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Title: D-cycloserine Enhanced Imaginal Exposure Therapy for Posttraumatic Stress Disorder (PTSD)

Coordinating Center: Weill Cornell Medical College, Department of Psychiatry

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SUMMARY

Posttraumatic stress disorder (PTSD) is a serious mental health condition that can develop after exposure to a traumatic event, such as an accident. Research has found that cognitive-behavioral treatment with exposure therapy, and also antidepressant medications, are effective treatments for PTSD. Cognitive-behavioral therapy involves learning more adaptive ways to interpret trauma-related memories and engaging in activities that help recovery from trauma, i.e. relaxation. Imaginal exposure therapy involves subjects repeatedly recounting memories of their trauma, within a controlled, supportive environment. However, research also shows that these treatments are not effective in as many as half of all subjects. The goal of this study is to develop more effective PTSD treatments. The study tests whether adding an antibiotic drug, D-Cycloserine (DCS), to cognitive-behavioral treatment with exposure therapy will make the treatment more effective. Pilot research studies suggest that DCS enhances the therapeutic effects of exposure therapy for subjects who have a fear of heights and for those with social anxiety. This study compares cognitive-behavioral treatment with exposure therapy plus DCS, versus cognitive-behavioral treatment with exposure therapy plus a placebo (sugar pill), to test whether subjects given the DCS will show a faster and larger improvement in their PTSD symptoms. Patients living in areas that are not geographically proximal to the Weill-Cornell Medical Center New York City campus will receive cognitive behavioral therapy using telemedicine (videoconferencing technology) as a way to investigate the feasibility and acceptability of using this technology to increase access to care for patients with PTSD.

RESEARCH DESIGN AND METHODS

The proposed study is a double blind placebo controlled evaluation of whether adding D-Cycloserine (DCS; Seromycin) to cognitive-behavioral exposure therapy improves treatment of posttraumatic stress disorder (PTSD) in survivors of trauma. Expert treatment guidelines for PTSD were published for the first time in 1999, recommending that cognitive-behavioral treatment (CBT) with exposure therapy should be the first-line therapy for PTSD[4]. Although there are unique aspects to each type of trauma exposure, CBT plus exposure therapy has been shown to be the most efficacious form of treatment for PTSD, with equally beneficial outcomes for survivors of a variety of traumatic events, including combat, motor vehicle and other accidents, burn injuries, physical and sexual assaults, and history of childhood abuse[4, 5]. Cognitive therapy involves identifying and challenging negative trauma-related thoughts that evoke anxiety, depression, and anger. Behavioral therapy involves re-engaging in pleasurable activities and re-connecting with loved ones so as to alleviate the PTSD symptoms of emotional numbness, anhedonia (loss of the ability to enjoy things), and social estrangement. Imaginal exposure and in vivo exposure are also types of behavioral therapy. For in vivo exposure, the clinician and subject construct a hierarchy of situations that the subject avoids because they are associated with the traumatic event. The subject then progressively works his/her way up the hierarchy, gradually confronting each situation until there is no more behavioral avoidance[5]. During imaginal exposure, subjects repeatedly recount memories of their traumatic event, within a controlled, supportive environment[5]. As they recount memories, subjects also rate their anxiety level every few minutes, so that the clinician can monitor this. Subjects recount the memories until their distress level declines, which usually takes 20-40 minutes, depending upon the initial level of distress. Exposure has been hypothesized to involve extinction of the aversive, symptomatic associations to the memory (or, in the case of in vivo exposure, to situations and environmental stimuli). Extinction itself is believed to involve active learning of a new set of associations and responses to the traumatic memory and trauma-related stimuli and situations.

The proposed study tests whether D-Cycloserine (DCS) can enhance the effects of exposure therapy for PTSD. DCS is a broad-spectrum antibiotic used in clinical trials over the last decade as a cognitive enhancer [6-9]. DCS is a partial agonist at the N-methyl-D-aspartate (NMDA) glutamatergic receptor, which has an essential role in learning and memory. DCS has been shown to enhance learning, including the

extinction of conditioned fear responses [10-11]. The proposed study will test the hypothesis that DCS will enhance the effects of imaginal exposure to alleviate PTSD symptoms. This hypothesis is supported by preliminary data from three sources. First, Ressler et al.[2] demonstrated that DCS combined with virtual reality (VR) exposure therapy for fear of heights significantly reduced the number of sessions needed to treat the phobia from six to only two sessions. Hoffman and colleagues[3] also found that DCS combined with imaginal exposure was an effective treatment for social anxiety. Lastly, we are currently conducting a double blind placebo controlled pilot study (IRB-approved Protocol #0411007625), in which we are comparing VR treatment plus DCS to VR treatment plus placebo for the treatment of PTSD in survivors of the World Trade Center attack. Preliminary results from the four subjects randomized thus far show a large effect size (d = 2.11) for the VR plus DCS intervention.

To evaluate the feasibility and acceptability of using existing telemedicine systems to deliver this treatment, ten patients will have their treatment delivered via the University of Vermont Medical Center's telemedicine technology (videoconferencing). Patients will go to the University of Vermont's Burlington Campus, where the telemedicince equipment is located, and be connected via videoconferencing with their therapist in NYC. The safety and well-being of the patient will be monitored by Dr. Rabinowitz, Medical Director of Telemedicine at University of Vermont Medical Center in Burlington. To increase recruitment potential and increase generalizability for the telemedicine portion of this study, we will include 20 additional participants with PTSD resulting from varied traumas, including OIF/OEF veterans, as well as individuals from occupations-at-risk for PTSD, such as law enforcement and disaster workers. We will also expand our potential recruitment locations to include residents in New York State, New Jersey, Connecticut, and Pennsylvania.
For patients outside of the Burlington area, we will use other Internet-based videoconferencing (e.g. Skype, Adobe Connect) to connect participants with the therapist, when Polycom equipment is not available. Multiple HIPAA-compliant Internet-based videoconferencing systems (e.g., Polycom, Skype, or Adobe Connect) will be used to connect the patient with the therapist, depending on what technology is avaialable and is most appropriate to each subject's situation. In this way, we hope to increase flexibility and accessibility and decrease cost.

After providing written informed consent, consecutively referred survivors of a variety of traumas will be assessed to determine initial eligibility for the study. See Section A6 for inclusion/exclusion criteria. An independent evaluator (unaware of treatment condition) will assess symptoms of PTSD and other psychopathology using structured clinical interviews and self-report measures with well-established psychometric properties at pre-treatment, during treatment, immediately post-treatment, and at six-month follow-up. Subjects who are diagnosed with a psychiatric disorder but who do not meet the inclusion criteria will be offered a referral for treatment to an appropriate provider. Prior to treatment subjects will also meet in person (or by video for telemedicine participants) with one of the two study physicians, Margaret Altemus, M.D. and Francis Lee, M.D., for medical clearance to participate. The physician will review each subject's medical history to ensure they have no contraindications to DCS treatment.

The treatment sample will be 144 subjects with PTSD as a consequence of any trauma (e.g., motor vehicle and accidents, burns and other injuries, combat, World Trade Center attack, etc.) (n=114), as well as telemedicine subjects with PTSD who live in Vermont, New York State, New Jersey, Connecticut, and Pennsylvania (n=30). Subjects will be randomly assigned to one of two treatment groups: imaginal exposure (IE) plus DCS (n=72) or IE plus placebo (n=72). Both experimental treatment groups will complete a standardized exposure therapy protocol similar to the IRB-approved protocol of the PI's current DCS VR exposure therapy study. The therapy is 12-14 weekly sessions that include well-validated and widely used cognitive-behavioral treatment (CBT) interventions: imaginal exposure, graduated in vivo exposure, psycho-education, relaxation training, engaging in pleasurable events, and cognitive reframing. Subjects will be instructed to take the pill they are provided (i.e., DCS or placebo) 90

minutes prior to all sessions that include exposure (sessions 3 on) and compliance will be assessed weekly. To assess emotional engagement and habituation during imaginal exposure, in 5-minute intervals, the subject rates his/her Subjective Units of Distress (SUDS) level, with 0 indicating no distress and 100 indicating the maximum. (Treatment is described under Section A.7 and a treatment manual is attached in Appendix A.) During treatment, subjects will be assessed by an independent evaluator after sessions 3, 6, and 10, to determine at what point, if any, differences between groups begin to emerge. Subjects will complete a limited battery of self-report questionnaires on a weekly basis prior to the treatment session and will be assessed for potential side effects at each session in which medication is taken.

The study instrumentation will be identical to that previously approved by the IRB for use in our current DCS study. During the evaluations subjects will be assessed with the following standardized instruments widely used in PTSD and clinical research: the Clinician Administered PTSD Scale (CAPS)[12], the Trauma History Questionnaire[13], the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-1)[14], the Posttraumatic Stress Disorder Checklist[15], the Peri-traumatic Dissociative Experiences Questionnaire (PDEQ) [16,] the Beck Depression Inventory[17], the State-Trait Anger Expression Inventory[18], the Brief Symptom Inventory[19], the Pittsburgh Sleep Quality Index[20], the WHO-Disability Assessment Scale[21], the Michigan Alcohol Screening Test[22], the UCLA Social Support Inventory[23], the Life Events Scale (LES) [24], and the Dyadic Adjustment Scale[25]. The Treatment Fidelity Rating Scale[26] will be used to assess clinicians' adherence to treatment by an independent protocol monitor.
Study-specific instruments include (1) the Patient Information Profile, a questionnaire assessing demographic information; (2) Expectancy of Therapeutic Outcome, a 3-item scale that evaluates the credibility of the treatment program used in the PI's other exposure therapy protocols; the (3) Usefulness of Treatment Inventory[27] which assesses preferences and usefulness of the specific skills and interventions, and is also used in the PI's other treatment studies; the Working Alliance Inventory Short Form[52], which measures therapeutic alliance; the Client Satisfaction Questionnaire[53], a treatment satisfaction measure; (4) Medication Side-effect Checklist, created by our research group to assess the 18 symptoms that have been named as potential side effects of DCS. The participant is asked to rate how much they experienced each symptom on the day the medication was taken on a 5-point Likert scale ranging from ―not at all to ―extremely. Any medical problems and medication taken since the last session (including dosage and frequency) will also be recorded. Study –specific instruments are attached in Appendix B. Telemedicine patients will complete these measures online as well as an online version of Telemedicine Satisfaction and Acceptance Scale[54], which assesses satisfaction with the videoconferencing technology used, and submit electronically using a secure site Internet site so that the clinician at WCMC will have access to this data before each session begins. Homework will be completed on hard copy and then scanned in to a computer and transmitted electronically (by fax or e-mail) to the clinician at WCMC. In addition to these instruments, all subjects will be genotyped for the BDNF SNP (Val66Met) by standard PCR methods from saliva samples. At the beginning of the first meeting, subjects will be asked to rinse their mouths with water and then salivate into a cup. Samples will be collected using the universal identifier for that subject, and transferred to the laboratory of Dr. Lee located in the Lasdon building, in batches for processing. (Telemedicine patients will receive assistance from local site staff and/or study assessor with the collection of saliva samples and mailing to Dr. Lee's laboratory at WCMC). Collection of saliva samples is non-invasive, reducing risks to both subjects and staff. Saliva samples will be collected using the Oragene system (DNA Genotek), which provides a number of benefits for a study with the proposed design. Primarily, samples can be stored at room temperature for extended periods of time.

Telemedicine patients in the Burlington area using Polycom will complete telemedicine sessions using equipment currently installed at Fletcher Allen Health Care (FAHC) or University Health Center (UHC), the teaching hospital and outpatient clinic respectively of the University of Vermont College of Medicine. Dr. Terry Rabinowitz or his designee will activate the videoconferencing connection with Weill Cornell

Medical Center and ensure that the videoconferencing systems between WCMC and UVMC are fully operational and connected. Current instrumentation used at UVMC and WCMC is state-of-the-art Polycom (www.polycom.com/home/) videoconferencing equipment and large-screen Liquid Crystal Display (LCD) or Cathode Ray Tube (CRT) monitors. These systems provide remote camera control and pan-tilt-zoom (PTZ) functionality as well as dynamic management of available bandwidth with an extremely low call failure rate. All instrumentation, whether ―clinician-side‖ or ―subject-side,‖ has the capability to control the other site's camera. That is, each has the ability to perform PTZ operations of the distant camera. In addition, all instruments have picture-in-picture (PIP) functionality—the ability to view oneself as one appears to the distant site (a small inserted real-time video image) while at the same time viewing the patient and others (the larger, full-screen video image on the same monitor) at the distant site. For this study, the distant sites' PIP and remote PTZ functionality will be turned off. We have found this helps to minimize patient distraction or confusion. Except for these modifications, all videoconferencing consultations will be fully interactive. Specifically, both clinicians and subjects will have real-time audio and video functionality. Transmission is via three Basic Rate Interface (BRI) Integrated Services Digital Network (ISDN) lines transmitting at a bandwidth of 384 kbps. Each facility will designate a room for imaginal exposure sessions that is comfortable, private, quiet, well-lighted, and uncluttered, in order to avoid distraction.

Dr. Rabinowitz or a designated associate will remain on the UVMC hospital grounds during all sessions, in case of medical emergency, and will be accessible by text-pager.

Other Vermont, New York State, New Jersey, Connecticut, and Pennsylvania participants will similarly utilize Polycom equipment with a minimum bandwidth of 384 kbps in a private room or will utilize other Internet-based videoconferencing equipment that is HIPAA compliant to connect with the therapist. When the Polycom equipment is used, a designated onsite staff person will activate the local videoconferencing connections, ensure that the connection is fully operational and connected to WCMC as well as be available during all sessions in case of any emergency.

The addition of a telemedicine component to the study does not constitute a new type of treatment, rather, it is implementing a technical addition designed to increase access to the already approved imaginal exposure treatment that has been in place at WCMC, using established telemedicine technologies. The aim of this pilot arm of the project is to evaluate the feasibility and acceptability of using telemedicine to deliver the imaginal exposure protocol as a way to increase access to evidence-based PTSD treatment.

A6. Inclusion criteria: (1) English-speaking; (2) between the ages of 18 and 70; (3) survivors of a variety of traumas (e.g., motor vehicle and accidents, burns and other injuries, combat, World Trade Center attack, etc.); (4) diagnosed with PTSD; and (5) in good health. For persons with chronic injuries/ conditions related to their accidents, ―good health‖ is defined as the injury being in a state of stabilization and able to attend weekly outpatient sessions. Exclusion criteria: (1) current organic mental disorder (2) schizophrenia or symptoms of psychosis/delusions; (3) bipolar disorder (4) current substance abuse or dependence (5) active suicidal/homicidal ideation, intent, or plan (6) use of pacemaker (7) significant health impairment including renal disease (8) taking oral anticoagulant medication, ethionamide, isoniazid, or anti-depressant medication (9) hypersensitivity to cycloserine (10) history of seizures; (11) pregnant or currently trying to conceive or breastfeeding.

A7. Treatment Plan:

Medication Administration: Subjects in the present study will take a standard dose of 100mg of DCS or a placebo capsule orally one time per week 90 minutes prior to each IE therapy session. The dosing regimen is based on the Ressler et al[2] study and our current protocol, #0411007625, which show that there was no difference in efficacy between the 50 and 500 mg dose, and on the Hoffman study[3] showing that 50mg was an effective dosing for social anxiety disorder. Thus, we are proposing to use a dose that will minimize the likelihood of side effects, and which is also consistent with our ongoing pilot study which includes a 100 mg dose. There were no reports of significant side effects in the Ressler study[2], the

Hoffman study[3], or the studies of human memory14-15 at doses of up to 500mg, and we have not observed any in our pilot study thus far. Thus, DCS appears to be well tolerated when delivered as proposed for this project. The study physicians, Margaret Altemus, M.D., and Francis Lee, M.D., will be available to evaluate subjects who experience any side effects in response to the medication.
We will use weekly dosing, occurring 90 minutes before the exposure sessions, because this dosing regimen was effective in the animal and human fear extinction studies[2], [37-38] and because there is evidence that daily, longer-term dosing can reduce the cognitive enhancing effects of DCS[39], possibly due to desensitization of the NMDA receptor over time with daily dosing[40]. The chosen dosing regimen will allow sufficient time for the medication to be absorbed into the bloodstream, and will allow the exposure session to be completed while circulating levels of the medication are still robust. Subjects will be instructed to take the dose of DCS 90 minutes prior to the start of the exposure session, because previous work in humans has shown that peak cerebral spinal fluid concentrations occur at 2 hours following a single oral dose of 250mg DCS[41] and that peak blood levels occur within 3-4 hours after dosing. DCS has a half-life of 10 hours[42-43]. In the Resslar et al. study[2], DCS was given 2-4 hours prior to exposure sessions, and in the Hofmann et al study[3] 1 hour prior to each exposure session. Similarly, the weekly dosing strategy used in the 2-week acrophobia and 5-week social anxiety treatment trials, and our own 10-week study, support the use of a weekly dosing strategy.
Following the procedures employed in our current DCS study, matching drug and placebo capsules will be prepared by the Research Pharmacy at the University of California, San Francisco. The pharmacy will pulverize 250mg capsules of DCS and 100mg of powder will be packed into a capsule. Lactose powder will be used for the placebo capsules. Randomization and drug dispensing will be performed by the Research Pharmacy of New York Presbyterian Hospital. Medication will be mailed to participants receiving treatment via telemedicine in New York State, New Jersey, Connecticut, Pennsylvania, and Vermont.

Therapy Protocol: The manual is attached in Appendix B. The protocol is 12-14 weekly 75-min. sessions. The number, frequency and length of IE sessions was chosen to be consistent with our DCS study and the DCS phobia treatment study by Ressler and colleagues[2] and closely follows the procedures adapted from the PI's DCS and other PTSD treatment projects [44-45]. During ET, the subject recounts a detailed description of the traumatic event until anxiety is sufficiently reduced (ideally, 50%), while the therapist monitor the subject's self-reported distress every five minutes. As described, treatment also includes empirically-supported, widely used CBT components[5]: (1) psycho-education for the subjects and significant other; (2) relaxation training; (3) in vivo exposure, in which the subject creates a hierarchy for avoided situations and confronts these outside of session; (4) behavioral activation (participation in pleasurable events); and (5) cognitive techniques (e.g., reframing, adaptive self talk, etc.).

Table 1: Preliminary Outline of Treatment Sessions

Session	Components of Treatment
1	***Psycho-education*:** subject learns about common reactions to trauma and PTSD. ***Review treatment plan*:** introduce and provide the rationale for all interventions
2	***Anxiety Management Techniques*:** controlled-breathing, guided-imagery relaxation, exercise, and engaging in pleasurable events ***Psycho-education for family member/significant other*:** subject brings family member/SO to session and person learns about common reactions to trauma and PTSD.
3	***Anxiety Management Techniques*:** review between session work ***Imaginal Exposure***: target 45 minutes ***Introduction to Cognitive Therapy Techniques:*** adaptive self talk
4	***Anxiety Management Techniques*:** review between session work ***Imaginal Exposure***: target 45 minutes ***Reinforce Adaptive self talk*** ***Introduction to In Vivo Exposure:*** creation of hierarchy
5	***Anxiety Management Techniques*:** review between session work ***Imaginal Exposure***: target 45 minutes ***In Vivo Exposure:*** subject reviews assignment and plans next assignment ***Cognitive Therapy:*** Teach restructuring, types of maladaptive thoughts, thought monitor
6-11	***Anxiety Management Techniques*:** review between session work ***Imaginal Exposure***: target 45 minutes ***In Vivo Exposure:*** subject reviews assignment and plans next assignment ***Cognitive Therapy:*** reinforce restructuring, review thought monitor
12	***Wrap up:*** Review of skills learned and progress in treatment Note: if clinically indicated, treatment can be extended to include up two 2 additional exposure therapy sessions, for a total of 14 sessions.

Statistical considerations (e.g. justification for sample size or "n"):
Sample size estimates were based on the formula outlined by Diggle et al.[46] for longitudinal studies. Although our pilot data and the published DCS phobia treatment studies suggest large effect sizes for a combined DCS treatment, we followed the recommendations by Kraemer et al.[47] who suggested that the critical effect size at which the power is computed to be 80% should be the threshold below which clinicians are unlikely to be interested in the effect. Adopting the procedures used in a large-scale study of Vietnam Veterans with PTSD[48], we designated a decline of 10 points on the CAPS (based on ½ a standard deviation) as the minimum clinically meaningful effect, which corresponds to a conservative (small-moderate) estimated effect size of d = .5. The calculations were based on the assumption of a strong correlation within subjects over time, rho = .6, and also assume alpha = .05. The number of assessments for the primary outcome measure (CAPS scores) was 5 (baseline, 3 clinical assessments during treatment, and post). A sample size of 34 per group was found to be sufficient at 80% power to detect the effect. Estimating an attrition rate of 30%, we plan to enroll 114 (57 per group) to ensure that an adequate sample remains by post-treatment and follow up. In addition, pilot subject data (n=10) will be collected to investigate the feasibility and acceptability of telemedicine to provide imaginal exposure (IE) therapy for PTSD.

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