Protocol for a Randomized Controlled Trial of Deprexis: Evaluation of a Web-Based 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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Protocol for a Randomized Controlled Trial of Deprexis: Evaluation of a Web-Based 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: Veterans will be recruited through the VA electronic medical record and through primary care and specialty clinics. First, qualitative interviews will be completed with a small subset of Veterans (*n*=16-20) to assess acceptability of treatment procedures. Then, Veterans (*n*=132) with mild-moderate depressive symptoms will be randomly assigned to the fully automated Deprexis intervention or a treatment-as-usual control group. Primary outcomes will be self-reported depressive symptoms and various dimensions of psychosocial functioning.

Results: Recruitment is expected to begin in May 2025, with initial results expected in May 2029.

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

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Data availability statement: A deidentified participant-level dataset may be available to the scientific community pending appropriate approvals.

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) compared to PTSD alone is also associated with elevated rates of disability in cognitive (d=1.03) and mental health (d=1.49) domains. Veterans with comorbid PTSD and MDD also reported decreases in quality of life (d=0.84) and a twice-fold risk of suicide compared to those Veterans with 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 [27,28] 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 [29]. 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. The primary goal in previous trials was to test Deprexis' effect on depressive symptoms. Although improvement in functional domains following Deprexis treatment have been reported [29] conducted assessments did not span the full range of functional outcomes. 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 Qualtrics [30] and the Deprexis website, respectively.

Eligibility Criteria

Potential participants include all Veterans irrespective of sex or gender and of all ages and 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 [31] 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[32]); 2) screen positive for Bipolar I Disorder (assessed via MDQ[33]); or 3) report current suicidal risk (assessed via BDI-II item 9[34]).

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. Pasticipants are provided a free of charge Deprexis voucher and will access the intervention through the Deprexis website. See Table 1 for an overview of session content and Figure 1 for Deprexis sample presentation.

>>>INSERT TABLE 1 HERE <<<

>>>INSERT FIGURE 1 HERE <<<

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 Veterans' real-time Deprexis usage data, and based on this usage data 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 2 for details on participant timeline.

>>>INSERT FIGURE 2 HERE<<<

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) which are administered through Qualtrics.

i. The *Quick Inventory of Depressive Symptomatology-Self-Report (QIDS-SR-16)*[31] is a 16-item self-report measure of depressive symptom severity. This measure takes approximately 5-7 minutes to complete and assesses the 9 DSM-IV symptom criterion domains for depression (e.g., “There is no change in my usual appetite”) and has been shown to be highly internally consistent (α=0.86). The QIDS-SR-16 demonstrates concurrent validity with measures assessing similar outcomes (correlation coefficient=0.86-0.65) and is sensitive to symptom change (Rush,2003). Scores above 6 are indicative of meaningful depressive symptoms. 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)*[35] is a 36-item self-report questionnaire, which takes 5-20 min to complete. The measure assesses functional disability across 7 domains; understanding and communicating, getting around, getting along with people, life activities, work, participation in society, self-care (e.g., “In the last 30 days, how much difficulty did you have in concentrating and doing something for 10 minutes”). The WHODAS total score is scaled (range 0-100), with a higher scores indicating increased disability. The WHODAS has high test-retest reliability (r=0.98), concurrent validity with measures assessing similar outcomes (correlation coefficient=0.45-0.65) and is sensitive to change following treatment [35].

iii. The *Sheehan Disability Scale (SDS)*[36] is a 3-item self-report measure of symptom-related disability (e.g., X), which has been used in previous Deprexis trials. The SDS takes approximately 5 min to complete and items are summed (range 0-30), with higher scores indicating greater disability. 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 (alpha=0.89), reliable (correlation coefficient=0.73) and to have high construct validity [37] and to be sensitive to treatment effects [38].

Secondary outcomes (measured at all timepoints).

i. The *Psychiatric Diagnostic Screening Questionnaire (PDSQ)*[32] 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. The PDSQ takes approximately 15-20 min to complete, with scoring and cut-offs varying by individual scale (see 34 for further details). This scale shows good internal consistency (α=0.82), test-retest reliability (correlation coefficient=0.84), and discriminant, convergent (mean correlation coefficient=0.17) and concurrent (mean

correlation coefficient=0.72) validity [32].

ii. The *Beck Depression Inventory-Second Edition (BDI-II)*[34] is a 21-item self-report measure assessing depression symptom severity, completed in approximately 10 minutes. Items are scored on a 4-point (range 0-63) with higher scores reflecting increased endorsement of depressive symptoms. A score of 15 or above indicates the presence of clinically significant depressive symptoms [39]. The BDI-II has high internal consistency (α=0.90), good test-retest reliability (correlation coefficient=0.73-0.96), and correlates highly with interview-based measures of depression (correlation coefficient=0.66-0.75) [40]. 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)*[41] is a 32-item self-report measures assessing the interference of depressive thoughts, behaviors and symptoms across various psychosocial domains (e.g., "It is hard for me to join in on groups"). The measure takes approximately 10-15 minutes to complete. The measure consists of 8 scales consisting of 4 items each. Scores are averaged (range 0-4), with higher scores indicating greater interpersonal problems. The IIP-SC is sensitive to treatment effects and has demonstrated internal consistency (α=0.64-0.87) and test-retest reliability (correlation coefficient=0.56=0.81) [42].

iv. The *Inventory of Interpersonal Support-Short Form (ISEL-SF)*[43] is a 12-item self-report 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). The measure

takes approximately 5 minutes to complete, with higher scores indicating presence of increased social support. There is evidence that perceived social support improves following internet-delivered interventions for depression [44]. The ISEL-SF has been found to be internally consistent (alpha=0.83) and has demonstrated convergent construct validity with other measures of social support (correlation coefficient=0.45).[45]

v. The *Quality of Life Scale (QLS)*[46] 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. Ratings in domains (e.g., "Health, being physically fit and vigorous") are made on a 7-point anchored scale ranging from "delighted" to "terrible" (range 12-116), with higher scores indicating improved quality of life. The measure takes approximately 10 minutes to complete, with higher scores indicating higher perceived quality of life. The QLS has excellent internal consistency (α=0.82 to 0.92) and test-retest reliability (correlation coefficient= 0.78 to r = 0 .84) and demonstrated convergent validity with similar measures (correlation coefficient = 0.67 to 0.75) [47]. Further, the QLS is able to discriminate between populations with expected differences in quality of life (i.e., those with and without chronic illness)[48].

vi. The *PTSD Checklist for DSM-5 (PCL-5)*[49] 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 (e.g., In the past month were you

bothered by “Repeated, disturbing, and unwanted memories of the stressful experience”). Scores range from 0-80, with scores above 31 being indicative of probable PTSD (ref). The measure takes approximately 10 minutes to complete. The measure has good internal consistency (α=0.94), test-retest reliability (correlation coefficient= 0 .82) and convergent and discriminant validity (correlation coefficients= .31 to .60) [49]. 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 ($r_{alerting\text{-}CV}$=0.94 and $r_{contrast\text{-}CV}$=0.92) [50].

Moderators/covariates (measured at baseline):

i. The *Credibility and Expectancy Questionnaire (CEQ)*[51] is a 6-item self-report survey used to measure participants’ perceived treatment expectancy and credibility of clinical outcome studies (e.g., “At this point, how logical does the course offered to you seem”). The measure takes approximately 5 minutes to complete, with higher scores indicating increased treatment credibility. Treatment credibility predicts therapy outcome[52] and was an important predictor of Deprexis treatment response in the general population RCT[53]. The measure has good internal consistency (α=0.84), test-retest reliability (correlation coefficient= 0 .83)[52].

ii. The *Client Satisfaction Questionnaire-8 (CSQ)* [54] will be administered at post-treatment to assess quality of services, treatment satisfaction and willingness to recommend the treatment to others (e.g., “How would you rate the quality of service that you received”). The self-report measure takes approximately 5 minutes to complete, and consists of 8 items scored on a 4-point scale (range 4-32), with higher scores representing greater acceptability. The measure has good internal consistency (α=0.91), and has been shown to correlate with treatment attendance (correlation coefficient=0.54) and outcomes (correlation coefficient=-0.35).[55].

iii. Participants will self-report on demographic variables including their sex, gender, race, age, ethnicity, marital status, employment, income. The demographic questionnaire will take approximately X minutes to complete.

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 [56]. 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 (i.e., did not complete post-treatment or follow-up questionnaires).

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 [57], 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. Given that we only use self-report measures involvement of research staff in responses will be very limited, and rater effects are unlikely.

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 using established methods for qualitative research[58]. Debriefings will occur 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 [59] , a qualitative data management software tool, for review using Applied Thematic Analysis. 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 [60] 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 [61]. 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[62]. Simulations suggested this effect size estimate was most stable and robust for these types of treatment designs [63]. 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 [64]. 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 [65]. 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 [66], 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 [29]); 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, Version 1.8.2 package in R [67] 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 [68]. 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.

Ethics approval

The protocol has been approved by the Central Texas Veterans Affairs Healthcare System IRB (protocol number 2024-001). Any changes to the study protocol will be promptly communicated to relevant stakeholders.

Confidentiality

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, which require that electronic and paper data be kept for the duration of the study and for six fiscal years thereafter (for details on storage and disposition of data, please refer to Department of Veterans Affairs record control schedule 10-1[69]). 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 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.

Results

This study was funded in September of 2023, anticipated data collection will occur between May

2024 and April 2029, currently no subjects have been recruited into this study. Results are expected in November of 2029.

Discussion

The research examining computer-delivered interventions in Veterans lags the research conducted in general population samples. This study gathers qualitative experiences of Veterans with a computerized intervention and conducts the first RCT of a self-guided computerized interventions for depressive symptoms and functional impairment in Veterans. Results from the described study will demonstrate if positive results in general population trials of computerized interventions generalize to the Veteran population. Further, we broaden the target population of these types of 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. This study centralizes and significantly expands the assessment of psychosocial functioning across domains.

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.

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 [53]. 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.

Despite the above outlined strengths, this study also has several limitations. The choice of a TAU control group is a relatively weak comparator. Follow-up studies comparing Deprexis to active treatment conditions would provide further evidence for the relative impact of the intervention. All assessments administered in this study are self-report questionnaires, which are prone to certain types of bias (e.g., desirability bias). If the efficacy of Deprexis is supported in this trial, examining if change also generalizes to other assessments, such as ecological momentary assessment or tracking, may be merited. Related, as no clinical interviews are conducted we are not able to assess the presence or absence of clinical diagnoses. Lastly, usage will be closely monitored in this trial, which may not be feasible in clinical settings. Automating usage reminders may be an important step to promote successful uptake in the VA.

Despite these limitations, we believe the study described above will provide much needed initial evidence for 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. This is especially pertinent given that demand for VA behavioral health care outpaces supply, resulting in increased outsourcing of behavioral health care in the form of community care referrals[70]. Building a diverse arsenal of psychosocial interventions, including computerized interventions, potentially allows more Veterans to receive behavioral health care within the VA. Further, giving Veterans additional options as they approach their mental health care could improve overall engagement with treatments[71]. We believe that results of this study could potentially extend and advance routine care for Veterans with depressive symptoms, which is an essential step towards closing the treatment gap and providing the highest quality care for Veterans with complex mental health needs.

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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

Supplementary Files

Figures

Table 1: Deprexis module content[27].

Module	Content
Introduction	Overview of Deprexis program; Psycho-education about the relationships between thoughts, feeli behaviors; Observing and accepting of thoughts and feeling; Mindfulness exercise; Worksheet to regular program use
Behavioral activation	Exploring the relationship between activity and depressive symptoms; Psych-education on basic p needs (e.g., need for competence, social relatedness); Selecting and scheduling activities that satis psychological needs using a checklist and log; Exploring and problem-solving barriers to complet
Cognitive modification	Psycho-education on automatic thoughts; Exploring antecedents and consequences of automatic th Common cognitive distortions; Strategies for correcting cognitive distortions (e.g., birds-eye view perspective)
Relaxation, physical exercise and lifestyle modification	Relationship between lifestyle habits (e.g., sleep, exercise, diet) and depression; Instruction and p various relaxation exercises to help mitigate stress (e.g., diaphragmatic breathing and visual imag
Acceptance and mindfulness	Illustrate the difficulty of controlling thoughts and feeling and the alternative of calmly accepting thoughts and feelings using metaphors and exercises; Mindfulness exercises that promote accepta 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 ter achievable goals, generating a variety of potential solutions, evaluating solutions, implementing th solution, and evaluating outcomes
Childhood experiences	Exploring difficult childhood memories and using coping skills such as expressive writing, accept forming new positive memories and forgiveness
Interpersonal skills	Psycho-education about the relationship between interpersonal functioning and depression; Explo communication styles (e.g., assertive, passive-aggressive, aggressive, non-verbal communication) communication techniques (e.g., non-blaming communication)
Positive psychology	Psycho-education about positive psychology; Focusing on strengths instead of deficits; Fostering 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

Deprexis Sample Presentation.

Participant Timeline.