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Examining the efficacy of D-cycloserine to augment therapeutic learning in depression☆

Michael W. Otto[a,*], **Josephine Lee**[a], **Stefan G. Hofmann**[a], **Bridget A. Hearon**[a], **Jasper A.J. Smits**[b], **David Rosenfield**[c], **Maurizio Fava**[d], **Jesse H. Wright**[e]

[a]Department of Psychological and Brain Sciences, Boston University, United States

[b]Institute for Mental Health Research and Department of Psychology, University of Texas at Austin, United States

[c]Department of Psychology, Southern Methodist University, United States

[d]Department of Psychiatry, Massachusetts General Hospital and Harvard Medical School, United States

[e]Department of Psychiatry and Behavioral Sciences, University of Louisville School of Medicine, United States

Abstract

Despite advances in individual and combined treatments for major depression, issues with non-response and partial-response remain relatively common, motivating the search for new treatment strategies. This study aims to develop one such novel treatment. In this proof-of-concept study, we are investigating whether the treatment enhancing effects of D-cycloserine (DCS) administration can be extended outside the extinction-learning paradigms where they have been primarily examined. Using uniform delivery of cognitive behavioral therapy (CBT) content via computer-administered interventions for depression, we are assessing the value of pre-session administrations of DCS for retention of therapeutic learning. Recall of this information is evaluated in conjunction with performance on standardized tests of memory recall with both emotional and non-emotional stimuli. Specifically, in a randomized, double-blind trial we will compare the benefits of two pre-session administrations of DCS augmentation to those achieved by similar administrations of modafinil or placebo. Because modafinil is associated with a number of discriminable effects in addition to cognitive enhancement (e.g., feelings of vigor, alertness, positive mood); whereas these effects would not be expected with DCS, we will assess drug context effects in relation to memory augmentation effects.

Keywords

Cognitive behavioral therapy; D-cycloserine; Modafinil; Depression; Declarative memory

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*Corresponding author at: Department of Psychological and Brain Sciences, Boston University, 648 Beacon St. 5th Floor, Boston, MA 02215, United States. mwotto@bu.edu (M.W. Otto).

1. Introduction

Despite clear advances in both pharmacotherapy and cognitive-behavior therapy (CBT) for major depression, non-response and partial-response remain relatively common [1,2]. Moreover, even with the combination of these modalities of treatment simultaneously [3,4] or sequentially [5,6] in accordance with NICE [7] and APA [8] guidelines, non-response remains an all-too-frequent outcome (e.g., [6]), motivating the search for new treatment strategies. This study is concerned with the development of one such novel treatment, the augmentation of cognitive-behavior therapy (CBT) with D-cycloserine (DCS).

Using animal paradigms, studies suggest that DCS enhances the consolidation of extinction learning [9,10], and this work has been translated to the augmentation of exposure-based CBT for anxiety and trauma-related disorders in over a dozen studies [11]. Our research team is now seeking to extend DCS augmentation to CBT that does not rely on extinction learning for its therapeutic effects. In support of this agenda, animal literature has noted positive DCS augmentation effects for hippocampal-dependent learning tasks (e.g., [12,13]). In our own translational studies of these findings to humans, we investigated whether 50 mg of DCS augmented verbal and nonverbal learning, proposing that successful augmentation of this learning would provide a model for augmenting the therapeutic learning from cognitive restructuring interventions. Although we failed to find benefit for single-dose administrations of 50 mg DCS in this paradigm [14], our pessimism for this approach was reversed by a 2010 study by Onur et al. [15] who reported that a single 250 mg dose of DCS facilitated speed of learning on an Item-Category Association Task, and that this effect was associated with greater activity in the hippocampus [16]. Investigators suggested that DCS effects on hippocampal functioning may be dose dependent, requiring a 250 mg dose rather than the 50 mg that is sufficient for augmentation of extinction learning in humans.

In the present study, we will investigate the efficacy of 250 mg DCS for declarative memory enhancement in depressed individuals. We are also studying an active comparison agent: single doses of modafinil administered prior to the learning session. Modafinil is a wake agent used to treat sleep disorders, which offers cognitive enhancing effects among both sleep deprived and non-sleep deprived individuals [17–21], presumably by increasing glutamatergic and dopaminergic neuronal activation in the hippocampus and in the prefrontal cortex respectively [22]. There is some evidence for more reliable cognitive benefits with 100 mg modafinil compared to 200 mg modafinil in non-sleep deprived healthy adults [23]; hence, single doses of 100 mg modafinil was selected for the current study. We will also investigate whether DCS has advantages over modafinil for retention of therapy-relevant learning, due to potential drug context effects introduced by detectable changes in alertness, positive mood/vigor, tension/anxiety associated with modafinil. A placebo condition was also implemented to control for possible expectancy effects as well.

The overarching goal of this research agenda is to evaluate whether DCS, or an alternative agent (modafinil) can be used to augment CBT for patients with depression. The current proof-of-concept study is the first step in this process, evaluating whether the mechanistic target (improved retention of therapeutic learning) is adequately engaged by the augmentation strategies.

2. Methods

2.1. Study design and objectives

The current study is funded by the R21 grant (R21MH102646) by the National Institute of Mental Health (Principal Investigator: Michael W. Otto). Boston University granted Institutional Review Board approval for the study. The primary aim of the study is to assess the novel treatment strategy in augmenting therapeutic learning in depression with DCS administration. Specifically, we will compare the relative efficacy of 250 mg DCS to 100 mg modafinil or pill placebo for the enhancement of declarative learning as measured by retention of computerized cognitive therapy intervention and other logical memory tests in adults diagnosed with major depressive disorder. The design calls for baseline assessment (Week 1), followed by two weekly sessions when the randomized study drug is administered, and a final week (Week 4) when retention is assessed under the conditions of no study drug. The drugs under study may have differential effects on immediate recall at the time the drug is taken vs. retention effects one week later. As such, the memory tests include both items unique to a given study week (i.e., the Item-Category Association Task, Digit Span backward, and Hopkins Verbal Learning Test), and memory tasks that are repeated over time (i.e., Wechsler Memory Scale—Revised Logical Memory, Emotional Logical Memory Test, Cognitive Therapy Awareness Scale). Primary outcomes will be cognitive therapy content and retention of logical memory (with exploratory examination of CBT skill use).

Because daily dosing of modafinil can offer mood-enhancing effects when used in conjunction with antidepressant medications [24], we want to differentiate direct cognitive effects of modafinil from those that may depend on mood effects. Evaluation of both mood and fatigue effects and interaction between study conditions and antidepressant use is included in the analytic plan. We also investigate whether DCS has advantages over modafinil for retention of therapy-relevant learning, due to potential drug context effects introduced by detectable changes in alertness, positive mood/vigor, tension/anxiety associated with modafinil. Hence, we evaluate memory enhancement effects both during the period of drug action as well as one week later when no drug is taken, allowing for the specific examination of the differential drug-context effects from either DCS or modafinil augmentation. The following aims will be addressed by this design:

Specific Aim 1: Examine differences in memory outcomes between study drugs, specifically testing the hypothesis that significantly greater retention of cognitive therapy content, logical memory content, and cognitive therapy skill usage will be achieved with 250 mg DCS and 100 mg modafinil as compared to placebo.

Specific Aim 2: Test the hypothesis that 250 mg DCS will show less drug-state context effects than modafinil augmentation (as evaluated by the change in delayed memory performance between weeks 3 and 4).

Specific Aim 3: Test whether modafinil will confer significantly better performance on the unique immediate memory assessments on weeks 2 and 3 only.

Specific Aim 4: Exploratory Aim: To examine predictors (potential moderators) of all drug effects.

These aims (centrally Aim 1, as refined by the subsequent aims) will be used to inform a go/no go decision on the likely utility and subsequent randomized study of DCS or modafinil to augment psychosocial treatment outcome for depression.

2.2. Participants

The sample will consist of 85 adult participants (to achieve completer data on 77 participants). Recruitment, which began September 2014 and is expected to continue through 2016, will comprise of depressed adults from the local Boston community. Inclusion criteria for the study are (1) a DSM diagnosis of major depression or persistent depressive disorder with those specifiers indicating presence of a current major depressive episode as determined by structured diagnostic interview, (2) free of psychotropic medications other than serotonin selective reuptake inhibitors (SSRIs) for at least 2 weeks, (3) absence of current active suicidal ideation, (4) between the ages of 18 and 65, and (5) proficiency in English.

Exclusion criteria include: (1) a lifetime history of bipolar or psychotic disorders; eating disorder or substance abuse/dependence (other than nicotine) in the past 3 months; organic brain syndrome, mental retardation or other potentially interfering cognitive dysfunction; (2) significant suicidal ideation or suicidal behaviors within 1 year prior to intake; (3) concurrent use of psychotropic medication (including stimulants) other than SSRIs; (4) concurrent use of phenytoin, isoniazid, or propranolol or known sensitivity to modafinil or cycloserine; (5) serious medical illness or instability (e.g., renal, endocrine, hepatic, respiratory, cardiovascular, hematologic, immunologic or cerebrovascular disease, or malignancy, or poorly controlled hypertension); (6) a history of seizures; (7) pregnant and/or breastfeeding women, and women planning to be pregnant (2 months post study intake); (8) daily use of alcohol or regular binge alcohol use as determined on the medical screen; (9) receipt of adequate CBT in the previous five years; (10) and a history of head trauma causing loss of consciousness, seizure or ongoing cognitive impairment.

2.3. Primary outcome measures

The timing of assessments is outlined in Table 1.

2.3.1. WMS-Logical Memory Test (WMS-LMT; [25])—

The Wechsler Memory Scale—Revised Logical Memory paragraphs will be used for the assessment of therapy-relevant learning of verbal material [14]. This test assesses memory for a brief story passage; two stories are available (forms A and B of the test). The stories are divided into multiple discrete information units; the total number of units recalled is the primary outcome. For baseline assessment, form A of the story will be used for immediate recall. Form B will be subsequently administered, with assessment of 1-week delayed recall at weeks 3 and 4.

2.3.2. Emotional Logical Memory Test (ELMT)—

The Emotional Logical Memory Test is used for the assessment of “therapy-relevant” learning of emotional verbal material of

a brief emotional story passage. The study team has constructed a scoring method similar to that used by the WMS Logical Memory Test.

2.3.3. Cognitive Therapy Awareness Scale (CTAS)—The Cognitive Therapy Awareness Scale [26] serves as the core CBT encoding task under investigation. The CTAS is a 40-item multiple choice measure evaluating knowledge of basic CBT concepts and methods. The CTAS was originally designed to measure comprehension of CBT skills in a study examining the efficacy of a computerized CBT program (similar to the program utilized in the current study; [27]); this measure will be used to assess delayed memory for cognitive therapy content from the computerized CBT program adapted for the current study.

2.3.4. Skills of Cognitive Therapy (SoCT)—The Skills of Cognitive Therapy [28] broadly measures patient understanding and use of basic cognitive therapy skills from both the patient and therapist perspective. This measure was included to assess spontaneous application of CBT principles from the computerized program. In the patient version, the respondent rates 8 items using a 5-point Likert type scale reflecting the extent to which each skill or strategy was used in the past month (Note: a one-week time frame will be used in the current study). In initial validation analyses, the SoCT demonstrated strong internal consistency and moderate patient-therapist correlations [28]. In addition, SoCT scores at mid-treatment were predictive of acute CT outcomes [28].

2.4. Secondary outcome measures

2.4.1. Wechsler Adult Intelligence Scale-IV — Digit Span Subscale (WAIS-IV; DS)—The Digit Span subtest of the Wechsler Adult Intelligence Scale-IV [25] is the most commonly used measure of immediate/working verbal recall. Scores for digits forward and digits backward will be used as a baseline covariate and digits backwards will be used as a unique weekly memory task.

2.4.2. Hopkins Verbal Learning Test (HVLT)—The Hopkins Verbal Learning Test [29] is a test of secondary verbal memory. Participants receive three consecutive trials of the presentation of a list of 12 nouns (with three semantic categories), each followed by a free-recall test. Each participant will start with one of the six lists on their first testing session and receive a different list for each subsequent weekly session.

2.4.3. Item-Category Association Task (ICAT)—The Item-Category Association Task has been shown to identify differences between 250 mg DCS and placebo [15]. For the ICAT, participants will make computer key press responses to judge the category membership (A or B) of three-digit numbers presented repeatedly on screen. Category membership remains constant over the six presentation trials in each run, allowing participants to improve categorization from visual feedback (“correct” or “incorrect”) provided for each categorization response. Visual feedback is provided for correct and incorrect categorizations, allowing participants to improve across trials.

2.4.4. Benton Controlled Oral Word Association Test (COWAT)—The Benton Controlled Oral Word Association Test [30] is one of the most commonly used measures of verbal fluency. The COWAT employs a word-list generation procedure during which subjects are asked to produce a list of words according to some linguistic rule or category in a limited amount of time. The total number of correctly generated words of the COWAT will serve as a covariate.

2.4.5. Delis-Kaplan Executive Function Scale — Trail Making Test (D-KEFS; Trail Making Test)—The Trail Making subtest of the Delis-Kaplan Executive Function Scale [31] will be utilized to assess psychomotor speed and mental flexibility. Raw scores indicate time to completion with greater scores indicating worse performance. Trails B will be used as a covariate indexing executive functioning.

2.5. Measures of mood and fatigue

2.5.1. BDI-II—The BDI-II [32] is a widely used 21-item self-report depression screening measure designed to assess severity of depressive symptoms. Items are presented with headings (e.g., “Sadness”) indicating the topic for response options (e.g., 0 = *I do not feel sad* to 3 = *I am so sad or unhappy that I can’t stand it*). Respondents are instructed to select how they felt during the “past two weeks, including today”. Responses are summed for a total score ranging from 0 to 61, with greater scores indicating greater severity in depressive symptoms.

2.5.2. Profile of Mood States (POMS)—The Profile of Mood States [33] is a widely used 65-item measure that assesses for fluctuating affective mood states. The POMS consist of 6 subscales including: 1) tension-anxiety, 2) anger-hostility, 3) fatigue-inertia, 4) depression-dejection, 5) anger-hostility, and 6) confusion-bewilderment. Mood descriptors (e.g., “Friendly”) are rated on a 5-point Likert type scale ranging from 0 (*Not at all*) to 4 (*Extremely*). Respondents are instructed to select how they have been feeling during the “past week, including today”.

2.5.3. Fatigue Survey Schedule (FSS)—The Fatigue Survey Schedule [34] is a 9-item measure that assesses for fatigue severity. Items are rated on a 7-point Likert-type scale ranging from 1 (*strongly disagree*) to 7 (*strongly agree*). Items on the FSS are averaged for a composite score, with higher scores indicating greater levels of fatigued-induced impairment. The FSS has demonstrated sufficient psychometric properties [34].

2.6. Safety monitoring

Patients complete a medical history form that provides assessments of medical exclusion criteria, with subsequent review of the form and interview with the study physician and vital signs (i.e., blood pressure and heart rate) are collected at the screening visit. Participants will be excluded from further study participation and referred for appropriate medical management, if any significant abnormalities in vitals (e.g., >150/90 mm Hg) are observed. Medications taken by the participant are assessed on the medical history form, with subsequent re-review in the assessment interview with the study staff member or study physician. Additionally, pregnancy tests will be performed on all female participants prior to

drug administrations on Study Visits 2 and 3. Drug adverse effects will be queried after a 90 min waiting period for symptoms over the last hour as well as emergent symptoms occurring after the last study session (applicable for Study Visits 3 and 4).

2.7. Procedures

2.7.1. Study Visit 1: screening and baseline assessments—Recruitment procedures include advertisements and direct referral from local clinics as well as advertisement posting to the general population. Individuals responding to these advertisements/referrals will undergo a brief phone screen prior to scheduling of an in-person evaluation that includes informed consent, a structured clinical interview (the Anxiety and Related Disorders Interview Schedule for DSM-5 (ADIS-5; [35]) to determine psychiatric inclusion and exclusion criteria, review of medical history, and a brief physical exam. For those meeting inclusion criteria, baseline questionnaires and cognitive assessment will be completed. Participants will then be scheduled for 3 subsequent weekly assessment sessions and receive a schedule delineating all appointment dates. All participants also receive reminder phone calls/emails approximately 24 h prior to study visits, and participants receive compensation for completion of study procedures.

2.7.2. Randomization and study pill administration—Following completion of the baseline assessment, randomization will occur in a double-blind fashion using a random number list to receive one of three study conditions (i.e., DCS, modafinil, or placebo). Randomizations are balanced across the blocking variables of sex and SSRI use. Study drugs will be provided in identical capsules and participants will receive one capsule of their randomized drug condition on Study Visit 2 and one capsule on Study Visit 3. At these visits, study capsule administration will be observed and precede cognitive testing by 90 min. Similar timing has been the standard in previous studies of DCS augmentation and takes into consideration the appropriate half-life of modafinil previously demonstrated [36]. All study drugs are stored in the refrigerated cabinet as per storage requirements (e.g., 36–46 °F for D-cycloserine).

2.7.3. Study Visit 2: study drug administration and assessment—As part of safety assessments at visits where study drug is administered, women will complete a pregnancy screening. All participants then complete the BDI and FSS followed by administration of the randomized study capsule 90 min before initiation of cognitive testing procedures. During the waiting period, magazines and television video-tapes will be provided. Drug adverse effects will be queried at the end of this waiting period for symptoms over the last hour as well as emergent symptoms occurring after the last study session. For cognitive testing, participants will listen to the WMS-LM story B, followed by immediate recall. Similar procedures will then be followed for the ELMT. Participants then complete unique versions (to the study week) of Digit Span-backward, and HVLT. Finally, participants complete a 45 min portion of computerized CBT.

2.7.4. Study Visit 3: study drug administration and assessment—At this visit, women will complete a pregnancy screening, and then all participants will complete the BDI and FSS followed by administration of the randomized study capsule approximately

90 min before queries about potential adverse events and initiation of cognitive testing procedures. For cognitive testing, participants will first complete one-week delayed recall of the WMS-LM story B, followed by one week delayed recall of the ELMT. Then, in turn, each story will be retold, and followed by an immediate recall session. Participants will then complete the Cognitive Therapy Awareness Scale and SoCT (for the previous week's CBT content) followed by a unique Digit Span-backward, a unique HVLT, and the ICAT. Finally, participants will complete a novel 45 min portion of computerized CBT which introduces participants to cognitive schema work.

2.7.5. Study Visit 4: final assessment—At this visit, no study drug is administered. Participants will first complete the BDI and FSS followed by one-week delayed recall of the WMS-LM story B, followed by one week delayed recall of the ELMT. Then, in turn, each story will be retold, and followed by an immediate recall session. Participants will then complete the CTAS and SoCT (for the previous weeks CBT content) followed by a unique Digit Span-backward, HVLT, and ICAT.

2.8. Computerized CBT program

To provide the computerized CBT content, we used a modified version of the empirically-validated *Good Days Ahead program* [26,27], offered through Empower Interactive. The version used in this study contains four modules of computerized CBT for depression broadly covering topics relating to identifying and challenging cognitive distortions, schemas and behavioral activation. Modules 1 and 2 focus on providing basic principles of cognitive therapy and cognitive errors (e.g., learning to identify and label automatic thoughts). Modules 3 and 4 of the computerized CBT program introduce activity planning and scheduling, and identifying and challenging negative core beliefs (i.e., schemas). These four modules were selected from the full twelve-module treatment package that comprises the *Good Days Ahead* program, as they provide patients with core CBT concepts for depression as well as map on to the content of the CTAS, our primary measure of therapy recall.

2.9. Data analysis

Analyses for outliers, non-normal distributions, nonlinear relations, and influence statistics will be conducted; data transformations will be considered where appropriate. We will perform repeated-measures ANOVAs using mixed-effects regression models (MRMs) in SPSS 22.0 to analyze the data. The MRM approach to repeated measures ANCOVA allows inclusion of all participants regardless of missing data (which improves power and generalizability), can model the covariance matrix of the repeated measures more flexibly than ANCOVA, and is the recommended method for longitudinal data analysis [37]. The ANCOVA will consist of 3 levels of the between-subjects independent variable (Treatment conditions) and 2 (or 3) levels of the within-subjects variable (Time). For delayed recall memory, Time will represent weeks 3 and 4, when recall for information presented at the previous session will be assessed. Three separate analyses will be performed, one for each of the 3 measures of delayed recall memory; retention of 1) cognitive therapy principles, 2) emotional narrative, and 3) WMS Story B. For immediate memory, Time will represent weeks 2 and 3, the time points of primary interest for the immediate memory tests (Digit

Span, HVLT, ICAT). Scores on the baseline memory assessments (week 1) and baseline antidepressant use will be included as covariates in all analyses. Since the relation between the covariates and outcome may be different among treatment conditions (e.g., the relation between baseline memory and drug influenced memory may be lower for 250 mg DCS and 100 mg modafinil compared to placebo), interaction terms will allow these relations to vary across treatment conditions. Similarly, because the relation between the covariates and the DVs may be lower at weeks 2 and 3 (with drug ingestion) compared to week 4 (no drug ingestion), interaction terms will also allow these relations to vary across Time. Non-significant interaction terms will be dropped.

2.9.1. Exploratory analyses—We will examine whether baseline antidepressant use, mood (BDI-II), fatigue (FSS), attentional/executive function (COWAT, TMT-B), HVLT total score, and/or digits backward performance moderates active study drug effects relative to the placebo condition. Examination of associations between performance on immediate memory scores and delayed recall (including ICAT performance at weeks 2–4) will also be examined in each study drug condition to help clarify the nature of in-session memory augmentation vs. retention effects across the weeks of testing. The effect of treatment condition on BDI will also be examined using the same analysis as Aim 1 (including pairwise comparisons among the groups). We expect BDI to be enhanced in 100 mg modafinil condition, and explore whether it will also be enhanced in 250 mg DCS. We will also examine if improved memory mediates the changes in BDI.

2.9.2. Power analysis—A sample size of 85 subjects was determined relative to a conservative estimate of a 10% dropout after Study Visit 3. We utilized PinT 2.12 (a program to calculate effect sizes in mixed models) to calculate the smallest effect size detectable with 0.80 power for the specific hypothesized comparisons in Aims 1, 2, and 3. Analyses showed that power was lowest for Aim 1, so Aim 1 determined the necessary sample size. If we use the Bonferroni correction for the 3 comparisons, p is set at 0.0167 (instead of the previous 0.0083), and the sample size necessary to detect a medium (e.g., d = 0.50) effect size with a power of 0.80 is $N = 77$. Hence, allowing for 10% dropout (8 individuals), 85 participants are to be randomized.

3. Discussion

In this application we propose to expand upon one of the areas of particular success of translational research, the use of single-dose applications of DCS to augment therapeutic learning from CBT. Despite its success in the anxiety disorders [11], it is not known whether DCS can enhance the therapeutic learning from CBT interventions that do not involve extinction learning. Initial applications in humans have provided mixed results [15,38], with some indication that more positive results may be achieved with a higher (i.e., 250 mg) dose of DCS. Our first step in a longer-term goal of augmenting CBT for depressive disorders is to examine whether learning of cognitive therapy content from computerized CBT can be augmented. To achieve this goal, we are conducting a proof-of-concept experiment to evaluate, in a double-blind, placebo-controlled investigation, the relative efficacy of 250 mg DCS and 100 mg modafinil compared to placebo for augmenting verbal declarative memory in depressed individuals. We can achieve these aims in a brief (4 visit) trial in

a non-treatment-seeking cohort of depressed individuals. We assess retention and use of CBT interventions material as well as performance on standardized cognitive tests, to test the relationship between cognitive impairment (and amelioration) and the magnitude of augmentation effects.

Use of a computerized program for CBT [26,27] in our protocol ensures reliable (exact) presentation of the to-be-remembered therapy content, and additional use of standardized cognitive tests allows us to examine the association between remembering therapy content and other cognitive skills, as well as the link between cognitive deficits and the amelioration of such deficits. The proposed augmentation strategies need not rely on amelioration of cognitive deficits, although cognitive deficits found in depression are assessed in the protocol and are a secondary target of amelioration, and strategies to ameliorate such deficits are needed to improve CBT for depression in specialty populations (e.g., elderly adults with Parkinson's disease; [39]). Because cognitive deficits predict poorer response for antidepressant medications (for a review [40]), investigation of psychosocial treatment augmentation is encouraged.

Overall, this protocol offers the following innovative elements: (1) extending DCS augmentation effects found for the anxiety disorders to a new learning paradigm and, potentially, to the future augmentation of CBT for depression (as well as other disorders and psychosocial interventions); (2) use of a proof-of-concept study that combines standardized memory paradigms with the examination of retention of computerized CBT content; (3) investigation of an active comparison agent (modafinil) that has shown promise as a cognitive enhancer and that may also have specific antidepressant actions; (4) investigation of the cognitive enhancing effects of modafinil in a single-dose paradigm to enhance learning rather than the daily dosing used in depression trials; (5) and investigation of the drug-context effects. All of these study elements will be useful for the subsequent investigation of the relative benefits of DCS and modafinil as augmentation strategies for CBT for depression.

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Table 1

Schedule of assessments.

Measures	Screening	Baseline/Study Visit 1	Study Visit 2	Study Visit 3	Study Visit 4
ADIS-5	X	.			
Medical screening	X				
Primary outcomes					
WMS-Logical Memory					
Immediate recall		X	X	X	X
Delayed recall				X	X
ELMT					
Immediate recall			X	X	X
Delayed recall				X	X
CTAS				X	X
SoCT				X	X
Secondary measures					
DS (Forward and/or backward)		X	X	X	X
HVLT		X	X	X	X
COWAT		X			
TMT		X			
ICAT			X	X	X
CBT			X	X	
Mood and fatigue measures					
BDI-II		X	X	X	X
POMS		X	X[a]	X[a]	X
FSS		X	X	X	X

Note: ADIS = Anxiety and Related Disorders Interview Schedule for DSM-5; WMS = Wechsler Memory Scale-Revised Logical Memory; ELMT = Emotional Logical Memory Test; CTAS = Cognitive Therapy Awareness Test; SoCT = Skills of Cognitive Therapy; DS = Digit Span; HVLT = Hopkins Verbal Learning Test; COWAT = Controlled Oral Word Association Task; TMT = Trail Making Test; ICAT = Item-Category Association Task; CBT = Computerized Cognitive Therapy Program; BDI-II = Beck's Depressive Index; POMS = Profile of Mood States; FSS = Fatigue Survey Schedule.

[a]Pre- and post-medication administration waiting period.