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

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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.



## 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

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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