STUDY PROTOCOL

for

Improving Therapeutic Learning in Depression: Proof of Concept

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D. RESEARCH DESIGN AND METHODS

We propose to study cognitive function and memory performance over 4 study sessions in **77** men and women with major depression, who, in a double-blind fashion, will be randomly assigned to either: (1) 250mg DCS, (2) 100mg modafinil, or (3) placebo administered on Study Weeks 2 and 3. The design calls for baseline assessment (Week 1), followed by two weekly sessions when 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 ICAT, digits backward, and HVLT), and memory tasks that are repeated over time (i.e., narrative memory tasks and the cognitive therapy content). Primary outcomes will be cognitive therapy content and retention of logical memory (with exploratory examination of CBT skill use).

Design Considerations

Why Investigate Baseline Cognitive Impairment? Cognitive (including verbal memory) impairments have been documented in unipolar depression (e.g., Castaneda et al., 2008; Otto et al., 1994), with poorer neuropsychological functioning predicting poorer antidepressant (e.g., Dunkin et al., 2000; Kampf-Sherf et al., 2004; *Withall et al., 2009) as well as CBT response (Dobkin et al., 2012; see also Caudle et al., 2007).* Because there is a potential for stronger cognitive enhancement effects among individuals with greater cognitive dysfunction (e.g., such effects have been reported for modafinil administration in healthy participants; Finke et al., 2010), baseline cognitive functioning will be examined as a potential moderator of augmentation effects in the present study. In addition, these baseline measures will serve as covariates, providing potentially greater power for detection of drug effects.

Why Utilize 2 Drug Administration Visits and A Follow-Up Visit? As noted in the "Context..." section above, this study examines the effects of study drugs on the day of administration and during subsequent weeks. By keeping the final visit drug-free, we will be able to examine retention of memory when individuals are drug-free (across drug-cue contexts). Use of two isolated administrations of study drug matches the original and subsequent applications of DCS for specific phobia (Ressler et al., 2004; Smits et al., in press).

Why Assess Mood and Fatigue During the Trial and Include SSRI Use? Given evidence that modafinil may interact with antidepressants to enhance mood effects (see "Modafinil" section above) we carefully considered the inclusion of individuals on antidepressants in the trial. In clinical practice, patients taking antidepressants are frequently referred for CBT; hence, to exclude this cohort would limit the generalizability. Including patients on antidepressants raises the possibility of mood interactions with modafinil (previous DCS studies have not noted significant differences among those taking and not taking antidepressants with single dose DCS administrations; e.g., Otto et al., 2010a; but see Poleszak et al., 2011), but this possible effect is targeted in the analysis plan. We will examine the link between any mood changes occurring during the trial (as assessed by the BDI and POMS) and cognitive enhancement effects. We will also examine whether cognitive modafinil effects are specific to (moderated by) the fatigue that can co-occur with depression.

Why Utilize the Specific Cognitive Tests And CBT Skill Assessments Proposed Below? *The frequency and quality of CBT skill use is a predictor of response to CBT for depression and protection from relapse (see Hundt et al., 2013; Strunk et al., 2007). Given that retention of session material is a logical prerequisite to recall and application of this material, our assessment of recall of session material with the CTAS is fully in line with the goal of assessing a core mechanism behind CBT – recall of CBT concepts. We also now use the SoCT (Jarrett et al., 2011) to provide a broader assessment relevant to CBT skill use (e.g., restructuring negative cognitions); such assessment would be most appropriate to a treatment outcome study (which this proof-of-concept study is not), but nonetheless, spontaneous application of CBT principles from the computerized program is of interest as an exploratory outcome.* Also, the standardized cognitive tests administered across weeks represent many of those utilized in our previous study of verbal memory enhancement in response to 50mg DCS (Otto et al., 2009a) as well as the core test used by Onur et al. (2010), as well as select tests shown to be sensitive to modafinil use. The test battery is not designed to be a comprehensive assessment, but to hone in on the sort of cognitive functions that may affect retention of CBT.

Randomization and Study Drugs

Participants will be block randomized (by sex and SSRI use) to one of the ***3*** drug conditions. Study drugs will be provided in identical capsules. Patients will receive one capsule of their randomized drug 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 minutes. Similar timing has been the standard in our studies of DCS augmentation; and is appropriate to the absorption and half-life of modafinil (Darwish et al., 2010).

Study Participants

We plan to recruit **77** male and female participants between the ages of 18 and 65, willing and able to provide informed consent, attend all study visits, and comply with the protocol. Participants must have a DSM diagnosis of major depression as determined by structured diagnostic interview (SCID), must be free of psychotropic medications other than SSRIs for at least 2 weeks, and have no current suicidal ideation. Additional exclusion criteria include: (1) DSM diagnosis of dementia, neurodegenerative disease, or other organic mental disorder; substance use disorder other than nicotine or caffeine in the last 3 months; bulimia or anorexia within the last 3 months; lifetime history of psychotic disorder, bipolar disorder , or developmental disorder; medical illness including hypertension, cardiac disease, liver disease, pulmonary diseases, central nervous system disease, and epilepsy; (2) recent (1 year) suicidal attempts; (3) for women, currently pregnant, plans to be pregnant in the next 2 months, or currently breastfeeding; (4) treatment with phenytoin, isoniazid, or propranolol or known sensitivity to modafinil or cycloserine; (5) history of head trauma causing loss of consciousness, seizure or ongoing cognitive impairment; (6) use of psychotropic medication other than SSRIs; *(6) CBT in the last 5 years*; or (7) insufficient command of the English language (i.e., cannot carry on a conversation with an interviewer in the English language or read associated text).

Recruitment and Feasibility

Recruitment. Recruitment strategies will be based upon those employed in our previous studies of depressed individuals in the Boston University catchment area, including referrals directly from the Center for Anxiety and Related Disorders at BU and the BU Medical Center (BUMC). Our recruitment strategies will include area advertisements as well as advertisements/direct referrals from these treatment centers. Across all assessments and study procedures, participants will be compensated a total of $200 for complete adherence.

Feasibility: Dr. Otto has evidence of adequate recruitment rates of depressed individuals for augmentation studies. For example, Dr. Otto's team recruited 48 non-treatment-seeking depressed adults over a 17-month period (Calkins et al., 2013). Likewise, using strategies similar to those proposed here, in 2.5 months his team has recruited 12 individuals for participation in a study combining cognitive control training for depression with brief behavioral activation treatment. The study team also has the added resource of being able to study patients during their waiting period for treatment (often 8 weeks) at the Center for Anxiety and Related Disorders, or from patients at BUMC. Hence, given our recent recruitment history, we anticipate no difficulties meeting our recruitment goals

Procedures

- Visit 1: Screening and Baseline Assessment: Following phone screening, patients will be scheduled for an evaluation session where informed consent will be obtained. The psychiatric evaluation begins with the Structured Clinical Interview (SCID) to evaluate the presence of psychiatric inclusion and exclusion criteria. Patients will also complete a medical history form and interview with the study physician. If inclusion criteria are met, baseline questionnaires and cognitive assessment :administration of the WMS--Logical Memory (Story A), Digit Span, Hopkins Verbal Learning Test, Trails A and B, and the Controlled Oral Word Association Test (see below). Participants will then be scheduled for 3 subsequent weekly assessment sessions, with randomization in a double-blind fashion using a random number list to receive one of the 4 study conditions. Randomizations will be blocked by sex and SSRI use and will occur at week 2.
- Visit 2: Study Drug Administration and Assessment. At this visit, patients will first complete the BDI and FSS followed by administration of the randomized study capsule 90 minutes before initiation of cognitive testing procedures. During the waiting period, magazines and television videotapes 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 Logical Memory story B, followed by immediate recall. Similar procedures will then be followed for the Emotional Logical Memory Task. Participants will then complete unique versions (to the study week) of Digit Span-Backwards, HVLT, and ICAT. Finally, participants will complete a 45min portion of computerized CBT providing an overview of cognitive therapy and experience with cognitive errors.
- Visit 3: Study Drug Administration and Assessment. Study drug administration and assessment procedures match Visit 2, but with the addition of one-week delayed recall of both the WMS Logical Memory story B and the Emotional Logical Memory Task. CTAS and SoCT are specific to the previous week's content, and a novel 45min portion of computerized CBT (cognitive schema work) is presented.
- Visit 4: Final Assessment. No study drug is administered. Participants will first complete the BDI and FSS followed by one-week delayed recall of the WMS Logical Memory story B, followed by one week delayed recall of the Emotional Logical Memory Task. Then, in turn, each story will be retold, and followed by an immediate recall session. Participants will then complete the Cognitive Therapy Awareness Scale (for the previous weeks CBT content) ***and SoCT*** followed by a unique Digit Span-Backwards, HVLT, and ICAT.

Core Cognitive Assessments – Delayed Recall

- *Cognitive Therapy Awareness Scale* (CTAS; Wright et al., 2002). A modified CTAS will be used to assess delayed memory for cognitive therapy content from the computerized CBT. The CTAS will be modified to enhance specific content from the computerized CBT and to delete extraneous content. We have successfully used the CTA in previous study of computerized CBT (Wright et al., 2005).
- *Skills of Cognitive Therapy (SoCT; Jarrett et al., 2011) at the same assessment points as the CTAS, to provide a broader assessment relevant to CBT skill use (e.g., restructuring negative cognitions).*
- *WMS-Logical Memory Test*. For the assessment of therapy-relevant learning of verbal material, the Wechsler Memory Scale—Revised Logical Memory paragraphs will be used as per Otto et al. (2009a). This test assesses memory for a brief story passage; two stories are available (forms A and B of the test). For baseline assessment, Form A of the story will be used for immediate and 30 min delayed recall. Form B will be subsequently administered, with assessment of 1-week delayed recall at Weeks 3 & 4).
- *Emotional Logical Memory Test*. For the assessment of "therapy-relevant" learning of emotional verbal material the Wechsler Memory Scale—Revised Logical Memory paragraphs) will be used. This test assesses memory for a brief emotional story passage; the study team has constructed a scoring method similar to that used by the WMS Logical Memory Test.

Covariates and Weekly Immediate Memory Assessment Tasks

- *Digit Span Test.* The Digit Span test 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.
- *Hopkins Verbal Learning Test (HVLT).* The HVLT is a test of verbal memory. Participants receive three consecutive trials of the presentation of a list of 12 nouns, each followed by a free-recall test. Each participant will receive a different list for each subsequent weekly session.
- *Item-Category Association Task.* This task identified differences between 250mg DCS and placebo in the study by Onur et al., For the task participants will make computer key press responses to judge the category membership (A or B) of three-digit numbers presented repeatedly on screen. Visual feedback is provided for correct and incorrect categorizations, allowing participants to improve across trials.
- *Controlled Oral Word Association Test (COWAT).* The COWAT is one of the most commonly used measures of verbal fluency. The task 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 will serve as a covariate.
- *Trail Making Test (TMT) (Trails A and B).* This task consists of Part A and Part B of the paper/pencil trail-making test of the Halstead–Reitan Neuropsychological Test Battery. It is a measure of psychomotor speed and mental flexibility. Trails B will be used as a covariate indexing executive functioning.

Adverse Events. The assessment of adverse events will occur at Weeks 2 and 3, and retrospectively at 4.
Mood and Fatigue. Depressed mood will be assessed with the BDI-II (Beck et al., 1996), other moods with the POMS (McNair et al., 1971), and fatigue with the Fatigue Survey Schedule (Krupp et al., 1989).
Quality Control Procedures for Missing Data. As formalized in Wisniewski et al. (2006), we will follow our own recommendations in 7 content areas--documentation, training, monitoring reports, participant contact, data entry & management, pilot data, and communication—for reducing missing trial data.
80 power to detect a medium effect size in all Aims.