An investigation of D-cycloserine as a memory enhancer

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1. Background and Significance

BDD is defined as a preoccupation with an imagined defect in appearance; if a slight physical anomaly is present, the concern is markedly excessive (American Psychiatric Association [APA], 1994). Preoccupations may focus on any body area but commonly involve the face or head, most often the skin, hair, or nose (Phillips et al., 1993). These preoccupations have an obsessional quality, in that they occur frequently and are usually difficult to resist or control (Phillips et al., 1998). Additionally, more than 90% of BDD patients perform repetitive, compulsive behaviors (Phillips et al., 1998), such as frequent mirror checking (Alliez & Robin, 1969), excessive grooming (Vallat et al., 1971), and skin picking (Phillips & Taub, 1995).

Accordingly, a core component of Cognitive-Behavioral treatment for BDD is exposure and response prevention (ERP). Exposure and response prevention involves asking patients to gradually expose themselves to situations that make them anxious (e.g. talking to a stranger, going to a party) while refraining from engaging in any rituals (e.g. excessive grooming or camouflaging) or safety behaviors (e.g. avoiding eye contact). Rituals and safety behaviors are thought to maintain the fear response because they prevent the sufferer from staying in contact with the stimulus long enough for his or her anxiety to extinguish. By exposing the patient to the feared situation while preventing the rituals and safety behaviors, the patient's anxiety is allowed to naturally extinguish and he is able to acquire a sense of safety in the presence of the feared stimulus.

We know from basic research that such fear extinction does not reflect unlearning of the original association but rather the formation of new associations that compete with the previously learned conditioned response (e.g., Rescorla, 2001), i.e., extinction is new learning. Fear extinction has been shown to be blocked by N-Methyl-D-Aspartate (NMDA) receptor *antagonists* (e.g., Cox & Westbrook, 1994; Lee & Kim, 1998). Thus, it has been proposed that NMDA receptor *agonists* could facilitate fear extinction (e.g., Walker, Ressler, Lu, & Davis, 2002). D-cycloserine (DCS) is an NMDA partial agonist and therefore has recently come under study for this purpose.

Initial work examining the effect of DCS focused primarily on learning and memory, in general. For example, DCS has been shown in pre-clinical studies to enhance performance on visual recognition tasks in primates (Matsuoka & Aigner, 1996), avoidance learning in rats and mice (e.g., Land & Riccio, 1999), eyeblink conditioning in rabbits (Thompson, Moskal, & Disterhoftt, 1992), and maze learning in rats and mice (e.g., Monahan et al., 1989; Pitkanen et al., 1995; Pussinen et al., 1997). In clinical studies, DCS has been found to improve cognitive abilities and disorder-related symptoms in populations including individuals with Alzheimer's Disease, schizophrenia, and posttraumatic stress disorder (PTSD; Heresco-Levy et al., 2002; Javitt et al., 1994; Schwartz et al., 1996; Goff et al., 1999; Tsai et al., 1999).

More recently, however, research on DCS has shown that it may specifically promote the extinction of conditioned fear. This is of particular clinical relevance because a reduced ability to extinguish fear associations is a significant problem in a variety of anxiety disorders, such as height phobias, panic disorder, PTSD, and OCD (e.g., Morgan et al., 1995; Fyer, 1998; Gorman et al., 2000). The treatment of anxiety disorders commonly involves the extinction of maladaptive fear associations (e.g., Zarate & Agras, 1994; Foa, 2000). Thus, it seems reasonable that pharmacological enhancement of fear extinction by DCS could be of great clinical relevance (Davis, 2002). Indeed, recent clinical studies suggest that DCS can facilitate extinction-based behavioral treatments. In the first study demonstrating this effect, Ressler and colleagues randomized patients with height phobia to received DCS (500mg/d or 50mg/d) or placebo prior to 2 sessions of exposure therapy (Ressler, Rothbaum, Tannenbaum, Anderson, Graap, Zimand, Hodges, & Davis, 2004). Those patients who received DCS prior to the therapy improved significantly more than the placebo comparison group. There were no differences between the group who received 50mg/d and the group who received 500mg/d, although there may have been a slight trend in favor of the latter (Ressler et al., 2004).

Since this initial trial, DCS has been found to augment behavior therapy in the treatment of Social Anxiety Disorder (Hofmann et al., 2006), Obsessive Compulsive Disorder (Wilhelm et al., 2008; Kushner et al., 2007) and Panic Disorder (Otto et al., submitted).

Side effects of DCS in human beings have been minimal. DCS has been widely used in the treatment of tuberculosis (500mg per day or higher), without causing neurotoxicity (e.g., Rivas Salazar, 1970). Goff et al. (1999) reported that only one patient dropped out of a schizophrenia study because of vague somatic discomfort. van Berckel et al. (1997) tested DCS in healthy participants and found that it was well tolerated and did not induce any side effects. In our recent trial examining the efficacy of DCS augmentation of behavior therapy for Obsessive Compulsive Disorder, no subjects reported any side effects as a result of the medication. DCS readily crosses the blood-brain barrier (Hanngren, Hansson, & Ullberg, 1961). Its half-life in serum is approximately 7 to 15 hours (Nair, Epstein, Baron, & Mulinos, 1956).

Altogether, when added to exposure therapy, DCS seems to be a promising treatment for patients suffering from anxiety. In the current study, we are planning to investigate DCS augmentation of exposure therapy for BDD. Consistent with our previous trial of DCS in OCD, we intend to administer 100mg of DCS one hour before each treatment session. The dose was chosen on the basis of a literature review and personal communication with Dr. Goff and Dr. Ressler (the lead-author of the above mentioned DCS height phobia trial). The timing of the dose relative to the therapy session was chosen on the basis of feedback from Dr. Ressler. As noted above, Ressler et al. (2004) found a significant reduction of height phobia severity

with 500mg/d of DCS, and they did not report any side effects at this dosage. In order to test whether DCS specifically works through augmenting fear extinction within ERP, DCS will only be administered one hour before each treatment session, and not on a daily basis. This will be in contrast to Goff et al. (1995), who administered DCS daily to improve negative symptoms in schizophrenia, but in accord with Ressler et al., (2004) who only gave DCS prior to each behavior treatment session for height phobia.

This trial also presents a unique opportunity to examine genetic and biological mediators of treatment response to extinction-based interventions. Accordingly, we have added an optional genetics component to this study for willing participants. Although genetic association studies have been plagued by concerns that reported associations may be spurious and difficult to replicate, a key strategy for minimizing the risk of Type I error is selecting candidate loci with the highest prior probability of association. Fortunately, compelling candidate loci with strong probability of involvement in NMDA-receptor mediated fear extinction are readily available due to the growing body of work on the molecular basis of this phenomenon. Specifically we will focus our analyses on genes that meet one or more of the following criteria: (a) encodes a subunit of NMDA receptors involved in fear conditioning/extinction, (b) involved in the action of DCS or d-serine co-activation of NMDA receptors, or (c) gene product shown to mediate fear extinction in preclinical models. Based on review of the literature, we selected loci that meet these criteria and have the strongest supportive evidence.

Studies of the molecular mechanism of fear memory acquisition on the one hand and extinction on the other have demonstrated that the receptors, ligands, and signaling cascades involved overlap but are not identical (Lin et al. 2003). We will therefore focus on genes involved specifically in extinction pathways. These include genes encoding NR1 and NR2 subunits that make up NMDA receptors subunits involved in fear extinction (Stoppel et al., 2006). In particular, ***GRIN1*** encodes the NR1 subunit that contains the glycine/serine binding site. NMDA receptor activation requires binding of glycine or serine as a co-activator and DCS binds to this site. The NMDA receptor NR2A subunit (encoded by ***GRIN2A***) and the NR2B subunit (***GRIN2B***) are also integral to NMDA receptors involved in fear extinction learning. It is now known that NR1-NR2A heterodimers constitute the functional unit of NMDA receptor ion channel opening (Furukawa et al., 2005). Transgenic overexpression of GRIN2B is associated with enhance fear extinction (Tang et al., 1999; Tang et al. 2001). The activity of d-serine at NMDA receptors is attentuated by its degradation by d-amino acid oxidase (encoded by ***DAAO***) (Mothet, 2000). Recently, genetic studies of schizophrenia led to the discovery of an activator of DAAO, now known as d-amino acid oxidase activator (***DAOA,*** formerly G72

In addition to these genes involved in NMDA receptor and d-serine activity, several additional proteins and genes have been strongly implicated in fear extinction. These include brain derived neurotrophic factor (***BDNF***). Chhatwal et al. (2006) and Rattiner et al. (2004) have demonstrated that amygdala BDNF signaling via the TrkB receptor (encoded by ***NTRK2***) is essential for consolidation of extinction memories. BDNF and TrkB signaling activate the intracellular MAPK and PI-3 kinase pathways that have been shown to be central to the facilitation of fear extinction by DCS (Yang et al., 2005; Ou et al., 2006). Of note, serum BDNF levels have been reported to differentiate good vs. poor responders to CBT for anxiety (specifically, panic disorder; Kobayashi et al., 2005), and variation at the *BDNF* Val66Met polymorphism has been associated with impaired memory function in humans (Egan et al., 2003; Hariri et al., 2003). The endogenous cannabinoid system also appears to play an important role in fear extinction (Wotjak, 2005). Cannabinoid receptor 1 (CB1) knockout mice show profound deficits in short-term and long-term extinction (though not acquisition) of conditioned fear (Kamprath et al., 2006; Marsicano et al., 2002), and these effects appear to be mediated by alterating signaling cascades and GABA-ergic neurotransmission (Kamprath et al., 2006; Marsicano et al., 2002). Injection of CB1 receptor antagonists mimics the impaired extinction phenotype of null-mutant mice (Marsicano et al., 2002); interestingly, this effect appears to be specific to fear extinction rather than extinction of an appetitive operant task (Holter et al., 2005). CB1 is expressed in the amygdala, a central structure for fear learning and extinction (Barad et al., 2006). The gene encoding human cannabinoid receptor 1 (***CNR1***) has been previously associated with substance dependence and schizophrenia in several studies (Ballon et al., 2006; Herman et al., 2006; Hofer et al., 2006; Martinez-Gras et al., 2006; Zhang et al., 2004).

In addition to those reviewed above, a larger number of proteins have been implicated in fear conditioning and extinction, including components of the MAPK and PI-3 kinase intracellular signaling cascades (Lin et al., 2003), the dopamine D1 receptor (Pickel et al., 2006), calcineurin (Lin et al., 2003), gephyrin (Chhatwal et al., 2005), AMPA glutamatergic receptors (Barad, 2005), and GABA(A) receptors (Davis & Myers, 2002). However, for this initial study of genetic influences on extinction learning and DCS augmentation, we believe it is prudent to limit multiple testing and Type I error by pursuing a focused analyses of a core set of extinction-related genes. Thus, we will examine key NMDA receptor-related genes (*GRIN1, GRIN2A, GRIN2B, DAAO, DAOA*) and extinction-related neuropeptides (*BDNF, NTRK2, CNR1*). Future studies in larger samples may permit analysis of a wider net of potentially relevant genes.

2. Specific Aims

Primary Aim:

The purpose of the proposed study is to conduct a double-blind, placebo-controlled trial of DCS augmentation of ERP in patients with BDD. Specifically, we intend to treat 50 BDD patients who will receive either DCS (100mg, n=25) or placebo (n=25) one hour before 8 of 10 behavior therapy sessions. We anticipate that some participants who sign consent for the study will be deemed ineligible after the initial screening visit. Consequently, our enrollment goal is 80 in order to reach our goal of 50 individuals who begin treatment.

We hypothesize that patients receiving DCS will show significantly more improvement in BDD symptoms, compared to patients receiving placebo. We intend to conduct the proposed study to collect sufficient pilot data to apply for an externally funded larger-scale research project.

Secondary Aim:

This treatment study also provides us with the opportunity to further explore the molecular genetics of BDD, as well as the genetic predictors of response to an extinction-based treatment. We will take a hypothesis-driven approach by focusing on genes and systems previously shown to mediate fear acquisition and NMDA-dependent extinction learning including NMDA-related glutamatergic loci (*GRIN1, GRIN2A, GRIN2B, DAAO, DAOA*) and three other genes strongly implicated in fear extinction (*BDNF, NTRK2, CNR1*). Other loci of interest in the molecular genetics of BDD include: the serotonin transporter gene, dopamine, GABA-A, and cytochrome P450 genes

We hypothesize that genes implicated in fear extinction will provide general prediction of the success of exposure treatment, and that the degree of additional benefit associated with DCS will be influenced by NMDA-related glutamatergic loci.

3. Subject Selection

Inclusion criteria are a diagnosis of BDD by DSM-IV standards and a BDD Yale-Brown Obsessive Compulsive Scale score greater than or equal to 24 in people 18 years of age or older. Subjects must be able to give informed consent, and females of childbearing potential must have a negative urinary beta-HCG test. Pregnant or breastfeeding women, people taking medications that may interfere with DCS, and people with a history of seizure disorder or other serious medical illnesses such as cardiovascular, hepatic, renal, respiratory, endocrine, neurological or hematological disease are excluded from this study. Other criteria for exclusion are comorbid

psychiatric diagnoses (alcohol dependence, bipolar disorder, psychosis, borderline personality disorder, organic mental disorder, or developmental disorder). Also excluded are patients taking medications that may lower the seizure threshold, including clozapine, pethidine, and the following antibiotics in high dosages: penicillins, cephalosporins, amphotericin, and imipenem. Those deemed to pose a serious suicidal or homicidal threat will be excluded. If patients have any other comorbid disorder, the BDD symptoms must be the primary concern. Furthermore, current psychotherapy and failure to benefit from ten or more sessions of previous CBT treatment are a rule-out. Moreover, if a patient is taking a psychotropic medication, he or she must be at a stable dose prior to enrolling in the study.

Participants will be withdrawn from the study if their clinical condition deteriorates substantially, as defined by a rating of 6 (much worse) or 7 (very much worse) on the Clinical Global Impressions-Improvement (CGI-I) scale. Participants may also be withdrawn if, in the judgment of the PI or therapist, remaining in the study poses a substantial risk to the participant, or if a higher level of care is needed.

There will be no exclusion based upon gender or minority status. Based upon the composition of the patient population at the BDD Clinic at MGH, we anticipate that at least 50% of the participants will be women. The percentage of minority participants is expected to be at least 5%. We will make vigorous attempts to increase this number by posting advertisement flyers in minority communities.

Subjects will initially be recruited through the General Recruitment Protocol (protocol # 2009P-002227), which includes general BDD advertisements. Every effort will be made to recruit subjects for whom English is a 2nd language. While some of our questionnaires have been translated and validated in a few languages, several have not. Therefore, for scientific validity purposes, we have to restrict our participants to those individuals with English as a 2nd language that have sufficient fluency to understand the questionnaires as well as our therapist during behavior therapy treatment.

Potential participants may be informed about the study by clinicians in the BDD Clinic at Massachusetts General Hospital (MGH) and by fliers posted at MGH, coffee shops, restaurants, Laundromats, barber shops, churches, daycares, libraries, newspapers, and on the internet.

Individuals who are interested in treatment or in learning more about the ongoing research in the BDD clinic usually call the BDD clinic's main number. As part of the usual intake process, the intake coordinator discusses with patients the reason for their call and their current symptoms. She also asks a number of screening questions to form a preliminary impression regarding whether the caller suffers from BDD, OCD, an OCD spectrum disorder such as trichotillomania, depression, or substance abuse. She notes

the patients' name, age, sex, address and phone number. The intake coordinator then informs all callers about evaluation and treatment options and asks whether he/she would potentially be interested in learning more about or participating in ongoing research projects. If so, the intake coordinator presents pertinent patient information in the BDD clinic's weekly staff meeting where the clinical staff (including the PI) determines which research project(s) are appropriate for interested potential participants. The intake coordinator is very experienced with screening potential patients and has been working at the BDD Clinic since 1999. Once interested participants are referred to this study, a research assistant will contact them and provide more detailed information about the study.

We never identify potential participants through medical records, and we never contact potential participants without their permission to be contacted. If a medical colleague identifies one of his or her patients as potentially appropriate for this study, we request that the colleague encourage the patient to contact a member of the study staff directly. Alternatively, the colleague may ask the patient to give permission to be contacted over the phone by a member of the study staff.

4. Subject Enrollment

Individuals who express an interest in participating will be screened by a research assistant over the phone. We only ask for the patient's name and contact information at the end of the phone screen if the patient is eligible and interested in participating (see attached phone screen). Before coming for their first visit, patients will be given information about the study via phone and allowed as much time for consideration and questioning as they need before the initial appointment is made. At that time, patients will be further informed about the study's purpose and procedures and advised regarding alternative treatment options in our clinic or elsewhere. Because the primary intervention in this study is a psychological treatment, consent will be obtained by the study therapist. However, the study physician will be available to answer any questions about the medication should they arise. Additionally, all eligible subjects will meet with the study physician at the first visit for the medical evaluation.

Eligible participants will be randomized to receive either the D-cycloserine (100 mg) or placebo. The MGH research pharmacy will create and maintain the coded randomization schedule for this double-blind design and prepare and dispense the study medication (DCS or placebo) to study staff. None of the investigators will be privy to the code, except for the study physician in case of an emergency.

5. Study Procedures

Overview

At the initial visit, we will first obtain informed consent from the participant. We will also have participants sign their initials and date if they consent to sharing their de-identified data with other researchers in our group or across studies for research purposes only. This procedure will save subjects time if they participate in more than one study at our clinic because it will eliminate repeating assessments shared between studies. The participant will then undergo a structured clinical interview and fill out several questionnaires assessing BDD symptoms, anxiety, and depression. If the participant is eligible for participation based on this evaluation, the study physician will then meet with him or her to conduct the medical evaluation (more detail below). If the participant remains eligible for the study after the medical evaluation then he or she will be randomized to receive either the D-cycloserine or placebo. The MGH research pharmacy will create and maintain the coded randomization schedule for this double-blind design and prepare and dispense the study medication (DCS or placebo) to study staff. None of the investigators will be privy to the code, except for the study physician in case of an emergency. Participants who choose to participate in the optional genetics component of the study will also have their blood drawn at this visit. In all, the initial visit will last approximately 3-4 hours. After randomization, the participant will come to the clinic for a psychoeducation/treatment planning session approximately one week later (see below for more detail). If we are unable to schedule the treatment planning session within 21 days of the screening visit, participants will be asked to complete a modified screening session directly prior to the treatment planning session. This visit will take approximately 30 minutes. This visit will last approximately 1.5 to 2 hours. The participant will not take the study medication/placebo prior to this visit. After this treatment planning session the participant will be scheduled for 10 once weekly behavior therapy sessions over a 10 week period. The first two therapy sessions will involve primarily cognitive interventions and so the study medication will not be administered prior to these sessions. The participant will be asked to come to the clinic one hour before sessions 3-10 to take the study medication/placebo in the presence of the therapist. Study medication will be kept at the clinic for the duration of the study. In addition to the therapy visits, comprehensive assessments of BDD symptoms, mood state and cognitions to assess the outcome of therapy will be given at midtreatment (after session #5), post treatment and at 1- and 6- month follow-ups. These assessments will take approximately 1 hour. BDD symptoms, CGI-I score, and depressive symptoms will be assessed via self-report questionnaires at every treatment session. These questionnaires

will take approximately 5 minutes to complete. A detailed assessment schedule is submitted for review.

Psychological Assessments

Comprehensive assessments of BDD symptoms, mood state and cognitions to assess the outcome of therapy will be given at pretreatment, midtreatment, post treatment and at 1- and 6- month follow-up. BDD symptoms, CGI-I score, and depressive symptoms will be assessed every treatment session.

The following instruments will be used and are submitted for review:
(1) Demographic information sheet. This sheet assesses general information such as age, years of education, etc.
(2) Structured Clinical Interview for DSM-IV (SCID; First, Spitzer, Gibbon et al., 1995). This instrument will be used to determine the Axis I psychiatric diagnosis(es).
(3) Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II; First et al., 1997). Patients will complete the SCID-II self-report questionnaire; for any personality disorder for which the patient's report approaches criterion (number of criteria required minus 1), the rater will administer all interview questions for that personality disorder.
(4) Yale Brown Obsessive Compulsive Scale modified for BDD (BDD-YBOCS). This reliable and valid 12-item semi-structured clinician-administered scale, which was adapted from the Y-BOCS (Goodman et al., 1989), rates current severity of BDD symptoms (Phillips et al., 1997). It will be the study's primary outcome measure. The BDD-YBOCS has excellent interrater and test-retest reliability (ICC for total score=.99 and .88, respectively), internal consistency (Cronbach's alpha=.80), convergent validity (r=.55 with the CGI), and sensitivity to change with treatment (Phillips et al., 1997).
(5) BDD-Symptom Scale (BDD-SS) The PI developed the BDD-SS to rate the severity of specific BDD symptoms.

(6) Clinical Global Impression Scale (CGI) This global rating scale, which ranges from 1 (very much improved) to 7 (very much worse) on levels of improvement (CGI-I) and from 1 (normal, not at all ill) to 7 (extremely ill) on severity (CGI-S), is commonly used in pharmacotherapy trials (Guy, 1976). The CGI will be a secondary outcome measure and will also be used to determine clinical deterioration of BDD.

(7) Brown Assessment of Beliefs Scale (BABS) This reliable and valid 7-item semi-structured clinician-administered interview, assesses current delusional thinking categorically and dimensionally (Eisen et al., 1998). Excellent interrater and test-retest reliability (ICC for total score=.96 and .95), internal consistency (Cronbach's alpha=.87), convergent validity (r's=.56-.85 with measures of delusionality), and divergent validity (r=.20 with the

BDD-YBOCS [158]) have been demonstrated (Eisen et al., 1998). The cutpoint for the presence of delusional thinking in BDD had a sensitivity of 100% and a specificity of 86%, and it correctly identified 90% of 20 participants as delusional or nondelusional (Eisen et al., 1998). It is also sensitive to change (Phillips et al., 1998).

(8) Multidimensional Body-Self Relations Questionnaire (MBSRQ) While the BDD measures include some assessment of body image, we will also use a standard body image scale that is not specific to BDD and which assesses body image more broadly. The MBSRQ is a widely used 69-item self-report scale that assesses 3 domains of attitudes towards one's body, including appearance (Cash, 1994). Test-retest reliability (r=.91) and internal consistency (α=.88) are good; concurrent validity (r=.66) is acceptable.

(9) Beck Depression Inventory II (BDI II; Beck, Steer & Brown, 1996). The BDI II is a 21-item self-report inventory that measures the severity of depression.

(10) Young Schema Questionnaire (YSQ) This 75-item self-report scale (Young & Brown, 1990) assesses the following areas of maladaptive schemas: emotional deprivation, abandonment, mistrust/abuse, social isolation, defectiveness/shame, failure to achieve, functional dependence/incompetence, vulnerability to harm and illness, enmeshment, subjugation, self-sacrifice, emotional inhibition, unrelenting standards, entitlement, and insufficient self-control/self-discipline. It has high internal consistency and discriminant validity (Waller et al., 2001). This scale will assess core beliefs and schemas as potential mechanisms underlying change, as several of these (e.g., defectiveness/shame) appear particularly relevant to BDD.

(11) Multidimensional Perfectionism Scale (MPS) The MPS is a self-report 45-item scale that assesses perfectionism from several perspectives: self-oriented (e.g., "When I am working on something, I cannot relax until it is perfect"), other-oriented (e.g., "I have high expectations for the people who are important to me"), and socially prescribed (e.g., "I feel people are too demanding of me") (Hewitt et al., 1991). It has good internal consistency (α=.74 to .88) and convergent validity (r's=.62-.69 with other measures of perfectionism) (Hewitt et al., 1991).

(12) Disability Inventory This 4-item self-report scale assesses work, social, and family disability on 10-point scales and overall disability on a 5-point scale (Leon et al., 1992). It has been used in pharmacologic studies and had acceptable reliability (internal consistency, factor structure) and satisfactory construct and criterion-related validity in a study of patients with panic disorder.

(13) LIFE-RIFT To assess psychosocial functioning in multiple domains, these 5- to 7-point rater-completed scales provide information about work, employment, household duties, student work, interpersonal relations with family and friends, recreation, overall life satisfaction, and global social

adjustment (Leon et al., 1999). The concurrent validity is moderate (R^2 = 0.56) and the internal consistency is good (α=.82).
(14) Expectancy Questionnaire This 4-item self-report questionnaire assesses patients' judgments about the credibility of the treatment rationale, expectancy of change, and treatment acceptability (Borkovec & Nau, 1972). It has good reliability (α=.81-.86), and validity is evident in its ability to differentiate between treatment rationales (Devilly & Borkovec, 2000). It will be given after the second visit when patients are familiar with the treatment protocol.
(15) The Client Satisfaction Questionnaire (CSQ) is a 8 item self-report questionnaire which assesses the satisfaction with clinical services received on a Likert scale. It has excellent internal consistency (α = .93; Larsen, Attkission, Hargeaves, & Nguyen, 1979).
(16) University of Rhode Island Change Assessment Questionnaire (URICA) This 32-item self-report questionnaire measures motivation to change (Greenstein et al., 1999). Its 4 scales (precontemplation, contemplation, action, and maintenance) have adequate internal consistency (α=.77-.89; Carey et al., 1999).
(17) Appearance Schemas Inventory-Revised (ASI-R) This 20-item measure consists of two subscales assessing one's cognitive-behavioral investment in one's own appearance—Self-Evaluative Salience (12 items) and Motivational Salience (8 items). Self-Evaluative Salience reflects the extent to which individuals define or measure themselves and their self-worth by their physical appearance. Motivational Salience pertains to the extent to which persons attend to their appearance and engage in appearance-management behaviors.
(18) The Brief Assessment of Appearance-related Beliefs (BAAB) This 2-item self-report measures the level of insight about the BDD symptoms the subject has. This measure was specially developed in our clinic in order to assess insight related specifically to BDD beliefs.
(19) Body Part Satisfaction Questionnaire (BPSQ) This 10-item self-report measure assesses the subject's satisfaction with various body parts (Wilhelm, 2006. *Feeling Good about the Way You Look*).
(10) The Brief Assessment of Motivation (BAM) This 3-item self-report measure assesses the motivation of the subject. This measure was specially developed in our clinic to assess the motivation of patients with BDD.
(21) Cognitive and Behavioral Change Measures (CBCM) These measures assess how much cognitive and behavioral change may have occurred within the session and between sessions.
(22) Parental Bonding Inventory (PBI) The PBI is a 25-item self-report that measures parental bonding styles and is completed for both mothers and fathers. The PBI consists of 12 items that measure parental "caring" and 13 questions that measure parental "overprotection."

(23) Multidimensional Perfectionism Scale-35 (MPS-35) This 35 item self-report measures perfectionistic tendencies on six subscores: personal standards, concern over mistakes, parental expectations, parental criticism, doubting of activities, and order and organization. Participants rate their agreement with 25 statements using Likert scales ranging from 1 (strongly disagree) to 4 strongly agree**.**
(24) Short Grit Scale (Grit-S) This 8 item self-report measures trait-level perseverance and passion for long-term goals. Participants rate their agreement with 8 statements using a Likert scale ranging from "very much like me" to "not like me at all."
(25) Difficulties in Emotion Regulation Scale (DERS) This 36-item multidimensional self-report measures individuals' characteristic patterns of emotion regulation.

Data Collection and Storage

Self-report measures will be collected using RedCap™, a platform for electronic data capture that streamlines data collection and management, and ensures data integrity, resulting in improved data quality. RedCap allows researchers to design and implement study surveys for collecting, storing, retrieving, and manipulating data electronically. Participants and/or research staff enter survey responses into electronic assessment forms. This electronic data capture obviates the need for subsequent data entry by staff, thus minimizing human error.

These surveys are completed securely via the internet by using any device with standard web access and browsers. For this study, participants and staff will complete the electronic assessments on computer terminals at the research site under the supervision of study staff. All users will have defined roles and privileges pre-determined by the system administrator. Thus, the PI can determine the level of access for each study staff such that only a limited number of people have access to sensitive study data.

Medical Assessment

At the initial study visit, one of the study physicians will evaluate the participant with regard to the medical and psychiatric exclusion criteria to be sure that none are met. Participants will be monitored in an ongoing manner for side effects or any adverse reactions to the study medication, and further evaluations will occur at any other times as necessary. Participants may contact the study physicians at any time to discuss their medication, side effects, or adverse reactions.

Also at this time a urine pregnancy test will be performed for women of child-bearing potential. If the test is positive, the participant will be

excluded. Additionally, women of child-bearing potential must agree to use a reliable form of contraception for the duration of the study. Males and Females will be asked to provide a urine specimen in order to drug screen for use of the following drugs: opiates, phencyclidine, barbiturates, benzodiazepines, cocaine, amphetamine, methamphetamine, and marijuana. The test will be done in the medical evaluation room and labeled with participant code number. If participant screens positive for drugs of abuse, the study doctor will discuss sharing of this information and ask if the participant would like a referral for substance abuse treatment. Results of drug screen will be confidential, will not be shared without explicit consent and will not become part of the medical record. *Testing positive for drugs of abuse, for which the participant does not have a valid prescription will make them ineligible to participate in this research study.*

Modified Screen

This appointment will only be for participants who can not schedule the treatment planning session within 21 days of the initial study visit. It would be completed directly prior to the treatment planning session. It would consist of assessment measures completed at the screening visit to ensure the information is accurate and up to date.

Treatment Planning Session

The second appointment will take 1.5-2 hours and will include psychoeducation about the theory of BDD and how it relates to the patient's specific symptoms. A detailed hierarchy of exposure exercises will be developed that is specific to the areas that are most relevant for each patient.

Behavior Therapy

Dr. Ragan, Hannah Reese, Kiara Timpano and Jedidiah Siev will administer the ERP treatment to the BDD patients. Dr. Ragan is a licensed clinical psychologist and has been working at MGH since 2004. She will meet weekly with Dr. Wilhelm for clinical research supervision. Hannah Reese has her masters degree in Clinical Psychology and is currently a doctoral student in Clinical Psychology at Harvard University. Kiara Timpano and Jedidiah Siev are clinical psychology interns in the final year of their doctoral programs. They will meet weekly with either Dr. Ragan or Dr. Wilhelm for clinical research supervision. Fifty patients will be treated with ERP. Treatment will follow the exposure principles outlined in "Feeling Good About the Way You Look," a self-help book for individuals with BDD written by the PI (Wilhelm, 2007). The treatment will consist of ten weekly sessions. Thus, the entire ERP treatment will take ten weeks. The first two sessions will include primarily cognitive interventions in order to lay the groundwork for effective exposure exercises in the remaining 8 sessions.

During the exposure sessions, the patient will be confronted with moderately anxiety-provoking situations or stimuli and will be asked not to engage in any rituals until the anxiety comes down. In this manner, the patient will learn that he or she does not have to perform the ritual to lower the anxiety. The last treatment session (#10) will also include relapse prevention. That is, the study therapist will provide the patient with information about how to schedule "self-therapy sessions" in which the patient will (1) review what he or she has learned during the course of therapy and (2) engage in exposure and response prevention. Furthermore, the study therapist will also discuss with the patient that the BDD symptoms may worsen during times of stress but that overall the BDD symptoms may be expected to improve if the patient keeps doing the exposure techniques learned during the course of the treatment.

Optional Genetics Component

Participants who agree to participate in the optional genetics component of the protocol will have their blood drawn at the first visit by a member of the study staff who has received formal training in phlebotomy.

DNA Collection and Extraction. DNA will be extracted from blood samples collected by a member of the study staff who is also a certified phlebotomist, labeled by coded identifiers, and sent to Dr. Smoller's laboratory at MGH for genotyping. If a patient is interested in providing a genetics sample but is unwilling to have their blood drawn, they will have the option to provide a saliva sample. Laboratory personnel will not have access to personal identifiers. Dr. Smoller's laboratory has extensive experience with the collection, extraction and genotyping of DNA. The process of DNA collection through blood and saliva samples is highly acceptable to participants and, in our hands, each sample provides approximately 60 ug of genomic DNA. Given that each genotyping assay requires only 2.5 – 5 ng of DNA, this yield will be more than adequate. After DNA extraction, sample yield is determined by picogreen analysis.

Genotyping Methods: Genotyping will be performed in Dr. Smoller's lab at the MGH Center for Human Genetic Research. Single nucleotide polymorphism (SNP) genotyping will be performed using the Sequenom MassArray system (Tang et al., 1999; Smoller et al., 2003). Genotyping will be performed in multiplex reactions in 384-well plates. For each assay, four duplicate samples and 4 blank samples will be included. SNPs will be used for association analyses only if they meet the following quality control criteria: 1) >90% of attempted genotypes for any SNP are successful, 2) alleles are in Hardy Weinberg equilibrium, and 3) agreement between all

duplicates and no more than 1 of 4 blanks with genotypes. Genotyping of the functional promoter variant in the *GRIN2A* gene (Itokawa et al., 2003) will be performed using the Applied Biosystems 3730 DNA Analyzer and standard protocols. GeneMapper v3.5 is used to analyze the raw results from the ABI3730, however, a genotype is not considered final until two laboratory personnel have independently checked (and corrected) the GeneMapper results and both individuals are in agreement.

Given the small number of genetic samples, we will add BDD DNA samples collected by the PI for a separate BDD treatment study of Lexapro discontinuation as well as BDD DNA samples collected by project collaborator Dr. Katharine Phillips at Brown University as part of a longitudinal BDD study. Both studies obtained consent for participants to collect DNA, to store this DNA at MGH, and to conduct genetic association studies for BDD. Only subjects who specifically consented for the genetic portion of the study had blood drawn and DNA extracted; therefore, only subjects who consented for the optional genetic study will be used for the current genotyping study. All DNA tubes/samples are fully de-identified. For the samples collected at Brown, no MGH investigators have any access to subject identifiers.

In order to conduct a BDD case-control genetic association study, we have obtained ancestry and gender-matched control DNAs from the Genome Superstruct Project (GSP), (Massachusetts General Hospital, Boston; PI: J. Smoller, R. Buckner, J. Roffman). All of these control samples were consented for genotyping in targeted and whole-genome association studies as well as for data sharing. No control subjects who did not consent to future sharing will be used in this study. Of note, we need to conduct direct genotyping of the BDD candidate genes to control for likely experimental confounds if the BDD case DNAs were genotyped and compared to control data generated on a different platform at a different site. The DNAs all exist in the MGH PNGU Core Lab, and are fully de-identified; thus, BDD study investigators have no way of knowing to whom the samples belong.

<u>Privacy and Confidentiality</u>

All information gathered will be kept strictly confidential. Participants will be assigned a code number, and the participants' names will not appear on any questionnaires or therapy protocols. Moreover, the data will be stored in locked file cabinets located in locked offices. Only the study personnel will have access to the data.

Participants may also choose to provide consent for the use of their samples in related research. We have included in the consent form a description of what information will be shared with any outside investigators.

6. Biostatistical Analysis

Please note: The blind may be broken after every ten subjects to conduct preliminary analyses to assess for the efficacy of D-cycloserine.

Primary analyses: Our primary hypothesis is that ERP in combination with DCS is more effective than ERP in combination with a placebo. To measure this, the BDD-YBOCS will be the primary outcome measure. The main analyses will compare the two patient groups at mid-treatment and post-treatment using analysis of variance (ANOVA) and analysis of covariance (ANCOVA, controlling for BDD-YBOCS-pretreatment scores). To further determine the clinical significance of these findings, we will use the Jacobson and Truax (1991) formula to calculate the percentage of patients who fulfill the criteria for reliable and clinically significant change in each treatment condition at mid-treatment and post-treatment. Fisher's exact test for differences in frequencies of responders between the two patient groups will be performed. We will further compare the two groups at the 1- and 6-month follow-up assessments.

Power analysis: A power analysis with a sample size of 25 per group and $p < .05$ reveals that this study will convey 80% power to detect a group difference in post-treatment BDD-YBOCS scores of $d = 0.78$, which is a large effect size. Moreover, we will estimate between-group effect sizes of this pilot study to be used in designing future studies.

Secondary analyses: We hypothesize that patients who receive DCS augmentation will have greater improvement on the CGI-I, BDI, BDD-SS, and Disability Inventory at mid-treatment, post-treatment and 1- and 6-month follow-up assessments than patients who receive the placebo. ANCOVAs (controlling for pretreatment scores) and multivariate ANCOVAs (MANCOVAs) will be used for these analyses as described above, and effect sizes will be computed. Furthermore, the Cognitive and Behavioral Change Measures will be used to identify in more detail within which session, or between which sessions, any changes occurred.

Predictors of outcome: We also wish to evaluate whether ERP in combination with DCS is particularly effective or ineffective for different symptoms (as measured by the BDD Symptom Scale), attitudes (i.e., patient's judgments about the credibility of the treatment, as measured by the Expectancy Rating), or comorbid problems (e.g., depression). These factors will be included in regression analyses. We also intend to explore the relationship between minority status and treatment outcome; however, power will be limited given the small sample size.

Mechanisms of improvement: We are also interested in potential mechanisms of change during treatment. These can be tested with multiple regression procedures via hierarchical regression models. Treatment group (DCS vs. placebo) will be the independent variable, changes in BDD symptom severity (BDD-YBOCS) the dependent variable, and, for example,

changes in beliefs as measured by the Schema Questionnaire will be the mediator. We will follow the procedures for establishing statistical mediation outlined by Baron and Kenney (1986), using residual gain scores as the measure of change in both the dependent variable and the mediator (Cohen, 1983). These residual scores will give a reliable estimate of changes in symptom severity and beliefs independent of differences in baseline severity. We will interpret our results with caution because the absence of statistical significance may reflect the somewhat limited power with only 50 patients.

Genetic Analyses: We will use quantitative trait association analytic methods to examine whether alleles and/or haplotypes of the loci selected for analyses are associated with outcome of ERP with or without DCS. Analyses will be conducted in two stages. The initial analyses will examine whether any of the genetic variants are associated with ERP outcome indexed by change in BDD-YBOCS score from baseline (at end of treatment and at 1-month and 6 month follow-up). The analyses will include a main effect analysis of each genetic variant as well as a gene x treatment interaction analysis, to examine whether allelic effects on outcome differ by treatment condition (DCS vs. placebo). If evidence of interaction is detected, we will also examine allelic effects within treatment group. For example, we expect that genes involved in NMDA receptor function (e.g. the *GRIN1* gene whose product includes the glycine (DCS) binding domain) may mediate response to DCS.

In the second stage, genetic predictors demonstrating univariate association will be entered into a multivariable linear regression model along with other predictors of treatment response in an effort to build a model that parsimoniously explains the greatest proportion of variance in response to ERP (with and without DCS). For genes in which more than one polymorphism shows evidence of association, we will select the SNP with the minimum p value to enter into the multivariable model.

Univariate single marker and haplotype-based analyses will be conducted using WHAP (Curran et al., 2005; http://www.broad.mit.edu/~shaun/whap/). Using an approach similar to those of Schaid et al. (2002) and Zaykin et al. (2002), WHAP is based on a two-stage method. The primary test is a regression-based analysis of association between marker (or haplotype) and trait, with one regression coefficient per marker (or haplotype). The independent secondary test analyses the relationship between marker (or haplotype) similarity and regression coefficient similarity. Evidence from the primary and secondary stages can be combined to provide a more powerful test of association, by combining log-transformed P values. The method is based on a mixture of regression models which accounts for the potential ambiguity in individuals' statistically-inferred haplotypes. For *H* haplotypes, a single omnibus test is performed to test jointly for any difference in haplotype effect, which is an *H*

– *1* single-degree-of-freedom test. The independent secondary test assesses whether pairs of more similar haplotypes show more similar effects. A multivariate weighted least squares regression of haplotype effect similarity on haplotype genetic similarity is used and empirical significance levels are determined by permutation testing. We will define haplotype blocks using the conservative definition of Gabriel et al. (2002) as implemented in Haploview (Barrett et al., 2004).

Evaluation of Population Structure. It has been well recognized that ethnic admixture or population stratification may confound case-control genetic association studies, although the importance of this phenomenon has been debated (Freedman et al., 2004; Wacholder et al., 2002). Nevertheless, we will evaluate the possibility of confounding due to population stratification, by typing a panel of 100 informative unlinked (null) SNPs. The main approach used will be that described by Purcell and Sham (2004), which implements a method very similar to that of Pritchard et al. (2001) and Satten et al. (2001). All these approaches look for Hardy-Weinberg disequilibrium and LD between unlinked markers, and probabilistically break down the sample to a number of subgroups, within which Hardy-Weinberg equilibrium and linkage equilibrium hold (as one would expect in a homogeneous population). We will evaluate population structure by performing analyses using the L-POP program (Purcell et al., 2004). Because the sample is expected to be primarily Caucasian, if more than one subgroup is detected, we expect that only one subgroup will have sufficient power for analysis. Thus our analyses would focus on the largest subgroup.

7. Risks and Discomforts

Patients may feel uncomfortable due to the sensitive nature of the questions they may be asked.

Side effects. The potential side effects associated with the administration of DCS include drowsiness, headache, prolonged or momentary dizziness, seizures, confusion, hallucinations, weakness, coma, rash, vitamin B_{12} deficiency and/or folate deficiency (both of which may cause weakness and anemia (low blood counts)), liver enzymes increases (which could cause weakness or bleeding), and shaking. However, these side effects are most commonly related with doses greater than 500mg/day, which is five times what is administered in this study. The use of DCS at doses of 100 mg (as in this study) does not appear to be associated with significant emergent adverse effects. Indeed, in our recent trial examining the efficacy of DCS augmentation of behavior therapy for individuals with OCD no subjects reported any side effects as a result of the study medication.

Interactions.

(1) Intake of alcohol at the same day may increase the possibility and risk of epileptic episodes. Thus, we will exclude patients with current alcohol dependence. Furthermore, we will instruct the patients not to consume any alcohol 12 hours prior to and 24 hours after receiving the study medication. To ensure that patients have not consumed alcohol prior to taking the study medication we will administer a saliva test to measure BAC levels immediately before dispensing the medication.

(2) Intake of Isoniazid at the same day may result in increased CNS side effects. Thus, we will exclude patients who currently take Isoniazid.

Optional Genetics Component

There is a risk associated with the sensitivity of the genetic information. The results of genetic analyses will be kept confidential and will not be returned to participants in this study. Consequently, the potential risks of subjects learning sensitive genetic information or of discrimination related to participation in a genetic study should be avoided. There is a theoretical risk of discrimination by employers or insurers should subjects' enrollment into or the results of the study unintentionally become known despite procedures in place to maintain confidentiality. The following steps will be taken to protect the confidentiality and privacy of the genetic data:

a. No genetic research data will be entered into the medical record.
b. The results of the genetic analyses will not be shared with participants or their family members.
c. Only coded identifiers, rather than personal identifiers, will be used in any analytic datasets. The genetic laboratory will not have access to personal identifiers.

To protect confidentiality, information about subjects will be stored in research files identified only by code. The code key connecting IDs to identifying information will be kept in a separate secure location at the research site at which a participant is enrolled. Data in databases is similarly identified only by coded ID number and is password-protected.

Minimizing of Risks and Safety Reporting. Subjects will be monitored in an ongoing manner for side effects or any adverse reactions to the study medication. The study physicians, Drs. Dougherty and Jenike, will review all reports of adverse events and forward them to the IRB. Patients may also contact them at any time to discuss their medication, side effects, or adverse reactions.

Adverse event reporting: In case of an adverse event and in accordance with Partners Human Research Committee Adverse Event Reporting Guidelines, we will complete the appropriate adverse event form and forward it to the IRB within the required time frame for reporting.

8. Potential Benefits

Patients may benefit by experiencing some relief from their BDD symptoms. Our research will help us better understand what treatments are beneficial in this disorder.

9. Monitoring and Quality Assurance

Dr. Ragan and Hannah Reese will be responsible for ensuring that all study procedures are conducted according to the IRB-approved protocol and reviewing the accuracy and completeness of source documents. Dr. Ragan and Hannah Reese will meet with Dr. Wilhelm regularly to discuss the study procedures and progress. Drs. Wilhelm and Ragan will be responsible for ensuring that the study treatment is delivered appropriately.

Subjects will be monitored in an ongoing manner for side effects or any adverse reactions to the study medication. The study physicians will review all reports of adverse events and forward them to the IRB according to Partners guidelines. Participants may also contact the study physicians at any time to discuss their medication, side effects, or adverse reactions. The PI, in collaboration with the study physicians will ultimately be responsible for determining whether the research should be altered or stopped.

Participants will be withdrawn from the study if their clinical condition deteriorates substantially. Deterioration will be defined by a rating of 6 (much worse) or 7 (very much worse) on the CGI-I. Participants may also be withdrawn if in the judgment of the PI or therapist remaining in the study poses a substantial risk to the participant or a higher level of care is needed.

In case of an adverse event and in accordance with Partners Human Research Committee Adverse Event Reporting Guidelines, we will complete the appropriate adverse event form and forward it to the IRB within the required time frame for reporting.

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