midstudy medication period, poststudy medication period, post-ERP, at 3- and 6-month follow-up; baseline served as the reference category for the time indicators), and the corresponding time indicator by group interaction terms as fixed effects and person identification as random effects. Between-group effect sizes were based on predicted means from the LMM and standardized using pooled baseline SDs (according to the PPC2 method).[58] Effect sizes were reported as Cohen's *d*.

To explore whether DCS facilitates treatment effect in specific patient groups, based on the literature, the following patient subgroups were examined: (1) responders versus nonresponders, with response defined as 25% or greater symptom reduction on the MI "alone" score, measured directly post-ERP (after session 12); (2) early responders versus late responders, with early response defined as 25% of greater symptom reduction on the MI "alone" subscale directly after session 7 versus later or no response; and (3) severely versus mildly affected patients at baseline. Here, severely affected indicates a baseline MI "alone" score above the median.

Subgroup analyses were performed, extending the LMM by interacting all fixed-effects parameters with the specific subgroup indicator. For each subgroup analysis, it was tested whether the effect of DCS was heterogeneous by evaluating a 3-way interaction term of DCS treatment by time by subgroup indicator.

To compare pre-DCS to post-DCS, LMMs were repeated with 3 groups (pre-DCS, post-DCS, and placebo).

To examine whether the effects of DCS are moderated by end fear levels of the previous exposure session (in an attempt to replicate earlier findings by Smits et al[40]), we tested if (1) end fear or credibility SUD scores moderated the effect of DCS (or placebo) on the MI "alone" score at the next session and (2) if lower end fear or credibility SUD scores across the 6 augmented sessions interacted with DCS (or placebo) predicted the postexposure

clinical outcome. Similar to the analyses of Smits et al,[40] the data were transformed into "long format." For (1), the data concerning sessions 3 and 7 fitting an LMM for the outcome variable MI "alone at the next session" was used with random effects at the individual level and the following fixed effects: group (DCS or placebo), begin fear (or begin credibility), end fear (or end credibility), and the condition-by-beginning fear and by-beginning credibility interaction terms and controlling for baseline MI "alone" scores.

For (2), the data of the first 4 measurements (up to and including the post-ERP measure) were used and fitted by LMM with random effects at the individual level and the following fixed effects: group (DCS or placebo), linear time, average begin fear or begin credibility, average end fear or end credibility across all sessions, and the 3-way interaction terms concerning time by group by average end fear or average end credibility.

RESULTS

Table 1 shows baseline characteristics. As can be observed, mean ages differed between the study groups, with patients receiving DCS before an exposure session being significantly younger than the other study groups (F[2.54] = 5.09; P = 0.009). There were no between-group differences on other sociodemographic variables at baseline nor were there between-group differences on MI, BAI, BDI, or PDSS scores. Moreover, comorbidity rates were similar between the 3 treatment conditions, as was the use of antidepressants (including SSRIs, serotonin–norepinephrine reuptake inhibitors, and tricyclic antidepressants) and benzodiazepines. Figure 1 shows predicted mean scores for all outcome measures.

Dropouts

Of the 57 patients experiencing panic disorder with agoraphobia, 14% (n = 8) dropped out during therapy (see patients flow chart, Supplemental Digital Content, Figure 1S, http://links.lww.com/JCP/A458). There were no differences between completers and dropouts on the baseline MI "alone" score or on sociodemographic or treatment condition parameters. However, the dropped-out patients had significantly higher depression scores at baseline than the completers (mean baseline BDI scores in completers of 17.4 vs 26.6 in dropouts (F[1.55] = 7.29; P = 0.009).

D-Cycloserine Versus Placebo

The upper part of Table 2 indicates the time course on the primary and secondary outcome measures comparing the combined pre- and post-DCS groups to the placebo group from the baseline measurement up to 6-month follow-up. Within-group effects were observed with a 30% decrease in the MI "alone" score, with large effect sizes for both groups at 6-month follow-up, Cohen's d is equal to 0.9 both for the DCS group and for the placebo group.

Furthermore, a within-time effect was found on all secondary outcome measures (mean score on MI "accompanied," BAI, PDSS, and BDI; Table 2). However, no significant between-group effects were found on the primary and secondary outcome measure (all P-values > 0.121).

D-Cycloserine Augmentation in Pre-Exposure and Postexposure Sessions

The upper part of Table 3 demonstrates the time course of the primary and secondary outcome measurements comparing DCS pre-ERP with DCS post-ERP between baseline and 6-month follow-up. Within-group effects were found for both active conditions, revealing moderate to large effect sizes at 6-month follow-up of Cohen's d = 0.7 and d = 1.1 for pre-DCS and post-DCS, respectively. At 3-month follow-up, the post-DCS group exhibited greater symptom reduction on the MI "alone" subscale compared with the pre-DCS group (the estimated between-group difference was −0.24; 95% confidence interval [CI], −0.95 to −0.01; t (228.3) = 2.62; P = 0.009), a difference that corresponds to an effect size of 0.6 (see the bottom part of Table 3). However,

TABLE 1. Baseline Characteristics (N = 57)

	Pre-DCS (n = 19)	Post-DCS (n = 19)	Placebo (n = 19)	Total (N = 57)
Sociodemographics				
Age, mean SD, y	29.5 (6.2)	38.4 (11.3)	38.3 (11.4)	35.4 (10.6)*
Sex (female), % (n)	57.9 (11)	63.2 (12)	57.9 (11)	59.6 (34)
Education, mean (SD), y	12.7 (3.7)	13.1 (2.8)	14.2 (2.9)	13.3 (3.1)
Marital status (married), % (n)	10.5 (2)	31.6 (6)	47.4 (9)	29.8 (17)
Primary outcome measure				
MI "alone," mean (SD)	2.8 (1.1)	3.2 (0.7)	2.8 (1.1)	2.9 (1.0)
Secondary outcome measures				
MI "accompanied," mean (SD)	2.1 (0.9)	2.4 (0.7)	2.0 (0.7)	2.2 (0.8)
BAI, mean (SD)	27.8 (10.2)	25.7 (11.9)	21.3 (10.2)	25.0 (10.9)
PDSS, mean (SD)	15.3 (3.8)	14.6 (5.2)	14.7 (5.0)	14.9 (4.6)
BDI, mean (SD)	18.1 (7.5)	19.7 (11.2)	18.4 (9.6)	18.7 (9.4)
Comorbidity				
No comorbid disorder, % (n)	68.4 (13)	63.2 (12)	42.1 (8)	57.9 (33)
Current comorbid other anxiety disorder, % (n)	0 (0)	31.6 (6)	15.8 (3)	15.8 (9)
Current comorbid depressive disorder, % (n)	15.8 (3)	0 (0)	31.6 (6)	15.8 (9)
Medication				
Use of antidepressant medication (yes), % (n)	15.8 (3)	27.3 (5)	42.1 (8)	28.1 (16)
Use of benzodiazepines (yes), % (n)	10.5 (2)	10.5 (2)	21.1 (4)	14.0 (8)

*Significant difference in baseline age (F(2.54) = 5.09, P = 0.009).

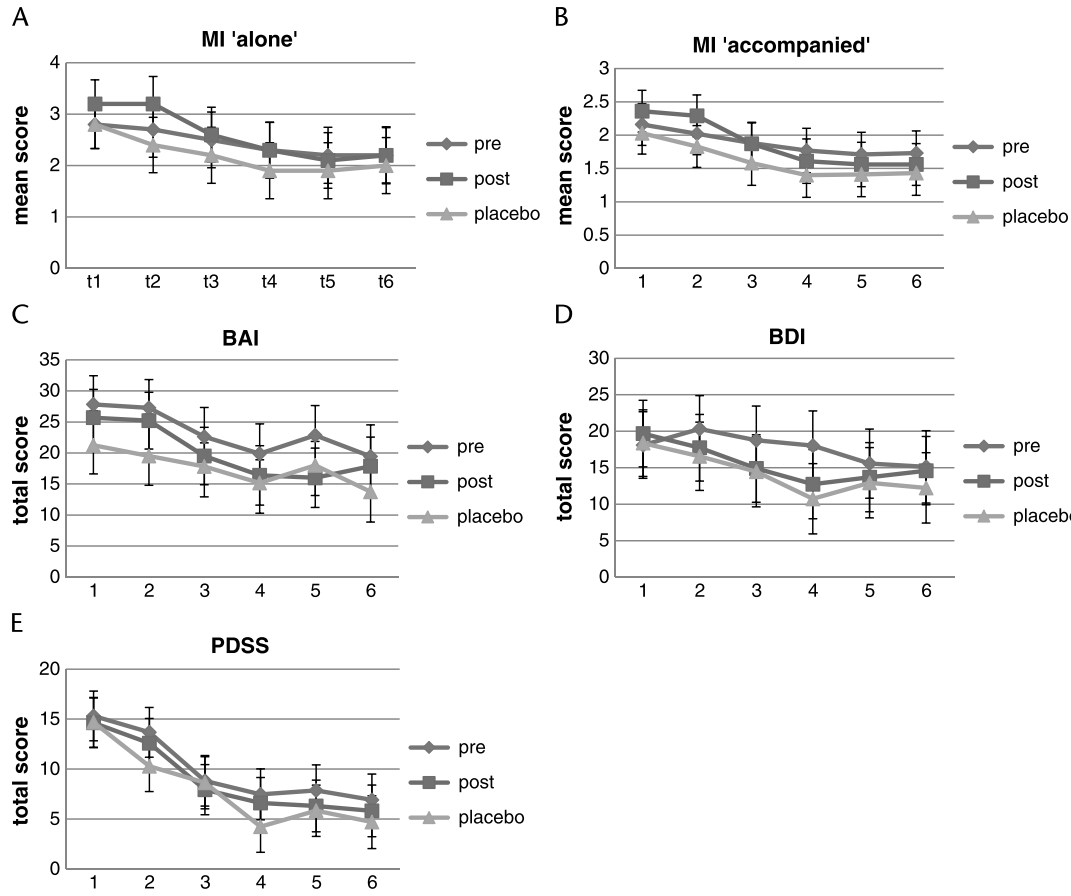

FIGURE 1. A, Predicted means based on linear mixed models for primary outcome measure MI "alone." B, Predicted means based on linear mixed models for secondary outcome measure MI "together." C, Predicted means based on linear mixed models for secondary outcome measure BAI. D, Predicted means based on linear mixed models for secondary outcome measure BAI-II. E, Predicted means based on linear mixed models for secondary outcome measure PDSS. Pre-DCS indicates D-cycloserine half an hour before exposure; post-DCS, D-cycloserine directly after exposure; T1, baseline; T2, midstudy medication; T3, poststudy medication; T4, postexposure therapy; T5, follow-up after 3 months; T6, follow-up after 6 months.

no differences in effect were found between pre-DCS and placebo or between post-DCS and placebo.

With regard to the secondary outcome measures, significant differences in between-group effects were found in favor of DCS augmentation postexposure relative to DCS augmentation preceding exposure sessions. At 3-month follow-up, the post-DCS group displayed a significantly larger reduction of anxiety scores compared with the pre-DCS group: the estimate between-group difference in BAI score was −6.46; 95% CI, −12.9 to −0.3; $t(229.3) = -1.98$; $P = 0.049$. However, no differences were found on these measures between pre-DCS administration, post-DCS administration, and placebo (for all data we refer to the Supplemental Digital Contents, Tables 1S and 2S [http://links.lww.com/JCP/A459, http://links.lww.com/JCP/A460]).

Ancillary Analyses

Additional post hoc analyses were conducted to investigate whether specific subgroups of patients experienced a relative advantage of DCS administration. Yet, none of the mixed-model analyses of the subgroups responders versus nonresponders, early versus late responders, and severely versus mildly affected patients yielded a time x group interaction effect (data not shown).

Moreover, no associations were found between low end fear SUD scores of an exposure session and MI "alone" scores among patients who had received DCS, relative to those who had received placebo ($b = -0.051$, $t(42.6) = -0.189$, $P = 0.851$) at any of the measurements (after sessions 4, 7, 12), neither was low credibility at the end of an exposure sessions associated with MI alone scores ($b = 0.202$, $t(28.1) = 1.42$, $P = 0.167$).

The summed average end fear SUD scores of sessions 2 to 7 did not moderate the effect of DCS ($b = 0.024$, $t(31.7) = 0.57$, $P = 0.575$), nor did the average level of end credibility SUD scores at sessions 2 to 7 ($b = -0.043$, $t(35.7) = -0.72$, $P = 0.478$).

Adverse Effects

When patients reported any symptoms or complaints (measured with the Fawcett side effects list), the treating clinician immediately checked if these adverse effects required action. Yet, none of the symptoms needed immediate action. After unblinding, it became apparent that 4 patients receiving DCS had reported mild adverse effects, which might have been due to study medication as measured with the Fawcett side effects scale (nausea, fatigue), but none of these reported adverse effects necessitated

TABLE 2. Predicted Mean Scores of Primary and Secondary Outcome Measures Based on Linear Mixed Models at Different Times for DCS (n = 38) Versus Placebo (n = 19) and Within-Group Effect Sizes for the Primary Outcome Measure (top part) and Estimates for the Condition × Time Interaction Terms and Derived Between-Group Effect Sizes of the Primary Outcome Measure (bottom part)

	Condition	T1	T2	T3	T4	T5	T6
Primary outcome measure							
MI "alone"	DCS	3.03	2.93	2.55*	2.30*	2.18*	2.18*
	Placebo	2.77	2.41†	2.18*	1.90*	1.93*	1.96*
Within ES for MI "alone"	DCS	reference	0.1	0.5	0.8	0.9	0.9
	Placebo	reference	0.4	0.6	0.9	0.9	0.8
Secondary outcome measures							
MI "accompanied"	DCS	2.26	2.15	1.87*	1.69*	1.63*	1.63*
	Placebo	2.03	1.83	1.58‡	1.40*	1.41*	1.43*
BAI	DCS	26.76	26.24	21.05*	18.15*	19.43*	18.74*
	Placebo	21.25	19.53	17.81	15.18†	18.03	13.77‡
PDSS	DCS	14.97	13.13†	8.38*	7.04*	7.10*	6.37*
	Placebo	14.68	10.28*	8.63*	4.24*	5.83*	4.69*
BDI	DCS	18.89	19.03	16.79	15.38†	14.62‡	14.95‡
	Placebo	18.37	16.57	14.44	10.74*	12.94‡	12.24‡
Between-group effects MI "alone"							
DCS vs placebo	Estimate	reference	−0.26	−0.11	−0.14	0.01	0.04
	95% CI		(−0.60 to 0.07)	(−0.45 to 0.24)	(−0.49 to 0.21)	(−0.34 to 0.36)	(−0.32 to 0.39)
	P		0.121	0.542	0.421	0.936	0.844
	ES		−0.3	−0.1	−0.1	0.0	0.0

Estimate: estimate of the condition × time interaction term from the linear mixed model at different times, where a negative sign indicates placebo reduces the outcome measure more than DCS.

ES indicates effect size; T1, baseline; T2, midstudy medication; T3, poststudy medication; T4, postexposure therapy; T5, follow-up after 3 months; T6, follow-up after 6 months.

Significance level of within group effects: *$P < 0.001$, †$P < 0.05$, ‡$P < 0.01$.

action. Thus, it can be concluded that important adverse effects of DCS did not occur during this study.

DISCUSSION

Although the sample size of this study was still relatively small, this is one of the largest studies on patients with panic disorder with agoraphobia investigating the added value of DCS as an exposure treatment enhancer, and the first study to directly compare DCS augmentation pre-exposure sessions with DCS postexposure sessions.

We found no DCS augmentation effect relative to placebo on 6 exposure sessions within the 12-session ERP protocol. Moreover, the ancillary analyses in specific groups of patients with varying degrees of symptom severity or speed of treatment response did not reveal any preferential effects of DCS compared with placebo. Furthermore, although similar analysis methods were used, we were unable to replicate the recent findings of Smits et al[40,41] who suggested that DCS specifically augmented exposure sessions leading to low end fear SUD ratings (as a proxy of successful ERP sessions) in height phobia and social phobia subjects.

The only 2 previously published studies on panic disorder with or without agoraphobia revealed more positive outcomes.[22,23] As described in the introduction, Otto et al[22] reported a significantly greater symptom reduction (effect size of 1.1) directly posttreatment with DCS than with placebo before 3-weekly interoceptive exposure sessions. In an RCT in patients with panic disorder and agoraphobia using post hoc comparisons, Siegmund et al[23] demonstrated that patients at the more severe end of the spectrum who were augmented with DCS tended to show faster symptom reduction than the placebo group.

A possible explanation for the current study's "null" finding might be the dosage of DCS and the frequency of augmentation. Although no dose-finding studies have been performed as of yet, it seems that lower dosages might be more likely to enhance treatment than higher dosages,[36] and that tolerance to DCS administration can occur.[59] This study used 125 mg of DCS (a moderate dosage) possibly leading to tolerance and a suboptimal effect. However, 2 previous studies that used dosages as well as number of sessions enhanced that were comparable with the current study did find enhancing effects of DCS.[16,17] Another explanation might be differences in baseline study group characteristics between previous studies and ours. Although baseline symptom severity scores on PDSS, BAI, and MI in previous studies were highly comparable with our study, baseline BDI scores in the current sample were higher compared with the sample of Siegmund et al[23] with mean scores of 18.7 in our study versus 12.9.[23] This might partly explain the differences between the studies.

As previously mentioned, this is the first study to compare DCS pre-exposure with DCS postexposure in patients with panic disorder and agoraphobia. One previous study[27] compared DCS postexposure with placebo as an addition to 2 exposure sessions in 29 patients with acrophobia, but did not include DCS pre-exposure as a comparative treatment condition, and found no augmentation effect of DCS postsessions. In the present study, a favorable effect of DCS augmentation was found directly after exposure when compared with administration preceding exposure, with an effect size of 0.3 both on the primary outcome measure and on anxiety and depression scores. This outcome might

TABLE 3. Predicted Mean Scores of Primary and Secondary Outcome Measures Based on Linear Mixed Models at Different Times for pre-DCS (n = 19) Versus post-DCS (n = 19) and Within-Group Effect Sizes for the Primary Outcome Measure (top part) and Estimates for the Condition × Time Interaction Terms and Derived Between-Group Effect Sizes of the Primary Outcome Measure (bottom part)

Predicted Mean Score	Condition	T1	T2	T3	T4	T5	T6
Primary outcome measure							
MI "alone"	pre-DCS	2.81	2.67	2.48*	2.29†	2.23†	2.17†
	post-DCS	3.24	3.19	2.63†	2.31†	2.13†	2.22†
within ES for MI "alone"	pre-DCS	reference	0.1	0.4	0.6	0.6	0.7
	post-DCS	reference	0.0	0.6	1.0	1.2	1.1
Secondary outcome measures							
MI "accompanied"	pre-DCS	2.16	2.02	1.88*	1.77‡	1.71†	1.72‡
	post-DCS	2.36	2.29	1.87†	1.61†	1.56†	1.56†
BAI	pre-DCS	27.82	27.26	22.63*	19.90‡	22.86*	19.45‡
	post-DCS	25.68	25.21	19.51‡	16.39†	16.01†	17.86†
PDSS	pre-DCS	15.32	13.68	8.83†	7.47†	7.87†	6.92†
	post-DCS	14.63	12.63	7.99†	6.66†	6.36†	5.87†
BDI	pre-DCS	18.11	20.32	18.78	18.04	15.56	15.12
	post-DCS	19.68	17.74	14.89*	12.74†	13.70‡	14.60‡
Between-group effects MI "alone"							
Post-DCS vs pre-DCS	Estimate	reference	0.10	−0.28	−0.41	−0.52	−0.37
	95% CI		(−0.27, 0.46)	(−0.65, 0.10)	(−0.80, −0.02)	(−0.91, −0.13)	(−0.77, 0.03)
	P		0.609	0.151	0.041	0.009	0.067
	ES		−0.1	0.3	0.4	0.6	0.4
Pre-DCS vs placebo	Estimate	reference	0.22	0.25	0.35	0.25	0.17
	95% CI		(−0.16, 0.60)	(−0.14, 0.64)	(−0.04, 0.75)	(−0.15, 0.65)	(−0.24, 0.57)
	P		0.251	0.205	0.081	0.214	0.423
	ES		−0.2	−0.3	−0.4	−0.3	−0.2
Post-DCS vs placebo	Estimate	reference	0.32	−0.02	−0.06	−0.27	−0.21
	95% CI		(−0.06 to 0.69)	(−0.41 to 0.36)	(−0.45 to 0.34)	(−0.66 to 0.12)	(−0.59 to 0.18)
	P		0.097	0.903	0.779	0.179	0.298
	ES		−0.3	0.0	0.1	0.3	0.2

Estimate: estimate of the condition*time interaction term from the linear mixed model at different times, where a negative sign indicates that the latter treatment reduces the outcome measure more than former treatment.

ES indicates effect size; T1, baseline; T2, midstudy medication; T3, poststudy medication; T4, postexposure therapy; T5, follow-up after 3 months; T6, follow-up after 6 months.

Significance level of within group effects: *$P < 0.05$, †$P < 0.001$, ‡$P < 0.01$.

suggest that DCS enhancement posttreatment is preferred over pretreatment augmentation or, at least, that DCS postexposure is equally effective as DCS pre exposure. However, the clinical significance of our result is to be determined in larger study samples because neither DCS pre-exposure nor DCS postexposure revealed enhancing effects when compared with placebo. Yet, the therapeutic advantage of administrating DCS after successful exposure sessions might be important, because it may limit the possible risks of DCS administration preceding treatment sessions in which, erroneously, fear acquisition is enhanced.[39]

Strengths and Limitations

Some limitations of this study need to be mentioned. The most relevant limitation concerns the relatively small sample size, which might have resulted in too low power to reveal significant between-group effects, especially when taking 3 treatment arms into account. Another limitation might be the somewhat higher dosages of DCS compared with most recent studies, which might have led to reduced augmentation effect and enhanced tolerance. However, as long as the optimal dosage and timing of DCS administration in human studies have not been systematically evaluated, these issues remain speculative. Moreover, although daytime use of benzodiazepines served as an exclusion criterion, the use of benzodiazepines at night to enhance sleep might have hampered the direct effect of exposure therapy, which has been demonstrated in a previous study regarding DCS augmentation of CBT in PTSD.[29] However, baseline characteristics of the patients who used benzodiazepines as sleep medication did not differ from those who were benzodiazepine-free, and the sleep medication using patients were randomly distributed across the 3 treatment conditions. Finally, 16 patients (28%) in our sample used SSRIs, which might have interfered with an augmentation effect of DCS, as demonstrated in a recent RCT of DCS augmentation versus placebo in 128 patients with obsessive compulsive disorder.[30] However, additional analyses in our sample revealed no effect of SSRI with DCS interaction (data not shown). Moreover, in our sample, only 8 patients (21%) in the DCS condition (pre/post) received SSRIs versus 8 patients (42%) in the placebo condition, which renders a significant SSRI with DCS interaction effect less likely to be picked up.

In conclusion, the results of this study do not indicate a DCS augmentation effect in patients with severe panic disorder and agoraphobia, which is in line with the latest Cochrane review on

DCS across psychiatric disorders.[37] Moreover, no preferential effects were found in specific subgroups. However, the suggestion that DCS administered after exposure sessions might yield better results than when administered before the sessions warrant further study in larger study samples.

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AUTHOR DISCLOSURE INFORMATION

All of the authors were involved in the conception and design of this study and/or in the analysis and interpretation of data for this manuscript. All of the authors drafted the manuscript and/or contributed important intellectual content to its revision. The authors declare no conflicts of interest.

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