Protocol for a Randomized Controlled Trial of Deprexis: Evaluation of a Computerized Intervention to Decrease Depression and Restore Functioning in Veterans

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Abstract

Background: Depressive symptoms are common in Veterans, and the presence of these symptoms increases disability and suicidal thoughts and behaviors. There is, however, evidence that these symptoms often go untreated. Intervening before symptoms are severe and entrenched is related to better long-term outcomes, including improved functioning and less disease chronicity. Computer-delivered interventions may be especially appropriate for those Veterans with mild-moderate depressive symptoms, as these interventions can require fewer resources and have lower barriers to access, and thus have potential for wider reach. Despite this potential, there is a dearth of research examining computerized interventions for depressive symptoms in Veteran samples.

Objective: The aim of this study is to evaluate the efficacy of Deprexis, a computerized intervention for depressive symptoms and related functional impairment.

Methods: First, qualitative interviews will be completed with a small subset of Veterans (n=16-20) to assess acceptability of procedures. Then, Veterans (n=132) with mild-moderate depressive symptoms will be randomly assigned to the Deprexis intervention or a treatment-as-usual control group. Primary outcomes will be depressive symptoms and various dimensions of psychosocial functioning.

Results: Recruitment is expected to begin in April 2024, with initial results expected in April 2029.

Conclusions: Conclusion: This study will provide initial evidence for the efficacy of self-guided computerized interventions for depressive symptoms and functional impairment in Veterans. If effective, these types of interventions could improve treatment access to psychosocial interventions for Veterans receiving care in the VA. Clinical Trial: ClinicalTrials.gov ID: NCT06217198

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Rahel Pearson[1], Christopher G. Beevers[2], Joseph Mignogna[3,4], Justin Benzer[1,5], Paul N. Pfeiffer[6,7], Edward P. Post [6,7], & Suzannah Creech[1,5]

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Abstract

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Conclusion: This study will provide initial evidence for the efficacy of self-guided computerized interventions for depressive symptoms and functional impairment in Veterans. If effective, these types of interventions could improve Veteran access to low-resource psychosocial treatments.

Keywords: depression (930); eHealth (1755); mental health (1564); RCT (152)

Administrative Information

Title: A Randomized Controlled Trial of Deprexis; Evaluation of A Computerized Intervention to Decrease Depression and Restore Functioning in Veterans

Study Registration: ClinicalTrials.gov ID: NCT06217198

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Name and Contact Information for the Trial Sponsor: Rehabilitation Research & Development, Peter Hunt, Ph.D. , Scientific Portfolio Manager, Behavioral Health, and Social Reintegration. Email: peter.hunt@va.gov

Role of Sponsor: The sponsor has no role in the study design or writing of this or any manuscripts. They are not involved in the collected, analysis or interpretation of the data.

Disclosure: The contents of this manuscript do not represent the views of the U.S. Department of Veterans Affairs or the United States Government. Since Drs. Pearson, Mignogna, Benzer, Pfeiffer,

Introduction

Background and Rationale

Depression is the leading cause of disability worldwide [1] and those diagnosed with Major Depressive Disorder (MDD) are up to 7.6 times more likely to die by suicide compared to the general population [2]. Depressive symptoms are associated with severe and chronic impairment in occupational and social domains [3], decreased quality of life [4] and adverse physical health outcomes [5]. Depression is a significant problem for U.S. Military Veterans, with 13% of post-9/11 war Veterans meeting criteria for current MDD [6], and 46.5% of female Veterans and 36.3% of male Veterans meeting criteria for lifetime MDD [7]. High prevalence of depressive symptoms in Veterans not only has negative ramifications for social and interpersonal functioning, occupational participation and quality of life [8], but also markedly increases the risk for suicide. An average of 543 Veterans die by suicide each month [9], and MDD is the second most important predictor of Veteran suicide among all recorded mental health diagnoses [10]. Depressive comorbidity among Veterans with Post-Traumatic Stress Disorder (PTSD) is also associated with elevated rates of disability and occupational and academic impairment compared to PTSD alone [11]. Given the functional impairments and elevated suicidal risk associated with depressive symptoms, it is essential to provide Veterans with timely and appropriate intervention.

Addressing depression before symptoms are severe and become entrenched could substantially improve outcomes. Even mild-moderate and subthreshold depressive symptoms are associated with significant disease burden, including increases in disability and mortality, and decreases in quality of life [12]. Rates of transition to MDD for individuals with subthreshold depressive symptoms are exceedingly high both in the short- [13] and long-term [14]. When subthreshold symptoms progress to MDD, symptoms become chronic in the vast majority of cases, with 85% of

individuals with MDD experiencing recurrent episodes even when they received specialty mental health treatment [15]. Evidence suggests that interventions targeted at individuals with mild to moderate symptoms, including those with subthreshold symptoms of MDD, are effective in restoring functioning and preventing the progression to severe disease [16].

Although depressive symptoms often go undetected at mild to moderate or subthreshold levels in community settings [17], depression symptom screens are routinely performed on a population level in Veterans Affairs (VA) facilities. This provides a key opportunity to identify Veterans with depressive symptoms, even before these symptoms reach the diagnostic threshold, and provide rapid and high-quality intervention. Patient preference studies indicate that individuals with depressive symptoms prefer to receive psychotherapy over medication [18]. Although the VA has made significant strides improving access to psychotherapy, including through the expansion of primary-care mental health integration (PC-MHI) [19], many Veterans still struggle to access adequate psychotherapy. Research shows the majority of Veterans (61%) with diagnosed mental health disorders only attend one session of psychotherapy [20]. Shame and stigma around depressive symptoms and seeking mental health treatment, as well as difficulties attending mental health treatments due to lack of time or transportation are known barriers to adequate and timely intervention and care [21]. Although the expansion of virtual mental health care (i.e., telehealth) within VA facilities is effective at overcoming certain logistical barriers to treatment, telehealth is as resource intensive as traditional face-to-face psychotherapy, and access is dependent on provider availability. Further, VA telehealth services might be less appropriate for individuals with mild-moderate symptoms, whose symptom severity level might not merit individual psychotherapy, but who would nonetheless benefit from help. Thus, despite increased detection of depressive symptoms and an identified need for intervention, a significant treatment gap exists.

Internet-delivered interventions are well-positioned to fill this treatment gap, as these interventions are low-cost, easily accessible, and scalable. When compared to telehealth or traditional

face-to-face mental health care, internet-delivered interventions could alleviate Veterans' stigma concerns and provide increased flexibility of access in the presence of competing demands of work and childcare. Positive experiences with internet-delivered interventions could also facilitate the eventual transition into traditional mental health care if needed [22]. Meta-analysis of results from community samples provide evidence for the effectiveness of internet-delivered interventions for depressive symptoms, including Acceptance and Commitment Therapy (ACT) [23], Cognitive-Behavioral Therapy (CBT) [24,25], and mindfulness-based approaches [26].

Deprexis [27] is an internet-delivered intervention, which integrates ACT, CBT, psychodynamic and mindfulness-based approaches. The program consists of 10 core modules targeting depressive symptoms and associated functional impairment. Engagement with content is completely self-guided, and the program is accessed remotely. A randomized controlled trial (RCT) of Deprexis in a general population sample found that Deprexis was effective in reducing depressive symptoms, improving well-being and decreasing disability [28]. Despite these positive results in the general population, it is unknown if Deprexis is an effective treatment for Veterans with depressive symptoms, given the unique composition of the Veteran population in terms of gender-ratio, barriers to treatment, severity of comorbid conditions and socio-demographic characteristics. Furthermore, there is a need to understand whether this low-intensity, internet-delivered treatment for depression also addresses functional impairments in Veterans. A critical gap in the field is testing the effects of evidence-based mental health interventions on recovery outcomes. Deprexis has previously been associated with significant improvement in disability and well-being; however, these were secondary outcomes and assessment was limited to few functional domains. There is a need to centralize the assessment of psychosocial functioning in mental health delivery research generally and the study of Deprexis specifically.

Aims

Deprexis has not yet been rigorously evaluated with a Veteran population in a VA medical center

setting. The current study aims to fill this critical gap in the literature by testing whether Deprexis is acceptable and effectively decreases depressive symptoms and improves functional outcomes in Veterans (*N*=152) presenting for VA healthcare with mild-moderate depressive symptoms. *Aim 1* will assess perceptions, needs and preferences as they relate to Deprexis through conducting post-treatment assessment interviews with Veterans (*n*=16-20). The objective of this aim is to identify which components improve Veterans' experience and uptake of Deprexis. Results obtained in Aim 1 will be used to inform the roll-out of RCT procedures under Aim 2. *Aim 2* will be to complete a RCT comparing an 8-week course of Deprexis to a treatment-as-usual control condition. *Hypothesis:* Veterans engaged in Deprexis will show improvements on measures of functioning and decreases in depressive symptoms compared to the Treatment-as-usual (TAU) control group. To generate hypotheses for future study, exploratory *Aim 2b* will examine if demographic variables, baseline psychopathology, credibility and Deprexis usage moderate treatment effects on primary outcomes.

Trial Design

This study is an individually randomized parallel two group therapy trial. A total of 132 Veterans will be randomized in a 1:1 fashion to either Deprexis intervention or a treatment-as-usual control group.

Methods: Participants and Measures

Study Setting

Recruitment will occur within the Central Texas VA Healthcare System. All assessment and intervention components will occur remotely, through a secure remote assessment platform (Qualtrics) and the Deprexis website, respectively.

Eligibility Criteria

Potential participants include male and female Veterans of all races/ethnicities who are: 1) able to comprehend and sign the informed consent form; 2) have reliable access to the internet and a computer, tablet and/or smartphone; 3) exhibit mild or moderate, but not very severe, levels of depression (QIDS-SR [29] score between 6 and 20 at the time of screening); 4) stable on psychotropic

medications (defined as no medication change in the 30 days prior to study entry). The last criterion is instated to ensure that symptoms evaluated during the pre-treatment assessment are due to underlying psychiatric conditions and not because of starting or stopping medications. Veterans will be excluded from study participation if they: 1) endorse any positive symptoms of a psychotic disorder (assessed via the PDSQ); 2) screen positive for Bipolar I Disorder (assessed via MDQ); or 3) report current suicidal risk (assessed via BDI-II item 9).

Recruitment

For the proposed study Veterans presenting with mild-moderate symptoms of depression will be recruited. Recruitment letters, including a link to the Qualtrics survey, will be sent out by US mail to Veterans identified through the medical record who screen positive on the PHQ-2 clinical reminder screen (score≥3). Initial eligibility criterion is purposefully broad (i.e., a positive PHQ-2 versus a positive PHQ-9) as we do not want to exclude treatment-receptive Veterans with mild depressive symptoms. Veterans' telephone numbers will be obtained from the medical record, and a research technician will contact Veterans by telephone to ensure that they have received their letters, answer any questions and provide them with a link to the Qualtrics survey if needed. Flyers in VA primary care and medical specialty clinics will also be posted and distributed, and information about the study and participant inclusion/exclusion criteria will be provided to VA primary care providers.

Informed Consent

A waiver of informed consent will be obtained for the completion of the eligibility screen. Informed consent will be obtained for the remainder of the study procedures. A paper watermarked copy of the informed consent will be included with the study recruitment letter. An electronic version of the consent form will be included in the Qualtrics eligibility survey. Veterans will be asked to review the consent form and they will be asked if they have any questions or concerns. Veterans who indicate that they have questions or concerns will be contacted by phone by the research technician. Once all questions and concerns are responded to, the research technician will verbally ask whether the

Veteran is still interested in the study, and if affirmative will send a link to DocuSign/consent via encrypted email. Veterans who indicate they do not have questions or concerns, will be asked in the Qualtrics eligibility screen if they are interested in participating in the study. If affirmative, they will be sent a link to DocuSign/consent via encrypted email.

Intervention Description

Deprexis is an internet-delivered treatment for depressive symptoms and related functional impairment. The intervention draws from various theoretical frameworks and consists of 12 modules: 10 core content modules and an introductory and summary module. Deprexis is designed to be interactive, includes answering questions and learning techniques and concepts through instruction and examples. Deprexis employs a software technology (Broca) that tailors content dynamically to the users' responses, resulting in a simulated conversational flow. To increase motivation, Deprexis features symptom-tracking, with accompanying graphical and text feedback, worksheets and summaries in printable format, audio recordings and illustrations. The content focuses on improving depressive symptoms (e.g., cognitive restructuring of depressogenic thoughts) and decreasing functional deficits associated with depressive symptoms (e.g., behavioral activation, interpersonal skills, healthy lifestyle choices). The program is self-paced, and every module takes between 10-60 minutes to complete. See Table 1 for an overview of session content and Figure 1 for Deprexis sample presentation.

Table 1: Deprexis module content

Module	Content
Introduction	Overview of Deprexis program; Psycho-education about the relationships between thoughts, feelings and behaviors; Observing and accepting of thoughts and feeling; Mindfulness exercise; Worksheet to encourage regular program use
Behavioral activation	Exploring the relationship between activity and depressive symptoms; Psych-education on basic psychological needs (e.g., need for competence, social relatedness); Selecting and scheduling activities that satisfy basic

	psychological needs using a checklist and log; Exploring and problem-solving barriers to completing activities
Cognitive modification	Psycho-education on automatic thoughts; Exploring antecedents and consequences of automatic thoughts; Common cognitive distortions; Strategies for correcting cognitive distortions (e.g., birds-eye view, scientist perspective)
Relaxation, physical exercise and lifestyle modification	Relationship between lifestyle habits (e.g., sleep, exercise, diet) and depression; Instruction and practice of various relaxation exercises to help mitigate stress (e.g., diaphragmatic breathing and visual imagery)
Acceptance and mindfulness	Illustrate the difficulty of controlling thoughts and feeling and the alternative of calmly accepting unwanted thoughts and feelings using metaphors and exercises; Mindfulness exercises that promote acceptance (e.g., leaves on a stream); Clarifying values and taking value-consistent action
Problem solving	Strengthening problem solving skills through defining problems in concrete rather than vague terms, setting achievable goals, generating a variety of potential solutions, evaluating solutions, implementing the chosen solution, and evaluating outcomes
Childhood experiences	Exploring difficult childhood memories and using coping skills such as expressive writing, acceptance, forming new positive memories and forgiveness
Interpersonal skills	Psycho-education about the relationship between interpersonal functioning and depression; Exploring different communication styles (e.g., assertive, passive-aggressive, aggressive, non-verbal communication); Practicing communication techniques (e.g., non-blaming communication)
Positive psychology	Psycho-education about positive psychology; Focusing on strengths instead of deficits; Fostering happiness by savoring positive experiences and identifying and fostering talents.
Dreamwork and emotion-focused intervention (Optional)	Coping with distressing dreams (e.g., keeping a dream journal, rewriting the ending of dreams); Reconceptualizing dreams as a way that our brain helps us problem solve

Figure 1: Deprexis Sample Presentation

Veterans randomized to the *control condition* will have access to standard VA treatment resources, including mental health treatment. Veterans will be provided with a list of available resources.

Criteria for discontinuing or modifying allocated interventions

Veterans can choose to discontinue study involvement at any time without consequences to them. We will actively monitor for any serious adverse events occurring during Veteran's study

involvement, and modifications to intervention components or procedures may be made at the discretion of the PI pending approval by the IRB and other relevant stakeholders.

Strategies to improve adherence to intervention protocols

Adherence will be optimized using strategies used in previous Deprexis trials. All Veterans will be sent brief text messages to increase engagement. The content of these text messages will target behavioral and cognitive processes which are known to maintain depressive symptoms. Additionally, text messages will provide Veterans with a reminder to use the Deprexis program. Research staff will also have access to the Deprexis "Cockpit" where Veteran usage data can be tracked in real-time. Based on Veteran usage of the Deprexis site, short encouraging emails will be sent to the Veteran by research staff. These emails will range from acknowledging the Veteran's usage to encouraging further engagement and decreasing discouragement. Research staff will also provide outreach to Veterans who have not activated their vouchers to provide technical support if needed. Contact between study staff and Veterans will occur if there is no engagement with Deprexis over a 2-week period.

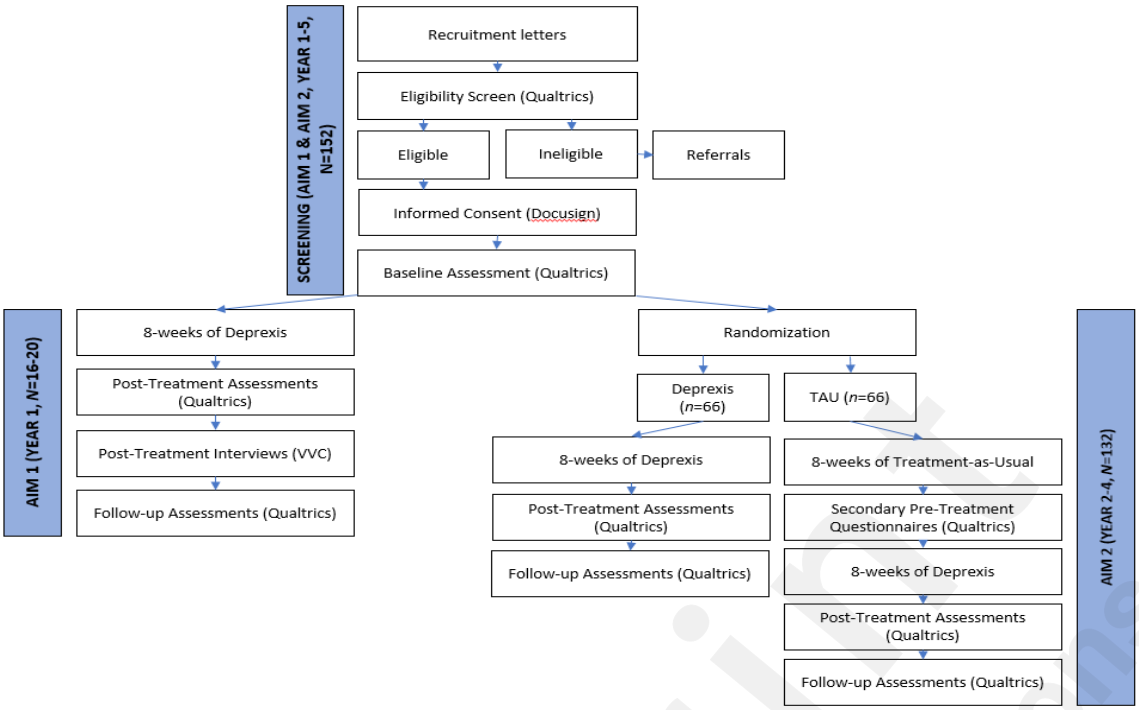
Relevant concomitant care and interventions that are permitted or prohibited during the trial

To participate, Veterans need to be stable (no changes in the last 30 days) on medications prescribed for a mental health disorder. Veterans randomized to either treatment group are allowed to start or continue any non-study treatment resources, including mental health treatment, during their participation in the trial.

Participant Timeline

See Figure 1 for details on participant timeline.

Figure 1: Participant Timeline



Outcomes

In *Aim 1* qualitative Veteran feedback on the Deprexis intervention and study procedures will be obtained and no quantitative analyses will be completed. Broadly, post-treatment interview questions will cover the following content areas: 1) motivation and barriers towards treatment and participation in the study; 2) Deprexis content, presentation, adherence, and usability; 3) perceptions of study procedures; and 4) changes experienced in mood, behavioral engagement or interpersonal interactions following Deprexis.

In *Aim 2a* we will test whether Deprexis is effective for decreasing depressive symptoms and improving functional outcomes in Veterans presenting for VA healthcare with mild-moderate depressive symptoms. Primary outcomes for this aim are depressive symptoms (assessed with the QIDS-16-SR) and functioning (assessed with the WHODAS and the SDS). Secondary outcomes are other psychopathology (assessed with PCL-5 and PDSQ), social functioning (assessed with ISEL and IIP-SC) and quality of life (assessed with QLS).

Exploratory analyses in *Aim 2b* will examine if demographic variables (Gender, Age, Race, Ethnicity, Education), PTSD symptom severity (assessed with the PCL-5), comorbidity (assessed

with the PDSQ), treatment credibility (assessed with the CEQ), Frequency of Study Support and Deprexis usage moderate treatment effects.

Measures

Primary outcomes (measured at all timepoints).

i. The *Quick Inventory of Depressive Symptomatology-Self-Report (QIDS-SR-16)*[29] is a 16-item self-report measure of depressive symptom severity. This brief measure assesses the 9 DSM-IV symptom criterion domains for depression and has been shown to be highly reliable, internally consistent, and sensitive to symptom change. The QIDS-SR-16 will be used as a primary eligibility criterion, namely a QIDS score from 6 to 20. To verify duration of depressive symptoms, we will include an item adapted from the Clinical Interview Schedule-Revised (CIS-R), which will assess duration of depressive symptoms on a 6-point scale.

ii. The *World Health Organization Disability Assessment Schedule-II (WHODAS)*[30] is a 36-item questionnaire assessing functional disability across 7 domains (understanding and communicating, getting around, getting along with people, life activities, work, participation in society, self-care) as well as a total score. The WHODAS has high test-retest reliability (r=0.98) and concurrent and construct validity [30].

iii. The *Sheehan Disability Scale (SDS)*[31] is a 3-item self-report measure of symptom-related disability, which has been used in previous Deprexis trials. The SDS was developed as a global measure of the impact of mental illness on work/school activities, family relationships and social functioning. The SDS has been found to be internally consistent, reliable and to have high construct validity [32] and to be sensitive to treatment effects [33].

Secondary outcomes (measured at all timepoints).

i. The *Psychiatric Diagnostic Screening Questionnaire (PDSQ)*[34] is a 125-item

questionnaire containing 13 subscales (e.g., major depressive disorder, anxiety disorders, alcohol and drug abuse/dependence) and is used to screen for the most common DSM Axis I Disorders. This scale shows good internal consistency, test-retest reliability, and discriminant, convergent and concurrent validity [34].

ii. The *Beck Depression Inventory-Second Edition (BDI-II)*[35] is a 21-item measure on a 4-point scale assessing depression symptom severity. Scores range from 0 to 63 with higher scores reflecting increased endorsement of depressive symptoms. The BDI-II has high internal consistency, good test-retest reliability and correlates highly with interview-based measures of depression [36]. The BDI-II will be used as a secondary measure of depression and to assess the suicidal ideation exclusionary criteria.

iii. The *Inventory of Interpersonal Problems-Short Circumplex Form (IIP-SC)*[37] is a 32-item measures assessing the interference of depressive thoughts, behaviors and symptoms across various psychosocial domains. The IIP-SC is sensitive to treatment effects and has excellent internal consistency and test-retest reliability [37].

iv. The *Inventory of Interpersonal Support-Short Form (ISEL-SF)*[38] is a 12-item measure assessing perceived social support across 4 subscales (1) appraisal support; the perceived availability of someone to discuss issues of personal importance, 2) tangible assets support; the perceived availability of material aid, 3) belonging support; the perceived availability of others to interact with socially, and 4) self-esteem support; the perceived availability of others with whom one compares favorably). There is evidence that perceived social support improves following internet-delivered interventions for depression [39]. The ISEL-SF has been found to be internally consistent and has high convergent construct validity.[40]

v. The *Quality of Life Scale (QLS)*[41] is a 16-item self-report measure of quality of life across

various domains, including material and physical well-being, relationships, social, community, recreational and civic activities, personal development and fulfillment and independence. The QLS has excellent internal consistency and test-retest reliability and demonstrated convergent and discriminant construct validity [42].

vi. The *PTSD Checklist for DSM-5 (PCL-5)*[43] will be used to identify if PTSD is a potential moderator of symptom change and to examine whether Deprexis produces meaningful changes in PTSD symptoms. The version of the PCL-5 used will include an assessment of the presence of a traumatic event meeting criterion A. If no traumatic event is endorsed, Veterans will not complete the remaining PCL-5 questions. Veterans who endorse exposure to a criterion A traumatic event will complete the 20-item PCL-5, which assesses PTSD symptom severity on a 5-point scale. The measure has good internal consistency, test-retest reliability and convergent and discriminant validity [44]. The PCL-5 is as sensitive to clinical change that occurs between pre-and post-treatment as golden standard interview-based measures of PTSD symptoms [45].

Moderators/covariates (measured at baseline):

i. The *Credibility and Expectancy Questionnaire (CEQ)*[46] is a 6-item self-report survey used to measure participants' perceived treatment expectancy and credibility of clinical outcome studies. Treatment credibility predicts therapy outcome[47] and was an important predictor of Deprexis treatment response in the general population RCT[48].

ii. The *Client Satisfaction Questionnaire-8 (CSQ)* [49] will be administered at post-treatment to assess quality of services, treatment satisfaction and willingness to recommend the treatment to others. There are 8 items scored on a 4-point scale (range 4-32), with higher scores representing greater acceptability. The CSQ has good psychometric properties and has been shown to correlate with treatment attendance and outcomes[49].

iii. Participants will report on demographic variables including their sex, gender, race, age, ethnicity, marital status, employment, income.

Sample Size

Aim 1: In determining the sample size for qualitative studies, the key goals are to develop case-oriented perspectives, select participants with a range of characteristics and perspectives and achieve saturation (i.e., point at which subsequent interviews fail to produce new themes [50]. Research typically indicates saturation is reached at 12-16 interviews. As we are also obtaining qualitative data on Veterans who did not adhere to the treatment (approximately 23% of the sample), we slightly increased our recruitment aim to 16-20 Veterans to allow for a sufficient sample of Veterans who completed Deprexis treatment, as well as those who terminated treatment early.

Aim 2: Effect sizes in the general population Deprexis RCT for participants with mild-moderate depression (QIDS<21) were *d*=0.65-0.9. Some evidence suggests that effect sizes for psychological interventions may be smaller for Veterans [51], so we estimate that effect sizes are at least medium (*d*=0.5) for measures of functioning and large (*d*=0.8) for depressive symptoms. To achieve 0.8 power at an alpha of 0.05, 102 participants need to be recruited. Accounting for 23% attrition over time, we will randomize 132 participants at baseline. In the general population trial, approximately 57% (*n*=213) of randomized participants were high-engagers (>90 min), and effect sizes were slightly higher in the high-engager group (d>0.67) than in the overall sample. Thus, we expect to be adequately powered for analysis in this subgroup.

Methods: Assignment of Intervention: Allocation

Allocation Sequence generation

Computer-generated stratified block randomization with block sizes of 4 and 8 will be performed by the research technician using a web-based application. As depression severity has previously been associated with Deprexis treatment response, randomization will be stratified by depression severity, consisting of three categories (QIDS>11 mild; QIDS<16 mild-moderate; QIDS<21 moderate).

Stratification was limited to depression severity, as minimizing the number of strata is recommended in trials which enroll relatively few participants.

Who will be blinded?

The utilization of a TAU-control condition precludes blinding of participants and research staff. Confounds due to research staff not being blinded will be minimal as all assessment and intervention components will be completed remotely without research staff support.

Methods: Data collection, Management, and Analysis

Plans to promote participant retention

Participants will receive text and email reminders with embedded link to their Qualtrics follow-up assessments. Research technicians will attempt to make phone contact with Veterans who fail to complete follow-up assessments within the designated timeframe.

Data management

Various steps will be taken to safeguard data quality. First, questionnaire data will be directly downloaded from Qualtrics into an excel file. Then, statistical software code will be used to score questionnaires. Questionnaires will be double scored by two different research technicians, and any discrepancies will be reviewed by the study PI (RP). All identifying participant data will be stored behind a VA firewall to ensure data security.

Statistical methods

Aim 1 preliminary analyses will be conducted through debriefings after each interview in the context of a structured audio review and matrix displays. The debriefing format will highlight the content and key findings from each interview and allow the study team to determine when saturation has been reached. Findings from these debriefings will be categorized into “rapid codes” on a matrix display signifying the key areas of the interview agenda they represent (e.g., barriers towards

treatment, Deprexis content and changes experienced in mood and functioning). Matrix displays create a visual representation of responses to key codes from each participant by lining up each primary response to a question side by side in one row of a spreadsheet. Rapid codes are summarized into themes and revised continuously and used to determine saturation and inform intervention content areas. Then, during formal analyses all interviews will be recorded, transcribed verbatim, de-identified and reviewed for accuracy against the recordings. Drawing from the literature, the interview agenda will be used to develop an initial coding structure that captures participant responses. An iterative process of transcript review will generate additional codes that will be added to the coding structure. The final coding structure will then be used to code and review all transcripts for concordance by the research team, and final codes will be entered in ATLAS.ti, a qualitative data management software tool, for review using Applied Thematic Analysis [52]. Applied Thematic Analysis is a systematic approach to coding, organizing, and interpreting qualitative data to best capture meaning via themes across participants' responses. For example, within any given code, this approach captures the breadth of responses to create an overall theme. In accordance with the purpose of Aim 1, which is to improve the further study and uptake of Deprexis in the RCT, we will look carefully for themes that describe the intended needs and desires of Veterans, perceived utility of Deprexis, changes noted in mood and/or functional domains and other emergent themes. These themes will be used to identify several potentially modifiable components of Deprexis, which can be used to guide current and future study efforts.

For Aim 2, linear mixed effects regression with restricted maximum likelihood estimates will be used to model continuous outcomes (e.g., changes in psychosocial functioning outcomes and depressive symptoms), and logistic models will be used to model change in dichotomous outcomes (e.g., significant change; ≥50% improvement in scores) over time. Linear mixed effects regression models will initially be fit with an interactive model (e.g., treatment condition + time + treatment condition x time) and compared to an additive model (e.g., treatment condition + time) using a likelihood-ratio

test. This nested comparison serves as a significance test of treatment x time interaction and will be reported as such in the analyses. Condition (treatment, TAU), time (pre, post, follow-up) and their interaction will be entered as fixed effects and participant will be entered as a random effect (i.e., random intercepts). Cohen's *d* for the treatment x time interaction will be calculated using an effect size derived from the mean pre-treatment to post-treatment/follow-up change in the treatment condition minus the pre-treatment to post-treatment/follow-up change in the TAU control divided by the pooled pre-treatment standard deviation. Simulations suggested this effect size estimate was most stable and robust for these types of treatment designs [53]. When comparisons are made within a time period, Welch's t-tests will be performed as Welch's t-tests are ideal when the two samples have unequal variances and/or unequal sample sizes [54]. When comparisons are made within a treatment condition over time (repeated measures), a paired samples t-test will be performed. As participants can engage in non-study mental health treatment, non-study treatment utilization will be included as a covariate in all analyses.

Methods for additional analyses

In an exploratory and hypothesis generating mode, potential moderators for Deprexis treatment effects will be examined. Generalized linear mixed models with robust maximum likelihood estimation will be will be used to model continuous outcomes (e.g., changes in psychosocial functioning outcomes and depressive symptoms) and logistic models will be used to model change in dichotomous outcomes (e.g., significant change; ≥50% improvement in scores) over time. Participants will be entered as a random effect (i.e., random intercepts). Each potential moderator will be examined in a separate model for change in primary outcomes (QIDS-16, WHODAS, SDS). Each model will contain main effects for the potential moderator and time (pre, post, follow-up), two-way interactions (moderator x time and time x treatment condition) and a 3-way interaction (moderator x time x treatment condition). To prevent spurious associations, the α-value will be Bonferroni corrected. A variable will be considered a moderator of treament effects if there is a

significant 3-way (moderator x time x treatment condition) at post-treatment and/or 8-week follow-up.

Definition of analysis population relating to protocol non-adherence, and any statistical methods to handle missing data

Consistent with CONSORT recommendations, Aim 2 analyses will be conducted across four groups: 1) the intention-to-treat group, which includes data from all randomized participants, regardless of treatment adherence or attrition; 2) the per-protocol group, which consists of participants who are considered treatment adherent (defined as ≥60 min of Deprexis use, which is consistent with previous research [28]); and 3) the high-engagement group, which consists of participants who demonstrated strong treatment uptake (defined as ≥90 min of Deprexis use; this cut-off is approximately 1 SD below the mean for the treatment adherent group in the general population Deprexis RCT; and 4) the completer group, which consists of participants who complete both baseline and post-treatment assessment. In the intent-to-treat group, the Amelia II package in R [55] will be used to impute missing data with an expectation-maximization and bootstrapping algorithm. All available variables will be used to impute missing data and the number of imputed datasets will be based on the proportion of missing data.

Dissemination of Results

Several manuscripts are planned, which align with the various study aims. In addition, results will be presented at research conferences, and summaries will be drafted for media releases. Author eligibility and order will be determined by the study principal investigator (RP).

Methods: Oversight, Monitoring and Confidentiality

Composition of the data monitoring committee, its role and reporting structure

The data safety monitoring board (DSMB) will be responsible for safeguarding the interest of trial

participant, assessing the safety and efficacy of interventions during the trial and for monitoring the overall conduct of the clinical trial. The DSMB will provide recommendations about stopping or continuing the clinical trial. To contribute to enhancing the integrity of the trial, the DMSB may formulate recommendations relating to the selection, recruitment and retention of participants, their management, improving adherence to protocol-specified regiments and procedures for data management and quality control. The DSMB will consist of at least three members, who are independent of the trial. Any protocol deviations or Unanticipated Problem involving Risks to Subjects or Other (UPRSO) will be reported to the DSMB within 5 days as well as to the IRB and summarized in the study progress report and submitted during continuing review.

Interim analyses

No interim analyses are planned.

Adverse event reporting and harms

In the case of an UPRSO or apparent Serious or Continuing non-compliance with the federal regulations for the protection or research subjects or the requirements or determinations of the IRB, a written report will be prepared for submission to the central IRB and DSMB within 5 business days of notification. The report will include a brief narrative summary of the event, a determination of whether a causal relationship existed between the study procedures and the event, whether the informed consent should be changed because of the event, and whether all enrolled participants should be notified of the event. All team meetings will begin by asking whether any such events have occurred.

Frequency and procedures for auditing trial conduct

Yearly auditing will occur by an IRB member who is independent of the study or its investigators. This to ensure that the study is compliant with the protocol and is meeting the standards of human subject research.

Institutional approval and confidentiality

The protocol has been approved by the Central Texas Veterans Affairs Healthcare System IRB. Any changes to the study protocol will be promptly communicated to relevant stakeholders. No participant data will be released in any way unless the investigators or study personnel are mandated to do so by law (e.g., because of risk to self or others). All study data will be kept in accordance with VA guidelines. Participants will be assigned a study ID, which is linked to identifying information in a password protected spreadsheet, which is stored behind the VA firewall. Study personnel who have access to study data will receive training in confidentiality policies and procedures.

Financial or competing interests

The principal investigator and the co-authors declare no financial or other competing interests.

Access to protocol, participant-level data and statistical code

All IRB approved study team members may have access to participant level data pending approval of the study PI. The full protocol and statistical code will be available at the discretion of the study PI. A deidentified participant-level dataset may be available pending appropriate approvals.

Results

Recruitment has not yet started for this study, we anticipate starting recruitment in May 2024 and to report on results in May 2029.

Discussion

Depressive symptoms, independent of comorbid trauma symptoms, are an important driver of functional impairment and suicidality in Veterans. When depressive symptoms are present with PTSD, these symptoms often persistent after trauma-focused treatments. Thus, depressive symptoms should be an urgent target of intervention in Veterans, even in the context of complex comorbid conditions. There is evidence that the depression treatment gap commonly described in community samples also exists for Veterans who receive their care at the VA [20]. Various reasons for the existence of this treatment gap have been suggested, and it seems likely that multiple individual, logistical and institutional barriers may prevent Veterans with depressive symptoms from receiving appropriate

care. Cost-effective, accessible computerized interventions would broaden the reach of depressive treatments available within the VA.

The research examining computer-delivered interventions in Veterans lags the research conducted in general population samples. This study is the first RCT of a self-guided computerized interventions for depressive symptoms and functional impairment in Veterans. Further, we broaden the target population of computerized interventions by including Veterans with subthreshold symptoms. The described trial has an explicit focus on functional outcomes, as there is evidence that symptomatic recovery and functional improvements do not consistently improve in tandem following mental health interventions. Deprexis has previously been associated with significant improvement in disability and well-being; however, these were secondary outcomes. Here, we centralize and significantly expand the assessment of psychosocial functioning across domains.

Importantly, the VA system is an appropriate site for testing an intervention such as Deprexis. The broad screening for depressive symptoms which occurs in all VA clinics (i.e., outside of specialty mental health clinics) and the integrated mental health record allows for the timely identification of Veterans presenting with relatively mild depressive symptoms. There is an opportunity to prevent chronicity and progressive disease by focusing treatment on mild-moderate depressive symptoms. There is evidence that Deprexis may be especially effective for those individuals with lower depressive symptom severity. Our long-term vision is that brief, computerized interventions like Deprexis can be integrated in a stepped-care approach, providing rapid intervention for Veterans with mild-moderate depressive symptoms, while reserving resource-intensive treatments such as face-to-face psychotherapy for individuals with severe symptomatology.

The study described above will provide initial evidence of the effectiveness of computerized interventions broadly, and Deprexis specifically, for Veterans presenting with depressive symptoms and functional impairment. Results obtained in this study could inform the roll-out of targeted computer-delivered interventions which address common barriers to mental health care in Veterans.

Building a diverse arsenal of psychosocial interventions will allow for a more tailored treatment approach, which is an essential step towards providing the highest quality care for Veterans with complex mental health needs.

References

1. Organization WH. *The Global Burden of Disease: 2004 Update*. World Health Organization; 2008.

2. Osby U, Brandt L, Correia N, Ekbom A, Sparén P. Excess mortality in bipolar and unipolar disorder in Sweden. *Arch Gen Psychiatry*. 2001;58(9):844-850. doi:10.1001/archpsyc.58.9.844

3. Broadhead WE, Blazer DG, George LK, Tse CK. Depression, disability days, and days lost from work in a prospective epidemiologic survey. *JAMA*. 1990;264(19):2524-2528.

4. Pyne JM, Patterson TL, Kaplan RM, Gillin JC, Koch WL, Grant I. Assessment of the quality of life of patients with major depression. *Psychiatr Serv*. Published online 1997.

5. Choi S, Lee S, Matejkowski J, Baek YM. The relationships among depression, physical health conditions and healthcare expenditures for younger and older Americans. *J Ment Health*. 2014;23(3):140-145.

6. Liu Y, Collins C, Wang K, Xie X, Bie R. The prevalence and trend of depression among veterans in the United States. *J Affect Disord*. 2019;245:724-727. doi:10.1016/j.jad.2018.11.031

7. Curry JF, Aubuchon-Endsley N, Brancu M, et al. Lifetime major depression and comorbid disorders among current-era women veterans. *J Affect Disord*. 2014;152-154:434-440. doi:10.1016/j.jad.2013.10.012

8. Maguen S, Griffin BJ, Copeland LA, et al. Trajectories of functioning in a population-based sample of veterans: contributions of moral injury, PTSD, and depression. *Psychol Med*. Published online November 25, 2020:1-10. doi:10.1017/S0033291720004249

9. VA National Suicide Data Report 2005–2015. :48.

10. Ilgen MA, Bohnert AS, Ignacio RV, et al. Psychiatric diagnoses and risk of suicide in veterans. *Arch Gen Psychiatry*. 2010;67(11):1152-1158.

11. Nichter B, Norman S, Haller M, Pietrzak RH. Psychological burden of PTSD, depression, and their comorbidity in the US veteran population: Suicidality, functioning, and service utilization. *J Affect Disord*. 2019;256:633-640.

12. Cuijpers P, de Graaf R, van Dorsselaer S. Minor depression: risk profiles, functional disability, health care use and risk of developing major depression. *J Affect Disord*. 2004;79(1-3):71-79. doi:10.1016/S0165-0327(02)00348-8

13. Cuijpers P, Smit F. Subthreshold depression as a risk indicator for major depressive disorder: a systematic review of prospective studies. *Acta Psychiatr Scand*. 2004;109(5):325-331. doi:10.1111/j.1600-0447.2004.00301.x

14. Fergusson DM, Horwood LJ, Ridder EM, Beautrais AL. Subthreshold depression in adolescence and mental health outcomes in adulthood. *Arch Gen Psychiatry*. 2005;62(1):66-72. doi:10.1001/archpsyc.62.1.66

15. Hardeveld F, Spijker J, De Graaf R, Nolen WA, Beekman ATF. Prevalence and predictors of recurrence of major depressive disorder in the adult population. *Acta Psychiatr Scand*. 2010;122(3):184-191. doi:10.1111/j.1600-0447.2009.01519.x

16. Cuijpers P, Smit F, van Straten A. Psychological treatments of subthreshold depression: a meta-analytic review. *Acta Psychiatr Scand*. 2007;115(6):434-441. doi:10.1111/j.1600-0447.2007.00998.x

17. Wells KB, Hays RD, Burnam MA, Rogers W, Greenfield S, Ware JE. Detection of depressive disorder for patients receiving prepaid or fee-for-service care: results from the Medical Outcomes Study. *Jama*. 1989;262(23):3298-3302.

18. Van Schaik DJ, Klijn AF, Van Hout HP, et al. Patients' preferences in the treatment of depressive disorder in primary care. *Gen Hosp Psychiatry*. 2004;26(3):184-189.

19. Farmer MM, Rubenstein LV, Sherbourne CD, et al. Depression quality of care: measuring quality over time using VA electronic medical record data. *J Gen Intern Med*. 2016;31(1):36-45.

20. Funderburk JS, Sugarman DE, Labbe AK, Rodrigues A, Maisto SA, Nelson B. Behavioral health interventions being implemented in a VA primary care system. *J Clin Psychol Med Settings*. 2011;18(1):22-29. doi:10.1007/s10880-011-9230-y

21. Hoge CW, Cotting DI. Combat Duty in Iraq and Afghanistan, Mental Health Problems, and Barriers to Care. *N Engl J Med*. Published online 2004:10.

22. Grubaugh AL, Gros KS, Davidson TM, Frueh BC, Ruggiero KJ. Providers' perspectives regarding the feasibility and utility of an Internet-based mental health intervention for veterans. *Psychol Trauma Theory Res Pract Policy*. 2014;6(6):624-631. doi:10.1037/a0035772

23. Brown M, Glendenning A, Hoon AE, John A. Effectiveness of Web-Delivered Acceptance and Commitment Therapy in Relation to Mental Health and Well-Being: A Systematic Review and Meta-Analysis. *J Med Internet Res*. 2016;18(8):e221. doi:10.2196/jmir.6200

24. Andrews G, Basu A, Cuijpers P, et al. Computer therapy for the anxiety and depression disorders is effective, acceptable and practical health care: An updated meta-analysis. *J Anxiety Disord*. 2018;55:70-78. doi:10.1016/j.janxdis.2018.01.001

25. Karyotaki E, Riper H, Twisk J, et al. Efficacy of Self-guided Internet-Based Cognitive Behavioral Therapy in the Treatment of Depressive Symptoms: A Meta-analysis of Individual Participant Data. *JAMA Psychiatry*. 2017;74(4):351-359. doi:10.1001/jamapsychiatry.2017.0044

26. Spijkerman MPJ, Pots WTM, Bohlmeijer ET. Effectiveness of online mindfulness-based interventions in improving mental health: A review and meta-analysis of randomised controlled trials. *Clin Psychol Rev*. 2016;45:102-114.

27. Meyer B, Berger T, Caspar F, Beevers C, Andersson G, Weiss M. Effectiveness of a novel integrative online treatment for depression (Deprexis): randomized controlled trial. *J Med*

Internet Res. 2009;11(2):e1151.

28. Beevers CG, Pearson R, Hoffman JS, Foulser AA, Shumake J, Meyer B. Effectiveness of an internet intervention (Deprexis) for depression in a united states adult sample: A parallel-group pragmatic randomized controlled trial. *J Consult Clin Psychol*. 2017;85(4):367.

29. Rush AJ, Trivedi MH, Ibrahim HM, et al. The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. *Biol Psychiatry*. 2003;54(5):573-583.

30. Üstün TB, Kostanjsek N, Chatterji S, Rehm J. *Measuring Health and Disability: Manual for WHO Disability Assessment Schedule WHODAS 2.0*. World Health Organization; 2010.

31. Sheehan D. *The Anxiety Disease*. Bantam; 1986.

32. Leon AC, Olfson M, Portera L, Farber L, Sheehan DV. Assessing psychiatric impairment in primary care with the Sheehan Disability Scale. *Int J Psychiatry Med*. 1997;27(2):93-105.

33. Sheehan KH, Sheehan DV. Assessing treatment effects in clinical trials with the discan metric of the Sheehan Disability Scale. *Int Clin Psychopharmacol*. 2008;23(2):70-83.

34. Zimmerman M, Mattia JI. The Psychiatric Diagnostic Screening Questionnaire: development, reliability and validity. *Compr Psychiatry*. Published online 2001.

35. Beck AT, Steer RA, Brown GK. *Beck Depression Inventory (BDI-II)*. Vol 10. Pearson London, UK; 1996.

36. Sprinkle SD, Lurie D, Insko SL, et al. Criterion validity, severity cut scores, and test-retest reliability of the Beck Depression Inventory-II in a university counseling center sample. *J Couns Psychol*. 2002;49(3):381.

37. Soldz S, Budman S, Demby A, Merry J. Inventory of Interpersonal Problems—Short Circumplex Form. *Assessment*.

38. Cohen S, Mermelstein R, Kamarck T, Hoberman HM. Measuring the functional components of social support. In: *Social Support: Theory, Research and Applications*. Springer; 1985:73-94.

39. Frenette É, Ouellet MC, Guay S, Lebel J, Békés V, Belleville G. The effect of an Internet-based cognitive behavioral therapy intervention on social support in disaster evacuees. *J Clin Psychol*. Published online 2023.

40. Payne TJ, Andrew M, Butler KR, Wyatt SB, Dubbert PM, Mosley TH. Psychometric evaluation of the interpersonal support evaluation list–short form in the ARIC study cohort. *Sage Open*. 2012;2(3):2158244012461923.

41. Flanagan JC. Measurement of quality of life: current state of the art. *Arch Phys Med Rehabil*. 1982;63(2):56-59.

42. Burckhardt CS, Anderson KL. The Quality of Life Scale (QOLS): reliability, validity, and utilization. *Health Qual Life Outcomes*. 2003;1(1):1-7.

43. Weathers FW, Litz BT, Keane TM, Palmieri PA, Marx BP, Schnurr PP. The ptsd checklist for

dsm-5 (pcl-5). *Scale Available Natl Cent PTSD Www Ptsd Va Gov*. 2013;10(4).

44. Blevins CA, Weathers FW, Davis MT, Witte TK, Domino JL. The posttraumatic stress disorder checklist for DSM-5 (PCL-5): Development and initial psychometric evaluation. *J Trauma Stress*. 2015;28(6):489-498.

45. Wortmann JH, Jordan AH, Weathers FW, et al. Psychometric analysis of the PTSD Checklist-5 (PCL-5) among treatment-seeking military service members. *Psychol Assess*. 2016;28(11):1392.

46. Borkovec TD, Nau SD. Credibility of analogue therapy rationales. *J Behav Ther Exp Psychiatry*. 1972;3(4):257-260.

47. Devilly GJ, Borkovec TD. Psychometric properties of the credibility/expectancy questionnaire. *J Behav Ther Exp Psychiatry*. 2000;31(2):73-86.

48. Pearson R, Pisner D, Meyer B, Shumake J, Beevers CG. A machine learning ensemble to predict treatment outcomes following an Internet intervention for depression. *Psychol Med*. 2019;49(14):2330-2341.

49. Attkisson CC, Greenfield TK. The UCSF Client Satisfaction Scales: I. The Client Satisfaction Questionnaire-8. Published online 2004.

50. Fusch PI, Ness LR. Are We There Yet? Data Saturation in Qualitative Research. Published online 2015:9.

51. Hundt NE, Barrera TL, Robinson A, Cully JA. A systematic review of cognitive behavioral therapy for depression in veterans. *Mil Med*. 2014;179(9):942-949.

52. Dhakal K. NVivo. *J Med Libr Assoc JMLA*. 2022;110(2):270.

53. Morris SB. Estimating effect sizes from pretest-posttest-control group designs. *Organ Res Methods*. 2008;11(2):364-386.

54. Delacre M, Lakens D, Leys C. Why psychologists should by default use Welch's t-test instead of Student's t-test. *Int Rev Soc Psychol*. 2017;30(1).

55. Honaker J, King G, Blackwell M, Blackwell MM. Package 'Amelia.' *Version View Artic*. Published online 2010.

Abbreviations

ACT: acceptance and commitment therapy
BDI-II: Beck Depression Inventory-Second Edition
CBT: cognitive-behavioral therapy
CEQ: Credibility and Expectancy Questionnaire
DSMB: data safety monitoring board
IIP-SC: Inventory of Interpersonal Problems-Short Circumplex Form
ISEL-SF: Inventory of Interpersonal Support-Short Form
MDD: major depressive disorder
PCL-5: PTSD Checklist for DSM-5

PC-MHI: primary-care mental health integration
PDSQ: Psychiatric Diagnostic Screening Questionnaire
PTSD: Post-Traumatic Stress Disorder
QIDS-SR: Quick Inventory of Depressive Symptomatology-Self-Report
QLS: Quality of Life Scale
RCT: randomized controlled trial
SDS: Sheehan Disability Scale
TAU: treatment-as-usual
UPRSO : Unanticipated Problem involving Risks to Subjects or Other
VA: Veterans Affairs
WHODAS: World Health Organization Disability Assessment Schedule-II