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Design challenges in transdiagnostic psychotherapy research: Comparing Transdiagnostic Behavior Therapy (TBT) to existing evidence-based psychotherapy in veterans with affective disorders

Daniel F. Gros*
Mental Health Service, Ralph H. Johnson Veterans Affairs Medical Center, Charleston, SC, United States

Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, Charleston, SC, United States

Abstract

Background: To address the limitations of disorder-specific approaches, newer transdiagnostic approaches to psychotherapy have been developed to provide a single treatment that is capable of addressing several, related disorders. However, the recruitment of multiple diagnoses presents many challenges to the traditional design of psychotherapy randomized controlled trials (RCTs).

Objective: The goal of the manuscript is to present the challenges and rationale for designing a RCT for transdiagnostic treatment to inform and aid in the development of future investigations.

Methods: A recently funded and ongoing RCT for Transdiagnostic Behavior Therapy (TBT) is used as an example to discuss the related design challenges. The TBT study involves the recruitment of 96 veteran participants with any of the following eight principal diagnoses: posttraumatic stress disorder, panic disorder, social anxiety disorder, obsessive compulsive disorder, generalized anxiety disorder, specific phobia, major depressive disorder, or persistent depressive disorder. Within the TBT study, participants will complete a semi-structured diagnostic interview and a series of transdiagnostic self-report measures to determine eligibility and assess baseline symptomatology. Qualifying participants will be randomized to TBT or control psychotherapy. Additional assessments will be completed at post-treatment and 6-month follow-up.

Conclusions: Due to the transdiagnostic nature of the sample, adjustments to the recruitment and randomization procedures, selection of measures, selection of control psychotherapy, and analysis plan were required. These adjustments have implications to future trials on transdiagnostic psychotherapy protocols as well as future research in line with the transdiagnostic focus of the National Institute of Mental Health's Research Domain Criteria (RDoC) funding strategy.

*Mental Health Service 116, Ralph H. Johnson VAMC, 109 Bee Street, Charleston, SC 29401, United States. grosd@musc.edu.

Keywords

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1. Introduction

Cognitive behavioral therapy (CBT) is an efficacious treatment for the affective disorders, including the Diagnostic and Statistical Manual for Mental Disorders 5th Edition (DSM-5) depressive disorders, anxiety disorders, obsessive-compulsive and related disorders, and trauma- and stressor-related disorders [1,2]. CBT involves several different evidence-based treatment components (e.g., psychoeducation, cognitive restructuring, behavior modification) that are typically delivered over the course of 10–20 weeks, and yet, the benefits of CBT typically persist following the termination of treatment [1,2]. However, despite its clear benefits, several limitations exist in the current delivery of CBT, including the number of different disorder-specific CBT protocols and the related expense, training, and time needed to master them [3]. To address these limitations, newer transdiagnostic treatments, or "those that apply the same underlying treatment principles across mental disorders, without tailoring the protocol to specific diagnoses" [4], have been developed. Transdiagnostic treatments are based on the notion that the affective disorders have common underlying symptoms (e.g., high negative affect) and their associated treatments involve highly overlapping disorder-specific CBT protocols. Transdiagnostic treatments propose to distil the highly overlapping components of the disorder-specific treatments into a single treatment and therefore address the symptoms and comorbidities across multiple disorders at once [5]. To date, a small number of transdiagnostic treatment approaches have been proposed for the affective disorders [5], with several developmental and initial evaluation manuscripts published [6–9].

With the growing number of transdiagnostic treatment approaches, more well-designed clinical trials are needed to investigate the efficacy of these treatments. However, the study of transdiagnostic treatments, as compared to single disorder investigations, may include several challenges and potential complications in the design and implementation of a randomized controlled trial. The traditional, disorder-specific randomized controlled trial (RCT) typically involves a single target diagnosis (e.g., posttraumatic stress disorder) being randomized into one of two or more disorder-specific psychotherapies or therapy modalities (e.g., prolonged exposure vs. patient-centered therapy; prolonged exposure in-person vs. prolonged exposure via telehealth), and with symptom monitoring based on disorder-specific measures (e.g., PTSD Checklist) [10–14]. In contrast, special considerations must be accounted for in transdiagnostic research regarding inclusion and exclusion criteria, selection of comparison group(s), randomization into groups, selection of assessment measures, and analyses of group differences. However thus far, the preliminary investigations of transdiagnostic protocols have either lacked randomization [7], focused on group psychotherapies [8,9], included wait-list control conditions [6,9], and/or were limited to a small number of diagnoses [9], potentially due in part to the complexities inherit in the design of transdiagnostic studies.

The present manuscript provides a thorough discussion of the design issues involved in studying transdiagnostic psychotherapy. A recently funded, ongoing RCT of a transdiagnostic psychotherapy, Transdiagnostic Behavior Therapy (TBT) [7], is used as an example transdiagnostic study. The TBT study is presented as it was designed and subsequently funded, with each of inherit challenges highlighted and with rationale for the selected option provided. The goal of the manuscript is to present the challenges and rationale for designing a RCT for transdiagnostic treatment to inform and aid in the development of future investigations.

2. Research design and methods

2.1. Recruitment procedures

Veterans will be recruited through the Primary Care — Mental Health Integration (PCMHI) program within a large Southeastern Veterans Affairs Medical Center (VAMC). The PCMHI program is the second step of the VAMC's stepped care model for mental health and the first step in which veterans are evaluated by a mental health provider (e.g., psychiatrist, psychologist, social worker), involving the completion of a brief diagnostic interview and self-report measures. If veterans endorse symptoms consistent with an affective disorder, the veteran's interest in participating in research is assessed and, if they are agreeable to research, they complete consent documentation. The PCMHI program was selected as the primary recruitment site as to increase the likelihood of recruiting participants that were not already involved in mental health treatments (e.g., evidence-based psychotherapy). A second assessment will be completed with the project staff to assess inclusion/exclusion criteria (with a targeted sample of 96 veterans; ≥72 completers), including a semi-structured clinical interview and self-report questionnaires focused on the psychiatric symptoms and quality of life.

2.2. Sample diagnoses

The majority of RCTs on the efficacy of psychotherapy investigate a single psychiatric disorder, typically with exclusions for select comorbid conditions [10–14]. This approach allows for control over the symptom presentation across the two or more groups. However, a transdiagnostic approach mandates a broader investigation of disorders and presentations to better capture the potential strengths of the treatment. For example, although TBT has been shown to be effective in posttraumatic stress disorder (PTSD) [7], a study limited to TBT versus a disorder-specific CBT for PTSD, such as Prolonged Exposure, in participants with PTSD would not investigate the potential strengths of TBT to address multiple principal diagnoses and comorbid combinations. Thus, to more fully investigate the transdiagnostic scope of TBT, the TBT study will recruit veterans with wide range of principal diagnoses.

2.2.1. Inclusion criteria—The TBT study included the following inclusion criteria. Participants must be clearly competent to provide informed consent for research participation. Participants also must meet DSM-5 diagnostic criteria for a principal diagnosis of an affective disorder, including PTSD, panic disorder (PD), social anxiety disorder (SOC), obsessive compulsive disorder (OCD), generalized anxiety disorder (GAD), specific phobia (SP), major depressive disorder (MDD), or persistent depressive disorder (PDD).

Diagnoses were based upon findings from the Anxiety Disorders Interview Schedule for DSM-5 [15]. Participants also must be between the ages of 18 to 80 years old to be included in the TBT study.

2.2.2. Exclusion criteria—Several exclusion criteria were included in the TBT study. Criteria were separated into two groupings. There are several potentially temporary criteria that will only delay participation in the TBT study after a specified duration, including 1) recent history of psychiatric hospitalization or a suicide attempt as documented in their medical record (≤ 2 months) and 2) recent start of new psychiatric medication (≤ 4 weeks). VAMC patients excluded due to these factors will be reconsidered for participation once the condition related to their exclusion is resolved or stabilized. There also are several criteria that will prevent participation in the TBT study altogether, including 1) current diagnosis of substance dependence on the structured clinical interview, 2) acute, severe illness or medical condition that likely will require hospitalization and/or otherwise interfere with TBT study procedures as documented in their medical record (e.g., active chemotherapy/radiation treatment for cancer, kidney dialysis, oxygen therapy for chronic obstructive pulmonary disease), 3) diagnosis of moderate-to-severe traumatic brain injury (TBI) in their medical record and/or endorsement of TBI screener questionnaire [16], or 4) diagnosis of schizophrenia, psychotic symptoms, personality disorders, and/or bipolar disorder. Participants endorsing a past moderate-to-severe TBI will be assessed by the project neuropsychologist to determine their additional assessment and treatment needs. The choice to exclude substance dependence was governed by the grant funding agency. Additional comorbid Axis I diagnoses that were not listed as exclusion criteria (e.g., eating disorder, adjustment disorder, or insomnia) are permitted as long as they are considered secondary to the principal diagnosis of an affective disorder. Ineligible veterans will be referred for non-study-related treatments within the PCMHI program at the VAMC.

2.3. Procedures

Participants who meet diagnostic criteria for the targeted disorders will be randomized into a study condition, and will be assigned to a project therapist. Because most veterans who meet study criteria likely will present with multiple affective disorders [17], principal diagnosis, or the most impairing of the diagnosable disorders, will be used to select veterans for participation. Eligible veterans will be randomized into TBT or the control treatment, Behavioral Activation Therapy (BAT) [18]. Both treatment conditions will include 12 weekly 60-minute individual sessions. The general format of sessions will involve: 1) brief check-in; 2) review of materials from previous sessions; 3) review of homework assignments; 4) overview of new materials and in-session exercises; and 5) assignment of homework for next session. Attendance and homework completion will be recorded.

2.3.1. Randomization procedures—As a result of the recruitment of 8 principal diagnoses that exist at different prevalence rates in veterans [19], randomization procedures were altered to balance diagnoses across the two conditions. Thus, a stratified random assignment based on principal diagnosis will be used for the most common principal diagnoses (MDD, PTSD, and PD) [19–21]. The remaining diagnoses (SOC, OCD, and PDD, SP, and GAD) were grouped together into a fourth category due to their less frequent

prevalence in veterans as a principal diagnoses. For example, OCD is found in only 1.9% of veterans [22], resulting in a small number of likely participants with the disorder and thereby making a separate stratification for the disorder challenging. Participants will be randomly assigned (1:1) to one of the two TBT study arms (n = 48 per arm) using a permuted block randomization procedure [23]. Randomization will be stratified by principal diagnostic group and block size will be varied to minimize the likelihood of unmasking. After determining eligibility and completing consent and baseline assessment materials, enrolled participants will be assigned to treatment groups using a computer generated randomization scheme. Randomization will occur at the participant level.

2.3.2. Assessment procedures—As presented in Table 1, the battery of self-report questionnaires and a diagnostic interview will be completed pre- and post-treatment and at the 6-month follow-up to track participants' progression through treatment and maintenance. A select number of measures also will be administered at biweekly sessions (sessions 1, 3, 5, 7, 9, and 11) to track rate of change during the course of treatment. These time points for the assessments are consistent with CBT research with veterans with affective disorders. Participants will be compensated $20 for completion of assessment procedures for an estimated total of $60 for the entire TBT study. To reduce the likelihood of missing data, the three primary assessment points will be scheduled separately from normal treatment sessions (intake appointment, one week following the final treatment session, and at 6-month follow-up). These assessment procedures will take 120–150 min to complete on average.

Self-report of general symptoms of the affective disorders (e.g., anxiety, depression, avoidance) and quality of life, rather than disorder-specific questionnaires, were chosen due to the transdiagnostic nature of the TBT study. For example, measures of disorder-crossing symptoms were selected, such as the Albany Panic and Phobia Questionnaire (APPQ) [24], State-Trait Inventory for Cognitive and Somatic Anxiety — Trait Version (STICSA-Trait) [25], Depression Anxiety Stress Scales 21-Item Version (DASS) [26], Illness Intrusiveness Rating Scale (IIRS) [27], Veterans Short-Form Health Survey (V/SF-36) [28], and Multidimensional Assessment of Social Anxiety (MASA) [29]. The one exception to this transdiagnostic assessment approach was the inclusion of the PTSD Checklist for the DSM-5 (PCL-5) [30]; however, previous versions of the PCL have been shown to be sensitive to other disorders [20,21]. Based on the focus of TBT, the combine measures include 7 clinician-rated and 7 self-reported subscales of various forms of avoidance. Indicators of feasibility and acceptability of the interventions also will be collected, including attendance, discontinuation rates, and homework completion. The Satisfaction with Therapy and Therapist Scale — Revised (STTS-R) was selected to assess patients' level of satisfaction with their therapeutic experiences [31].

2.4. Interventions

2.4.1. Transdiagnostic Behavior Therapy—TBT is an evidence-based, behavioral intervention that was developed for veterans with affective disorders. The transdiagnostic, unifying symptom of the affective disorders in TBT is avoidance. A more thorough session-by-session description of the protocol is available elsewhere [7]. In general, the first six sessions of TBT are designed to educate on, prepare for, and practice four

different types of exposure techniques for transdiagnostic avoidance (situational/in-vivo, physical/interoceptive, thought/imaginal, and [positive] emotional/behavioral activation) [7,32]. Daily exposure practices are regimented, and optional therapeutic modules can be incorporated into TBT to further improve exposure practices (e.g., response prevention, brief cognitive therapy, sleep hygiene, management of substance use, anger management, and pain management). Each module is designed as a single session of content that can be incorporated into existing exposure practices. The final session covers a review of treatment progress and relapse prevention strategies. The initial findings for TBT suggest that it provides excellent coverage of principal diagnoses of PTSD, MDD, and PD with various comorbid conditions [7].

2.4.2. Comparison group—To provide an evidence-based comparison for TBT, the second group of participants will receive manualized BAT [18]. BAT is based on early behavioral models that suggest that decreases in positively reinforcing healthy behaviors are associated with the development of negative affect [33,34]. In general, BAT involves teaching patients to monitor their mood and daily activities with the goal of increasing pleasant, reinforcing activities and reducing unpleasant events. BA is a brief treatment, can be administered in either individual or group formats, and has demonstrated reliable effectiveness across a wide range of university, community, civilian and veteran clinical samples with depression [33,34]. BAT also has been shown to be effective in the treatment of PTSD in Veterans with a medium effect size [35]. In the TBT study, the BAT condition will be manualized, following an existing protocol in the literature [18]. BAT will be structurally equivalent to TBT with the same session length (60 min), frequency of sessions (weekly), duration of treatment (12 sessions), and amount of homework. Although there will be some overlap between the BAT and TBT protocols (as TBT includes behavioral activation component for depressive symptoms), the primary exposure component and multi-disorder focus of TBT is missing from BAT.

BAT was selected as the control condition for two primary reasons. First, BAT is an evidence-based psychotherapy with reliable support in depressive disorders and some support in the anxiety disorders [18, 33–35]. Thus, BAT will provide a strong control group to investigate the efficacy of TBT in comparison to an established evidence-based CBT approach. Second, the 8 affective disorders targeted in the TBT study would require at least eight separate disorder-specific evidence-based treatments, not including separate protocols for various combinations of comorbidities. The training, therapists, and statistical analyses required to manage this number of control conditions would be extremely challenging to provide, especially when considering the likelihood of protocol drift and the added sample size requirements (i.e., 10–30 participants per principal diagnosis per condition for each of the 8 disorders; total sample in the 200–300 if all disorders/treatments are included) for such an approach. Thus, in an effort to balance restrictions in sample size, provider trainings, and comorbidity with the need of an evidence-based comparison condition, BAT was selected as a single disorder-specific evidence-based CBT that would benefit most/all of the potential participants. Based on the samples in the two pilot studies of TBT [7], BAT is empirically supported for at least 90% of the likely sample (e.g., participants with MDD and/or PTSD as a principal or comorbid diagnosis).

2.4.3. Treatment training and fidelity—The guidelines for training and fidelity will follow published recommendations from the literature [36]. Both TBT and BAT have established treatment manuals and associated fidelity checklists that outline the core components of each treatment session [7,18]. Four therapists will be trained to provide the two treatment protocols, including attendance of training workshops for the treatments and role-playing sample cases/sessions with an identified expert in each treatment. Weekly supervision of the ongoing cases will be held with the principal investigator who has had extensive training and completed clinical trials on both treatments [7,37,38]. Supervision will focus on maintaining treatment fidelity and limiting protocol drift, especially given the partial overlap between the two protocols as discussed earlier. Twenty percent of therapy session recordings will be assessed for treatment fidelity by independent, expert coders.

2.5. Analyses

2.5.1. Superiority versus non-inferiority trial—The comparison of TBT and BAT results in questions regarding the appropriateness of superiority versus non-inferiority methods to investigate the efficacy of interventions. The ultimate decision to select a superiority trial was based on several factors related to the potential strengths of TBT, as presented above. First, although a strong argument could be made that BAT may evidence similar outcomes in symptoms of depression [18], difference are likely in the two treatments' ability to address the other transdiagnostic symptom outcomes assessed in the TBT study, including anxiety (cognitive and somatic), stress, avoidance (situational, interoceptive, and thought), and related impairment. Second, the majority of previous studies on BAT focused on samples of patients with limited, if any, diagnostic comorbidity as is common in many RCTs [33]. Thus, it also is possible that TBT, developed in part to address diagnostic comorbidity, will outperform BAT in addressing symptoms of depression in veterans with diagnostic comorbidity. Together, these notions/hypotheses suggested that a superiority trial, rather than a non-inferiority trial, would be most appropriate for the RCT.

2.5.2. Sample size determination—The TBT study was designed to obtain preliminary indicators of intervention efficacy in reducing mental health symptoms and improving quality of life, to evaluate treatment feasibility and acceptability, and to obtain input information for the design of future efficacy and effectiveness RCTs. Therefore, sample size justification focuses on precision of estimates of effect sizes using 95% confidence intervals (CI) rather than power of statistical tests. For continuous efficacy and feasibility outcomes, with $n_1 = n_2 = 36$ participants randomly assigned (1:1) to TBT and BAT control conditions, 95% CI estimates of the difference in mean change scores for outcome variables (effect sizes) will have precision of approximately 0.4 standard deviation units. For outcome variables having standard deviations of change scores ranging from 1.0 to 10.0, for example, the 95% CI will have precisions in raw units ranging from ±0.46 to 4.62, respectively. For the dichotomous feasibility outcome, discontinuation proportion, the 95% CI for estimating the difference in discontinuation proportions between TBT versus BAT control condition will have precision ranging from ±0.15 to ±0.17 for hypothesized discontinuation proportions of 0.10 and 0.15 for TBT and BAT control conditions, respectively. These values are consistent with similar findings from the transdiagnostic CBT literature on individual psychotherapy [6,8,9]. For analyses involving hypothesis testing

of continuous outcome variables, there will be approximately 80% power to detect a standardized effect size (difference in mean change scores in units of standard deviation) of 0.67 s [assuming $n_1 = n_2 = 36$; independent sample t-test, Type I error rate (level of significance) = $\alpha = 0.05$, two sided test]. Based on the preliminary published effect sizes for individual transdiagnostic CBT compared to a control group (average *d*s = 0.89) [6], the power to detect an effect size of 0.67 should be sufficient at $\alpha = 0.05$.

To account for the "fraction of missing" information that must be imputed in the intent to treat sample and the dilution effect of intent to treat analyses [39], the sample size will be inflated by 25% to achieve a final intent to treat sample size of 48 subjects randomized to each treatment group ($N = 96$ total sample size). This conservative inflation of the sample was based on estimates from the preliminary studies (20.0% discontinuation in each) and available studies of individual transdiagnostic CBT (discontinuation rates ranged from 13.5 to 17.6%). [6,7].

2.5.3. Missing data—The management of missing data will be influenced by the final sample size and amount of observed missing data at the completion of the TBT study. The management strategies will be informed by the literature [40]. The full intent to treat (ITT) analysis set will comprise all randomized participants. Missing data in the full analysis set will occur if participants discontinue prior to the end of the TBT study. Participants will not be discontinued from the TBT study because of non-adherence and all will remain in the study unless consent is withdrawn or if there are concerns regarding participant safety. Missing data for the ITT analysis set will be imputed using multiple imputation methods [41]. The results of analyses using TBT study completers and protocol adherers (completer and per-protocol analyses) will be compared with results using the ITT analysis set to test sensitivity of study conclusions to study discontinuation and protocol non-adherence. Multiple imputation methods will likely be used to address missing data in the completer analyses, depending on sample size and amount of missing data on primary outcome measures. In addition, the information on the proportion of discontinuation will be used as one of the outcome measures of intervention feasibility.

2.5.4. Efficacy measure analyses—The primary outcome time point is at the end of the active intervenetion phase and the secondary time point is at the end of the naturalistic 6-month follow-up period. The difference in mean change from baseline to end-of-active intervention (effect sizes) for TBT versus BAT control condition will be estimated via 95% CI. For the secondary time-point analyses, TBT versus BAT control differences in change from immediate end-of-intervention to the 6-month follow-up will also be estimated using 95% CI. Efficacy outcome variables will be compared using the generalized linear mixed models (GLMM) approach. In the first set of primary hypothesis testing analyses, post-treatment scores for each outcome of interest will be used (separately) as the dependent variable in the model, intervention (TBT versus BAT control) will be included as the primary independent variable, and pre-treatment scores for the outcome of interest will be added as covariates. Additional covariates (e.g. age, number of psychiatric comorbidities, race, sex, combat theater, and number of treatment sessions) will be added to the model to adjust for putative confounding variables. In secondary analyses, the modeling procedure

will be repeated for the period between immediate-end-of-active intervention and end-of-six-month follow-up.

Due to the transdiagnostic nature of the TBT study, a large number of measures were selected to assess transdiagnostic symptomatology. However, for the purposes of the analyses, these measures were separated into primary and secondary outcomes based on those measures most theoretically likely to differ as a function of therapy. As such, the primary outcome measures include the DASS scales, ADIS avoidance scales, and IIRS, each of which were predicted to demonstrate significantly larger improvements in the TBT compared to the BAT group. The remaining secondary measures were included in the analyses for more exploratory purposes.

2.5.5. Feasibility and acceptability analyses—A 95% CI for proportions will be used to estimate the proportion of participants who exit the TBT study prematurely (discontinuation) within each intervention group and the difference in discontinuation proportions between the intervention groups. For the treatment satisfaction and adherence outcomes (STTS-R, proportion of missed sessions or homework assignments), the median and mean responses will be obtained within and between each intervention group. A 95% CI for difference in means will be used to estimate the between intervention differences in treatment satisfaction (STTS-R) and adherence (e.g. average proportion of missed sessions or homework assignments) for TBT versus BAT control conditions. Frequency distributions describing the participants' reasons for noncompliance and discontinuation of participation will be developed.

The GLMM modeling framework described for efficacy analyses will be used to compare the effect of TBT versus BAT on treatment satisfaction, retention (discontinuation), and treatment adherence (% missed sessions, % homework completion). Discontinuation proportions (dichotomous outcome) and % of missed visits and % homework completion will be compared between the intervention groups using GLMM, with logistic/binomial regression analyses as special cases for dichotomous and percentage outcomes; STTS-R will be modeled as a continuous outcome using an appropriate link function. The longitudinal profile of adherence as a dichotomous outcome at each visit also will be modeled (e.g. attended/did not attend a given session). This will allow us to evaluate the trends in session attendance and to determine if the trends differ by intervention (e.g. whether the probability of missing visits is less/greater at earlier or later time points).

2.5.6. Exploratory analyses of diagnostic groups—Exploratory analyses using GLMM modeling, as described above, will be carried out to determine if there is a preliminary suggestion that the effect of the intervention on efficacy and acceptability outcomes differ by principal diagnosis. For these analyses, a diagnosis by intervention group interaction term will be included in the model. Trends toward significance for the diagnosis by intervention interaction term would provide suggestive evidence of a possible differential diagnosis effect, suggesting that the change in the outcome variable is different for disorder groups (e.g., depressive disorders versus anxiety disorders) or between specific disorders (e.g., PTSD versus MDD). It is acknowledged that the TBT study may not be powered to fully evaluate the statistical significance of the diagnostic comparisons; however, for the

TBT study, trends toward statistical significance are sought for future ypothesis-driven study in a larger adequately powered trial, rather than confirmation of a hypothesized differential diagnosis effect.

3. Discussion

The goal of the manuscript is to present the challenges and rationale for designing a RCT for transdiagnostic treatment to inform and aid in the development of future investigations. Transdiagnostic treatments, such as TBT, have the potential to dramatically change how psychiatric patients are treated with evidence-based therapy, shifting the overwhelming requirement of learning tens of evidence-based protocols for the affective disorders down to only one [5,7]. Transdiagnostic treatments also have the potential to better address comorbidity, which is found in the majority of patients with affective disorders [17]. Additional well-designed research is needed to more thoroughly investigate these research questions; and, as highlighted above, transdiagnostic studies include many challenges in their design. The TBT study example involved many of the standard components of a RCT for psychotherapy, including randomization into treatment groups, clinician-rated and self-report measures at baseline, post-treatment, and 6-month follow-up, and superiority analyses. However, due to its transdiagnostic nature, the TBT study also involves the recruitment of participants with a principal diagnosis of any depressive or anxiety disorder. This one difference resulted in a series of challenges in the design, each of which had the potential to change to scope of the study.

The recruitment of eight principal diagnoses resulted in a surprising number of challenges in designing this study. Randomization procedures had to be altered based on the predicted prevalence of each disorder, resulting in three groups for the most prevalent disorders (PD, MDD, and PTSD) and an “other” group for the remaining, less prevalent disorders (SOC, OCD, GAD, SP, and PDD). Transdiagnostic assessment measures were selected to be sensitive to a wider range of disorders and related symptoms, as disorder-specific measures may reduce the detection of symptom improvements. The selection of the control treatment was particularly challenging as it needed to be an active treatment that has the potential to help the majority of participants, but not a transdiagnostic treatment that would significantly overlap with TBT. BAT was selected; however, this decision created other challenges regarding the decision of superiority versus noninferiority analyses. Together, the shift to transdiagnostic, multiple diagnoses had a significant impact on the design of the study.

These challenges in the design of transdiagnostic studies have implications for the current direction of psychiatric literature. More specifically, the National Institute of Mental Health (NIMH) introduced the Research Domain Criteria (RDoc) as a funding strategy to encourage research on the underlying mechanisms of psychiatric disorders [42,43]. The RDoC encourages research on the underlying neurobiological mechanisms and basic dimensions of functioning that may cut across disorders. One of the goals of the RDoC is to escape the DSM disorder categories through the development of this alternative framework. However, during the initial development and then transition period, the DSM disorder categories will still be needed for recruitment procedures, likely involving the recruitment of multiple DSM

diagnoses to inform the development of the dimensions of functioning [44,45]. Thus, the outlined design adjustments for a transdiagnostic study likely will be needed for a large portion of NIMH funded studies going forward.

There are several limitations of the TBT study that merit discussion as they have implications for the design of transdiagnostic research. The primary limitation of the study is the size of the project. Although this decision was based in part on the funding mechanism and initial investigation scope of the project, a larger sample size could afford more variation in the selection of the control group. For example, disorder-specific protocols could be used for each of the subgroups to provide a potentially better matching control treatment (e.g., Cognitive Processing Therapy for PTSD vs. TBT in participants with a principal diagnosis of PTSD). However, the limitations of this approach, such as protocol drift (discussed earlier), would still remain and should be considered in the design. A larger sample also would provide more power to detect differences in the disorder-specific outcomes, due to larger samples of the more prevalent disorders (MDD, PD, and PTSD).

In conclusion, the present manuscript reviews the challenges involved in designing a transdiagnostic psychotherapy RCT. These challenges included the selection of the number of disorder groups, randomization in study groups, selection of measures, selection of a control treatment, and the implications on the analysis plan. These challenges are likely to impact a large number of NIMH funded research due to the introduction of the RDoC strategy, especially during the initial development and transition phases of the transdiagnostic dimensions of functioning.

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Table 1

List of research measures, research assessment constructs, and research measurement time points.

Measure	Type	Construct assessed	Time points
ADIS-5	CS	Diagnosis and severity for affective disorders	BL, PT, FU
Background	SR	Demographic variables and military history	BL
Chart review	CS	Physical health conditions, medications, healthcare utilization	BL, FU
TBI screener	SR	History of traumatic brain injury and related symptoms	BL
APPQ	SR	Symptoms of agoraphobia, social anxiety, and interoceptive avoidance	BL, PT, FU
DASS	SR	Symptoms of depression, anxiety, and stress	BL, BWS, PT, FU
IIRS	SR	Impairment related to symptoms of depression and anxiety	BL, BWS, PT, FU
MASA	SR	Symptoms of avoidance, anhedonia, impairment, and coping with substance use	BL, PT, FU
PCL-5	SR	Symptoms of intrusions, avoidance, numbing, and arousal	BL, PT, FU
STICSA-Trait	SR	Symptoms of cognitive and somatic anxiety	BL, BWS, PT, FU
SF-36V	SR	Physical and mental health symptoms and related impairment	BL, PT, FU
STTS-R	SR	Satisfaction with therapy and therapist	PT, FU

Note. ADIS-5 = Anxiety Disorder Interview Schedule for the DSM-5; TBI = traumatic brain injury; APPQ = Albany Panic and Phobia Questionnaire; DASS = Depression Anxiety Stress Scales; IIRS = Illness Intrusiveness Rating Scale; MASA = Multidimensional Assessment of Social Anxiety; PCL-5 = PTSD Checklist for DSM-5; STICSA-Trait = State Trait Inventory for Cognitive and Somatic Anxiety — Trait Version; SF-36V = Veterans Short-Form Health Survey; STTS-R = Satisfaction with Therapy and Therapist Scale; CS = clinician scored; SR = self-report; BL = baseline; BWS = biweekly sessions (1, 3, 5, 7, 9, and 11); PT = post-treatment; FU = follow-up.