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The Unified Protocol for Transdiagnostic Treatment of Emotional Disorders compared with diagnosis-specific protocols for anxiety disorders: A three-year follow-up

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ABSTRACT

Objective: Compare the long-term efficacy of diagnosis-specific and transdiagnostic cognitive-behavioral therapies (CBT) from a randomized equivalence trial for the treatment of heterogenous anxiety disorders.
Method: Participants were treatment completers (N = 80; 58.8% female) from the parent equivalence trial treated with either the Unified Protocol (UP; $n = 44$) or the single-disorder CBT protocol (SDP; $n = 36$) for their primary anxiety disorder. Clinical interviews were conducted at 24- and 36-month follow-up and self-report questionnaire batteries were completed at 18-, 24-, 30-, and 36-month follow-up. With-in condition effect sizes were calculated to determine maintenance of treatment gains in each treatment condition over time and potential differences between treatment conditions were evaluated using the principal diagnosis clinician severity rating (CSR) from the Anxiety Disorder Interview Schedule (ADIS); additional outcomes included anxiety, depression, and functional impairment.
Results: Treatment gains within each condition were largely maintained at three years post-treatment, with small fluctuations in subclinical symptoms. At 36-month follow-up, the UP and SDP treatment conditions remained comparable on the principal diagnosis ADIS CSR. Although there were some differences on secondary outcomes favoring the SDP condition at intermediate time points, there were no significant differences between the UP and SDP conditions on ADIS CSR or any secondary outcomes at 36-month follow-up.
Conclusions: Results further support the utility of the UP as a single intervention that produces durable treatment effects for the most commonly occurring psychological disorders through demonstration of outcomes commensurate with current first-line SDPs.

1. Introduction

Anxiety disorders remain the most common class of mental health disorders, with a lifetime prevalence rate of 31% in the United States [1]. They are associated with significant distress and functional impairment in social, occupational, and health-related domains, resulting in considerable economic and societal costs [2–4]. Although there is a strong evidence base supporting the efficacy of cognitive behavior therapy (CBT) for the treatment of anxiety disorders in adults [5,6], most studies report exclusively on acute treatment outcome (i.e., post-treatment). Among treatment outcome studies that include a "long-term" follow up, the average follow-up assessment occurs less than six months post-treatment [5], with limited studies following participants for over a year.

However, because anxiety disorders are best characterized as chronic conditions that wax and wane over time, it is crucial that treatment outcome studies assess the efficacy of first line, "gold standard" treatments like CBT over a longer follow-up period. For example, among adults in remission from a past anxiety disorder, it is estimated that approximately 1 out of 4 will meet diagnostic criteria for an anxiety disorder over the course of a two-year follow-up period [7–9]. Although a recent meta-analysis of long-term outcomes of CBT for anxiety

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disorders found that CBT was associated with moderate symptom improvement compared to control conditions up to 12 months post-treatment, these findings are tempered by the low quality (e.g., concerns related to randomization and allocation concealment, unblinded outcome assessment) of most of the clinical trials that were available for inclusion [10]. Thus, there is a need for high-quality clinical trials with more than 12 months of follow-up to draw further conclusions on the long-term effectiveness of CBT for anxiety-related disorders.

The present study is a long-term follow-up of a large, randomized equivalence trial that compared gold standard, single-disorder CBT protocols for the treatment of social anxiety disorder (SOC), generalized anxiety disorder (GAD), obsessive-compulsive disorder (OCD), and panic disorder with or without agoraphobia (PD) with a transdiagnostic protocol [11]. The Unified Protocol for Transdiagnostic Treatment of Emotional Disorders (UP) [12] is an emotion-focused CBT treatment designed to target neuroticism, a temperamental vulnerability that underlies anxiety and related disorders [13,14]. Specifically, the UP addresses heightened negative affect, negative appraisals of emotional experiences, and efforts to avoid, escape, or dampen intense emotions [15]. Large meta-analyses and systematic reviews support the efficacy of the UP as a transdiagnostic intervention that demonstrates results in moderate to large effect sizes for symptom reduction across various clinical presentations over acute follow-up periods, increases in use of adaptive emotion regulation strategies, and benefits in the domains of functional impairment and quality of life [16–18]. The UP has also been found to outperform treatment-as-usual comparison conditions and to exert unique effects on neuroticism, with changes in neuroticism preceding improvements in symptoms of anxiety and depression [19–21].

The use of transdiagnostic protocols like the UP have the potential to address two of the primary challenges in the treatment of anxiety disorders: 1) high rates of comorbidity, and 2) low utilization of evidence-based psychotherapy treatments in routine practice [22]. By targeting shared mechanisms across disorders, the UP is a more cost-effective, efficient approach for addressing multiple emotional disorders concurrently that also could reduce training burden for providers. However, given the chronicity of anxiety disorders and previously reported rates of reoccurrence following treatment, it is necessary to establish the long-term efficacy of the UP relative to existing first-line diagnosis-led CBT treatments for anxiety and related disorders [23].

Results from the parent equivalence trial found that the UP was equally effective as the single-disorder protocols (SDPs) at reducing primary anxiety disorder symptom severity at post-treatment and at a six-month follow-up, with participants who received the UP more likely to complete treatment than those who received an SDP [11]. A recent follow-up study demonstrated that the equivalence between the UP and SDPs was maintained at 12-month follow-up across principal anxiety diagnosis clinical severity ratings, symptoms of anxiety and depression, and functional impairment [24]. The goal of the current study is to the extend these findings by evaluating outcomes over a longer (36-month) follow-up period. The primary objectives were 1) to evaluate whether treatment gains at post-treatment were maintained over a 36-month follow-up period within each treatment condition, 2) to determine whether long-term treatment outcome remained comparable between the UP and SDPs, and 3) to explore rates of treatment response and remission in each treatment condition. Based on prior follow-up studies of the UP [24,25], it is expected that any increases in symptoms will be small in magnitude and largely within the subclinical range, and that the UP and SDPs will remain comparable on principal anxiety disorder clinical severity rating.

2. Methods

2.1. Participants

The present investigation is an extended follow-up study of a recently completed clinical equivalence trial that compared two CBT approaches for anxiety disorders [11]. Participants in the parent study were treatment-seeking individuals who presented to the Center for Anxiety and Related Disorders (CARD) at Boston University. Study inclusion criteria were designed to be broadly inclusive to maximize external validity. Inclusion criteria included (1) a principal (i.e., most interfering, and severe) diagnosis of GAD, PD, OCD, or SOC, (2) 18 years or older, and (3) fluent in English. Exclusion criteria were restricted to conditions that required the prioritization of immediate or simultaneous treatment, including a diagnosis of bipolar disorder, schizophrenia, schizoaffective disorder, or organic mental disorder. In addition, individuals with recent substance use disorder, current high risk of suicide, and those who had received at least eight sessions of CBT within the past five years were excluded. Participants currently taking psychotropic medications were required to be stable for a minimum of six weeks prior to enrollment and agreed to maintain the same medication regimen during treatment.

To be eligible for the extended follow-up study, participants were required to meet the following additional inclusion criteria: (1) randomization to either of the two treatment arms (i.e., the UP or an SDP), (2) classification as a treatment completer as defined by completing 75% or more of prescribed number of treatment sessions (i.e., 9 out of 12 treatment sessions for PD, and 12 out of 16 sessions for SOC, OCD, and GAD), and (3) willing to engage in online assessments at four time points and phone or in-person assessments at two time points over an additional two-year follow-up period (i.e., three years post-treatment and two years following the final 12-month follow-up assessment completed in the parent trial). Study participation was limited to treatment completers to specifically determine the long-term effectiveness among participants who received full, comparative doses of the active treatment.

Of the 223 participants enrolled in the parent study, 179 were randomized to one of the two active treatment conditions. Of those 179, 140 completed 75% of their prescribed number of treatment sessions and were eligible for participation in the long-term follow-up study. Of those eligible, 80 participants were enrolled in the long-term follow-up study; see Fig. 1 for recruitment flow diagram. Participants had an average age of 31.2 years (SD = 10.9), 58.8% self-identified as female, the majority identified racially as White (87.5%), and were well-educated (71.4% of participants had a bachelor's degree or higher). Principal diagnoses were 32.5% (n = 26) GAD, 31.3% (n = 25) SOC, 18.7% (n = 15) PD, and 17.5% (n = 14) OCD; these percentages were comparable to full sample of participants in the parent trial.

2.2. Procedure

For the full description of study procedures for the parent trial, please see Barlow et al. (2017; clinicaltrials.gov identifier: NCT01243606). All procedures were approved by the Institutional Review Board at Boston University.

2.2.1. Treatment

Participants randomized to the SDP condition received the SDP for their principal diagnosis; participants with SOC were offered 16 sessions of Managing Social Anxiety: A Cognitive-Behavioral Therapy Approach, second edition [26], participants with OCD were offered 16 sessions of Treating Your Obsessive-Compulsive Disorder with Exposure and Response (Ritual) Prevention Therapy, second edition [27], participants with GAD were offered 16 sessions of Mastery of Your Anxiety and Worry, second edition [28], and participants with PD were offered 12 sessions of Mastery of Your Anxiety and Panic, fourth edition [29]. Treatment dose (i.e., 12 or 16 sessions) was determined by each SDP's recommended number of sessions. Participants randomized to the UP condition were treated with the UP [12] and received 12 or 16 sessions of the UP depending on their principal diagnosis to match the treatment doses offered in the SDP condition.

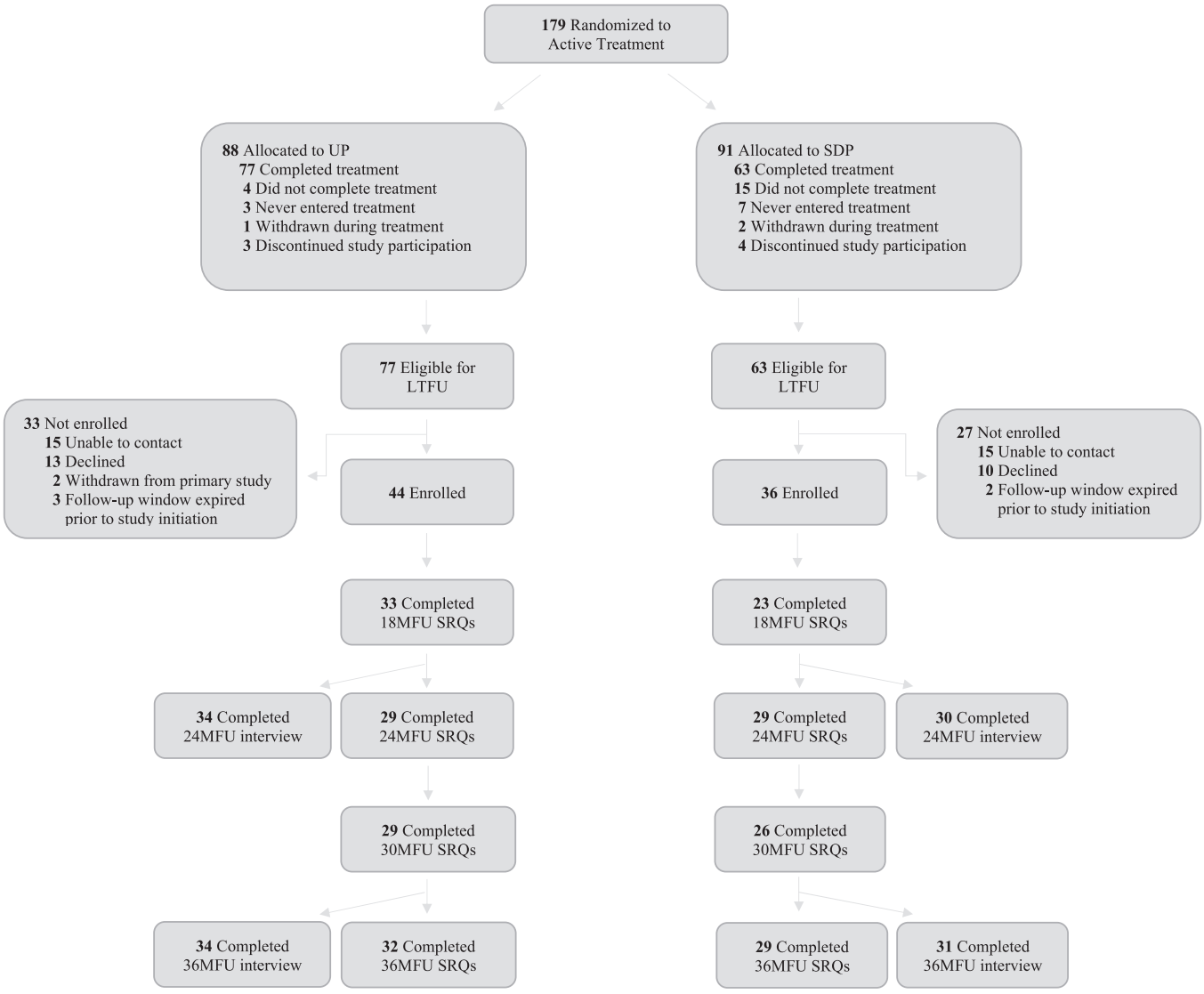

Fig. 1. *Recruitment Flow Diagram.Note.* UP = Unified Protocol for Transdiagnostic Treatment of Emotional Disorders; SDP = single-disorder protocol; LTFU = long-term follow-up; SRQs = self-report questionnaires.

2.2.2. Study recruitment

Participants in the parent trial who met the treatment completer inclusion criteria were informed of their eligibility for the extended follow-up study when their participation in the parent trial was complete (i.e., during or shortly following completion of the 12-month follow-up). Those who were interested in the extended follow-up study were then consented and enrolled.

2.2.3. Assessment

In the parent trial, participants completed self-report and clinician-administered assessments at 6- and 12-month follow-up and received $50 compensation for each assessment. For the extended follow-up study, participants were contacted to complete additional assessments occurring at 6-month intervals to obtain 18-, 24-, 30-, and 36-month follow-up data. In addition to the self-report battery administered at each assessment, participants were asked to complete a clinical interview at the 24- and 36-month time points. Participants in the extended follow-up study were compensated $25 and $50 for each self-report battery and clinical interview completed, respectively. Questionnaire batteries and assessment procedures were kept consistent with the parent trial; all clinician-rated questionnaires were administered by independent evaluators from the parent trial who were trained to a high level of inter-rater reliability and blinded to participant treatment condition [11].

2.3. Measures

Clinician-rated measures were assessed at 6- and 12-month follow-up in the parent study and 24- and 36-month follow-up in the present study. Self-report measures were completed at all time points (i.e., 6-, 12-, 18-, 24-, 30, and 36-month follow-up).

2.3.1. Principal diagnosis clinical severity rating

Participants were assessed for diagnosis and clinical severity using the Anxiety Disorders Interview Schedule (ADIS) [30,31], a semi-structured interview that assigns a dimensional clinical severity rating (CSR) on a scale from 0 (*no symptoms*) to 8 (*extremely severe symptoms*), with 4 or higher (*definitely disturbing or disabling*) representing the clinical threshold for *DSM* diagnostic criteria. The ADIS has demonstrated acceptable to excellent interrater reliability for the anxiety and mood disorders [32]. Consistent with the parent trial, the CSR for participants' principal diagnosis was used as the primary outcome for comparison between treatment conditions.

2.3.2. Global symptom severity and improvement

The Clinical Global Impression Severity (CGI-S) and Improvement Scales (CGI-I) [33] are widely used clinician-rated instruments that assess global severity across all diagnoses and improvement from baseline. The CGI-S assesses global severity on a 7-point scale ranging from 1 (*normal*) to 7 (*extremely ill*). The CGI-I assesses the degree of clinical change that has occurred from baseline to the current assessment point on a 7-point scale ranging from 1 (*very much improved*) to 7 (*very much worse*). The CGI scales have demonstrated reliability and validity as a clinical out measure across diagnostic groups, including sensitivity to change [34].

2.3.3. Clinician-rated symptoms of anxiety and depression

The Hamilton Anxiety and Depression Rating Scales [35,36] are among the most widely used clinical interview assessment tools for symptoms of anxiety and depression. The anxiety scale consists of 14 items that assesses both psychological and physical symptoms of anxiety, with scores ranging from 0 to 56. The depression scale consists of 17 items and similarly assesses for symptoms of depression and general somatic symptoms, with scores ranging from 0 to 68. Both scales were administered in accordance with the Structured Interview Guide for the Hamilton Anxiety (SIGH-A) [37] and Depression Rating Scale (SIGH-D) [38], which includes specific instructions on administration and anchor points for assigning severity ratings and has demonstrated superior inter-rater and test-retest reliability [39].

2.3.4. Self-reported symptoms of anxiety and depression

Participants rated their symptoms of anxiety and depression using the Overall Anxiety and Severity Impairment Scale (OASIS) [40] and the Overall Depression and Severity Impairment Scale (ODSIS) [41]. The OASIS and ODSIS are each brief 5-item questionnaires designed to assess dimensional symptom severity and associated interference for anxiety and depression, respectively. Scores range from 0 to 20, with a suggested clinical threshold of 8. Both measures have demonstrated good internal consistency, excellent test-retest reliability, and convergent and divergent validity [40,41].

2.3.5. Functional impairment

Interference related to symptoms was clinician-rated using the Work and Social Adjustment Scale (WSAS) [42,43], a 5-item descriptive measure assessing the degree of interference caused by the participant's symptoms in work, home management, private leisure, social leisure, and family relationships. Interference was rated over the past week on a 0 (*not at all interfering*) to 8 scale (*severe interference*), with total scores ranging from 0 to 40. The WSAS has demonstrated high reliability and sensitivity [44].

2.3.6. Additional treatment

At each clinical interview, participants were asked to report their current medication use and whether they had sought any additional treatment since their last study assessment (i.e., over the course of the past year), including CBT, psychotherapy or counseling, self-help or support groups, couples or marital counseling, or non-routine medical care. For any additional treatment, participants were asked to specify the reason for treatment (e.g., anxiety, depression, epilepsy, attention difficulties, etc.).

2.4. Data analysis

A series of chi-square analyses and one-way analyses of variance (ANOVAs) were conducted to determine (a) whether participants enrolled in the extended follow-up study differed from those who were eligible and did not participate in any key demographic variables or in any clinical characteristics at the point of study enrollment (i.e., 12MFU), and (b) whether participants who participated in the extended follow-up differed from the original intent-to-treat sample in any key demographic variables or in any clinical characteristics at the point of study enrollment (i.e., 12MFU). Receipt of additional treatment data during the follow-up period were reported qualitatively and chi-square analyses were conducted to determine whether participants who sought additional treatment for anxiety, depression, or related reasons during the extended follow-up window differed in any meaningful ways from those who did not seek additional treatment.

Analyses were conducted using Mplus version 7 [45] and IBM SPSS Statistics (Version 27) on the full sample that consented to the long-term follow-up (N = 80). Missing data were accommodated using multiple imputation (10,000 imputed data sets) in Mplus under a missing at random assumption. To test the hypothesis that treatment gains would be maintained across the 36-month period, within-condition changes across time-points were tested using a 95% CI of within-condition effect sizes (standardized gains, ES*sg*). To test the hypothesis that long-term outcomes would be comparable between treatment conditions, between condition differences in principal diagnosis ADIS CSR and secondary outcomes were tested using a 95% CI of between-condition effect sizes (Hedge's *g*).[1] Both within condition effect sizes (UP, SDP) and between condition effect sizes (UP vs. SDP) were calculated using the imputed datasets. Effect sizes are considered statistically significant if the 95% CI does not include zero. Notably, previous studies using this dataset [11,24] were designed (powered) to tested *equivalence* between UP and SDP, using slope difference scores from latent growth models (LGMs). Because only a subset of participants was enrolled in this extended follow-up study, the current sample is underpowered to test for equivalence and LGMs could not be estimated due to issues with model convergence and fit.

Consistent with previous papers published from the parent trial [11,24], treatment response also was examined by comparing the proportion of participants in each condition who no longer met criteria for their principal diagnosis (i.e., principal diagnosis CSR $\leq$ 3). Exploratory analyses were also conducted to examine the proportion of participants in each condition who no longer met criteria for any of the emotional disorders with which they were diagnosed at the baseline assessment.

3. Results

3.1. Group comparisons

For the first comparison (a), there were no significant differences between eligible participants who participated in the extended follow-up and eligible participants who did not in age, F (1, 133) = 1.77, p = .186; sex, χ^2 (1, N = 135) = .48, p = .488; race, χ^2 (4, N = 135) = 2.50, p = .644; treatment condition, χ^2 (1, N = 135) = .03, p = .876; principal diagnosis, χ^2 (3, N = 135) = 6.90, p = .075; SDP received, χ^2 (4, N = 135) = 1.64, p = .802, or; principal diagnosis CSR at the point of study enrollment (i.e., 12MFU), F (1, 124) = .370, p = .544.

For the second comparison (b), there were no significant differences between participants who enrolled in the extended follow-up study and the original intent-to-treat sample in age, F (1, 179) = .398, p = .529; sex, χ^2 (1, N = 179) = .69, p = .405; race, χ^2 (4, N = 179) = .4.28, p = .371; treatment condition, χ^2 (1, N = 179) = .1.97, p = .160; principal diagnosis, χ^2 (3, N = 179) = 5.86, p = .118, or; SDP received, χ^2 (4, N = 179) = 4.41, p = .354. At the point of study enrollment (i.e., 12MFU), there were no significant differences between participants who enrolled in the extended follow-up study and the original intent-to-treat sample in principal diagnosis CSR, F (1, 135) = .038, p = .847; self-reported anxiety on the OASIS, F (1, 126) = .006, p = .940; clinician-rated anxiety on the SIGH-A, F (1, 133) = .056, p = .813; self-reported depression on the ODSIS, F (1, 126) = .001, p = .977; clinician-rated

[1] We attempted to estimate latent growth models in Mplus, consistent with our prior studies, but issues surrounding model convergence and fit precluded this approach.

depressive symptoms on the SIGH-A, F (1, 133) = .056, p = .813, or; clinician-rated functional impairment on the WSAS, F (1, 134) = .177, p = .674.

3.2. Medication use and additional treatment

At 24-month follow-up, 80% of participants (n = 64; 30 in the SDP condition, 34 in the UP condition) completed the clinical interview portion of the assessment and therefore had current medication and additional treatment data available. For the 36-month follow-up, 81.3% (n = 65; 31 in the SDP condition, 34 in the UP condition) of participants completed the clinical interview and provided medication and additional treatment data.

At 24-month follow-up, 30 participants (46.9%) reported current use of psychotropic medication for anxiety, depression, or related reasons (e.g., OCD). Of these 30 participants, 15 were in the UP condition and 16 were in the SDP condition. At 36-month follow-up, 29 participants (44.6%) reported current use of psychotropic medication for anxiety, depression, or related reasons. Of these 29 participants, 12 were in the UP condition and 17 were in the SDP condition. This rate of psychotropic medication use was slightly lower than rates observed at baseline where 48 out of 72 long-term follow-up participants with available data (60%) were currently using psychotropic medication, with 27 of those being in the UP condition and 21 in the SDP condition. Differences in medication use between treatment conditions were not statistically significant at baseline, χ^2 (1, N = 78) = 0.29, p = .590, 24-month follow-up, χ^2 (1, N = 64) = 0.54, p = .462, or 36-month follow-up, χ^2 (1, N = 63) = 3.43, p = .064.

At 24-month follow-up, 13 participants (20.3%) reported receiving additional CBT or psychotherapy for anxiety and/or depression during the past year; eight participants were in the UP condition and five were in the SDP condition. At 36-month follow-up, 16 participants (24.6%) reported receiving additional CBT or psychotherapy for anxiety and/or depression during the past year; 11 participants were in the UP condition and five were in the SDP condition. There were no statistically significant differences between treatment conditions in the report of additional CBT or psychotherapy for anxiety and/or depression at 24-month follow-up, χ^2 (1, N = 49) = .783, p = .376, or 36-month follow-up, χ^2 (1, N = 52) = 2.07, p = .151.

3.3. Maintenance of treatment gains within treatment condition

Standardized gains effect sizes (ES*sg*) were calculated within each condition to evaluate maintenance of treatment gains from post-treatment to 6-, 12-, 18-, 24-, 30-, and 36-month follow-up among treatment completers. In the UP condition (*see* Table 1), there were no significant differences in outcomes between post-treatment and 36-month follow-up. There were some significant differences between post-treatment outcomes and intermediate follow-up time points that ranged from small to medium in magnitude. These differences reflected increases on self-report measures of anxiety and depressive symptoms and decreases in a clinician-rated measure of global improvement, suggesting that while there were some increases in symptoms during the follow-up period, these fluctuations stabilized over time and were no longer significant by 36-months post-treatment.

In the SDP condition (*see* Table 2), there were no significant differences in outcomes between post-treatment and 36-month follow-up. There was a significant decrease in the primary outcome (ADIS CSR) at both 12- and 36-month follow-up compared to post-treatment. However, at post-treatment, ADIS CSR scores were slightly (but non-significantly) higher in the SDP condition (M = 3.23, *SD* = 1.63) than the UP condition (M = 2.81, *SD* = 1.68), which may reflect a slower trajectory of change for participants treated with an SDP. There was also a significant decrease in self-reported depressive symptoms and associated interference (ODSIS) at 30-month follow-up for the SDP condition, but not at 36-month follow-up.

3.4. Clinical significance of symptoms over long-term follow-up

Across both conditions, the average principal anxiety disorder clinical severity rating (ADIS CSR) remained below diagnostic threshold (i.e., <4) during the extended follow-up period (*for descriptive statistics, see* Table 3). Clinician-rated symptoms of anxiety (SIGH-A) and depression (SIGH-D) reflected mild levels of anxiety [46] and subclinical levels of depression [47] across all time points. Self-reported symptom severity and associated interference attributed to anxiety (OASIS) and depression (ODSIS) also both remained below the clinical threshold (i.e., < 8) throughout the follow-up period. Participant ratings of their functional impairment across work, home management, private leisure, social leisure, and family relationships remained below the recommended cutoff score of 10. Global symptom severity (CGI-S) and improvement (CGI-I) ratings suggest that up to three years post-treatment, participants in both conditions remained in the borderline to mild overall symptom severity categories and much improved compared to their baseline symptom severity.

3.5. Between condition comparisons

There were no statistically significant differences between the UP and SDPs in the primary outcome of principal anxiety disorder severity rating (ADIS CSR) at any follow-up point (*see* Table 3; Fig. 2). Further, all between-condition effect sizes were small in magnitude (Hedges' *g* ranged from −0.11 to 0.26). Secondary outcomes for each condition are presented graphically with clinical thresholds in Supplement 1. At 24-

Table 1
Within Condition Effect Sizes, UP, n = 44.

Measure	ESsg Post-6MFU	ESsg Post-12MFU	ESsg Post-18MFU	ESsg Post-24MFU	ESsg Post-30MFU	ESsg Post-36MFU
Primary Clinician-Rated Outcome						
ADIS CSR	-0.05 (−0.27, 0.18)	-0.03 (−0.27, 0.21)		0.01 (−0.29, 0.21)		-0.11 (−0.38, 0.17)
Additional Clinician-Rated Outcomes						
CGI-S	-0.08 (−0.34, 0.17)	-0.09 (−0.34, 0.16)		0.13 (−0.20, 0.45)		0.03 (−0.29, 0.35)
CGI-I	0.24 (−0.04, 0.51)	0.16 (−0.19, 0.51)		**0.51 (0.11, 0.91)**		0.18 (−0.23, 0.60)
SIGH-A	-0.07 (−0.27, 0.13)	-0.02 (−0.22, 0.19)		-0.17 (−0.37, 0.03)		-0.11 (−0.37, 0.14)
SIGH-D	-0.02 (−0.24, 0.21)	-0.02 (−0.25, 0.21)		0.12 (−0.12, 0.37)		0.01 (−0.33, 0.34)
WSAS	-0.11 (−0.40, 0.18)	-0.05 (−0.33, 0.24)		0.13 (−0.18, 0.44)		0.05 (−0.24, 0.34)
Self-Reported Outcomes						
OASIS	0.13 (−0.14, 0.39)	0.22 (−0.04, 0.49)	**0.42 (0.11, 0.74)**	**0.33 (0.02, 0.64)**	**0.46 (0.14, 0.78)**	0.22 (−0.06, 0.51)
ODSIS	0.07 (−0.17, 0.31)	0.03 (−0.22, 0.28)	**0.30 (0.00, 0.61)**	0.21 (−0.11, 0.53)	0.20 (−0.10, 0.51)	0.03 (−0.28, 0.33)

Note. ADIS CSR = Clinical Severity Rating from the Anxiety and Related Disorders Interview Schedule for DSM-5. CGI-S = Clinical Global Impression-Severity. CGI-I = Clinical Global Impression-Improvement. SIGH-A = Structured Interview Guide for the Hamilton Anxiety Scale. SIGH-D = Structured Interview Guide for the Hamilton Depression Scale. OASIS = Overall Anxiety Severity and Interference Scale. ODSIS = Overall Depression Severity and Interference Scale. WSAS = Work and Social Adjustment Scale. Positive effect sizes denote an increase in scores and negative effect sizes denote a decrease in scores. Bold values represent statistically significant change (p < .05).

Table 2
Within Condition Effect Sizes, SDP, n = 36.

Measure	ESsg Post-6MFU	ESsg Post-12MFU	ESsg Post-18MFU	ESsg Post-24MFU	ESsg Post-30MFU	ESsg Post-36MFU
Primary Clinician-Rated Outcome						
ADIS CSR	-0.17 (−0.43, 0.09)	**-0.47 (−0.78, −0.16)**		-0.33 (−0.67, 0.01)		**-0.51 (−0.81, −0.21)**
Additional Clinician-Rated Outcomes						
CGI-S	-0.13 (−0.33, 0.07)	-0.22 (−0.51, 0.06)		-0.14 (−0.45, 0.18)		-0.28 (−0.58, 0.02)
CGI-I	-0.06 (−0.32, 0.20)	-0.13 (−0.41, 0.15)		0.06 (−0.33, 0.45)		-0.01 (−0.38, 0.35)
SIGH-A	0.01 (−0.24, 0.26)	-0.12 (−0.41, 0.18)		-0.07 (−0.48, 0.33)		-0.14 (−0.50, 0.22)
SIGH-D	0.13 (−0.15, 0.40)	-0.15 (−0.49, 0.19)		-0.22 (−0.63, 0.20)		-0.04 (−0.42, 0.34)
WSAS	-0.01 (−0.22, 0.20)	-0.07 (−0.40, 0.26)		-0.16 (−0.51, 0.19)		-0.06 (−0.38, 0.25)
Self-Reported Outcomes						
OASIS	-0.09 (−0.36, 0.18)	-0.10 (−0.39, 0.19)	0.13 (−0.31, 0.56)	-0.15 (−0.49, 0.18)	-0.18 (−0.51, 0.15)	-0.05 (−0.36, 0.25)
ODSIS	-0.09 (−0.32, 0.14)	-0.14 (−0.43, 0.14)	0.12 (−0.26, 0.51)	-0.29 (−0.66, 0.08)	**-0.38 (−0.74, −0.02)**	-0.23 (−0.57, 0.11)

Note. ADIS CSR = Clinical Severity Rating from the Anxiety and Related Disorders Interview Schedule for DSM-5. CGI-S = Clinical Global Impression-Severity. CGI-I = Clinical Global Impression-Improvement. SIGH-A = Structured Interview Guide for the Hamilton Anxiety Scale. SIGH-D = Structured Interview Guide for the Hamilton Depression Scale. OASIS = Overall Anxiety Severity and Interference Scale. ODSIS = Overall Depression Severity and Interference Scale. WSAS = Work and Social Adjustment Scale. Positive effect sizes denote an increase in scores and negative effect sizes denote a decrease in scores. Bold values represent statistically significant change ($p < .05$).

month follow-up, there were significant differences favoring SDPs over the UP for self-reported depressive symptoms and interference (ODSIS; UP M (SD) = 3.96 (4.47), SDP M (SD) = 2.03 (3.69), Hedges' $g = .46$) and clinician-rated depressive symptoms (SIGH-D; UP M (SD) = 7.65 (5.69), SDP M (SD) = 4.77 (3.96), Hedges' $g = .56$) that were moderate in magnitude. At 30-month follow-up, there were significant differences that were also moderate in magnitude between treatment conditions on both self-reported anxiety (OASIS; UP M (SD) = 6.17 (4.06), SDP M (SD) = 4.47 (3.36), Hedges' $g = .45$) and depression (ODSIS; UP M(SD) = 3.93 (4.36), SDP M (SD) = 1.87 (3.31), Hedges' $g = .52$) in favor of the SDP condition. However, at 36-month follow-up, there were no significant differences between treatment conditions on any outcomes and all the non-significant differences were small in magnitude.

3.6. Remission at long-term follow-up

The percentage of participants who no longer met diagnostic criteria for their principal anxiety diagnosis disorder was calculated for each treatment condition for the present sample of treatment completers who participated in the extended follow-up assessments. At post-treatment, 67.8% of participants in the UP condition no longer met criteria for their principal diagnosis, compared to 49.5% of individuals in the SDP condition. At 36-month follow-up, 61.6% of participants in the UP condition no longer met criteria for their principal diagnoses, compared to 73.2% of participants in the SDP condition.

Consistent with the parent study, the proportion of participants who met diagnostic criteria for any of the emotional disorders with which they were diagnosed at baseline was calculated within each condition across the follow-up period (*see* Table 4). In the present sample, 52.9% of participants treated with the UP and 48.6% of participants treated with an SDP achieved remission from any emotional disorder at 36-month follow-up.

4. Discussion

The objective of the present study was three-fold. First, the maintenance of treatment gains over a long-term follow-up of three years for two types of CBT interventions (i.e., transdiagnostic and diagnosis-led) for anxiety disorders from a randomized equivalence trial were evaluated. Results suggest that treatment gains observed at acute outcome in a sample of treatment completers were largely maintained up to three years later for both the UP and SDP treatment conditions. Any increases in symptoms across the follow-up period were small to moderate in magnitude, with average symptom and impairment scores remaining either below clinical thresholds or categorized as mild at all time points. Outcomes at 36-month follow-up did not significantly differ from post-treatment in either condition.

Second, long-term outcomes for the UP were compared to the current first-line treatment for anxiety disorders, SDPs, to determine whether the comparable outcomes observed between treatment conditions at post-treatment, 6-month, and 12-month follow-up in the intent-to-treat sample [11,24] were maintained in a sample of treatment completers. Symptoms of anxiety and depression were greater in the UP condition than the SDP condition at 24- and 30-month follow-up assessments, with small mean differences in symptom levels (e.g., 1–2 points on the OASIS and ODSIS, < 3 points on the SIGH-D). At the final assessment (i.e., 36-months post-treatment), both conditions were comparable across all outcomes. Third, rates of clinical remission were explored in each treatment condition. At 36-month follow-up, 61.6% and 73% of participants in the UP and SDP condition, respectively, were in remission from their principal anxiety diagnosis. These findings collectively demonstrate that treatment response to both types of intervention was robust and enduring.

In a prior study of the long-term outcome of the UP, participants evidenced marginal worsening from 6-month to 18-month follow-up that was most pronounced for self-reported symptoms of depression and anxiety [25]. It was unclear at 18-month follow-up if these small to moderate increases in symptoms reflected small symptom fluctuations that would stabilize with time or a gradual deterioration preceding full disorder reoccurrence. Participants treated with the UP in the present study demonstrated similar increases in self-reported symptoms of anxiety and depression between 12- and 30-months post-treatment; however, these small to moderate symptom increases appeared to return to post-treatment levels by 36-month follow-up. In the SDP condition, participants appeared to, on average, experience a small increase in self-reported anxiety and depressive symptoms around the 18-month follow-up and these increases seemed to return to post-treatment levels faster than in the UP condition. In the absence of further follow-up, it is unclear whether these mild symptom increases reflect less overall stability of treatment gains with the UP or a marginal worsening of symptoms that is not necessarily indicative of further deterioration.

It has been suggested that when comparing transdiagnostic interventions to established disorder-specific CBT protocols, transdiagnostic protocols might prove to be less efficacious for the treatment of the primary diagnosis and slightly more efficacious for comorbid disorders [23,48]. Data from the present study do not support these hypotheses and instead demonstrate that the UP was as efficacious as the SDPs on the principal anxiety diagnosis clinical severity rating across all time points. These findings are consistent with prior studies where the UP was found to be equally efficacious in reducing symptoms of comorbid emotional disorders as SDPs up to 12-months post-treatment [49].

The results of the present study must be considered in the context of several limitations. First, this study utilized a sample of treatment

Table 3
Descriptive Data and Between Condition Effect Sizes.

Measure	Treatment Group	Descriptive statistics Mean (standard deviation)							Effect sizes Hedge's *g* (95% confidence interval)						
		Post-Tx	6MFU	12MFU	18MFU	24MFU	30MFU	36MFU	Post-Tx	6MFU	12MFU	18MFU	24MFU	30MFU	36MFU
Primary Clinician-Rated Outcome															
ADIS CSR	UP $n = 44$	2.81 (1.68)	2.73 (1.73)	2.77 (1.52)		2.83 (1.81)		2.63 (1.76)	-0.26 (−0.70, 0.18)	-0.11 (−0.55, 0.33)	0.20 (−0.25, 0.64)		0.15 (−0.29, 0.59)		0.13 (−0.31, 0.57)
	SDP $n = 36$	3.25 (1.63)	2.93 (1.96)	2.44 (1.74)		2.57 (1.79)		2.40 (1.69)							
Additional Clinician-Rated Outcomes															
CGI-S	UP $n = 44$	2.95 (1.24)	2.84 (1.48)	2.83 (1.42)		3.13 (1.48)		3.00 (1.48)	-0.22 (−0.66, 0.23)	-0.15 (−0.59, 0.29)	-0.09 (−0.53, 0.35)		0.07 (−0.37, 0.51)		0.09 (−0.35, 0.53)
	SDP $n = 36$	3.22 (1.23)	3.05 (1.39)	2.94 (1.25)		3.04 (1.25)		2.87 (1.32)							
CGI-I	UP $n = 44$	2.08 (0.98)	2.36 (1.26)	2.27 (1.27)		2.67 (1.45)		2.29 (1.22)	-0.21 (−0.65, 0.23)	0.10 (−0.34, 0.54)	0.09 (−0.35, 0.53)		0.23 (−0.22, 0.67)		0.38 (−0.06, 0.83)
	SDP $n = 36$	2.29 (0.99)	2.23 (1.17)	2.17 (0.93)		2.36 (1.25)		1.87 (0.88)							
SIGH-A	UP $n = 44$	9.85 (7.52)	9.28 (8.13)	9.72 (7.65)		8.90 (6.82)		9.02 (6.86)	0.28 (−0.16, 0.73)	0.18 (−0.26, 0.62)	0.38 (−0.06, 0.82)		0.25 (−0.19, 0.69)		0.32 (−0.13, 0.76)
	SDP $n = 36$	7.84 (6.22)	7.91 (6.60)	7.17 (5.18)		7.38 (5.01)		7.04 (5.22)							
SIGH-D	UP $n = 44$	7.15 (5.58)	7.02 (7.21)	7.03 (5.96)		7.65 (5.69)		7.18 (5.33)	0.26 (−0.18, 0.71)	0.08 (−0.36, 0.52)	0.36 (−0.08, 0.81)		**0.57 (0.12, 1.02)**		0.31 (−0.14, 0.75)
	SDP $n = 36$	5.78 (4.60)	6.47 (5.87)	5.11 (4.22)		4.77 (3.96)		5.58 (5.04)							
WSAS	UP $n = 44$	6.92 (6.43)	6.19 (6.86)	6.59 (6.97)		7.89 (7.67)		7.23 (6.82)	-0.03 (−0.47, 0.41)	-0.12 (−0.56, 0.32)	-0.02 (−0.46, 0.42)		0.27 (−0.17, 0.71)		0.08 (−0.36, 0.52)
	SDP $n = 36$	7.08 (5.94)	7.01 (7.13)	6.69 (5.72)		6.08 (5.30)		6.72 (5.91)							
Self-Reported Outcomes															
OASIS	UP $n = 44$	4.51 (2.96)	4.99 (4.27)	5.26 (3.65)	6.04 (4.05)	5.76 (3.91)	6.17 (4.06)	5.28 (3.80)	-0.18 (−0.62, 0.26)	0.05 (−0.39, 0.49)	0.15 (−0.29, 0.59)	0.12 (−0.32, 0.57)	0.34 (−0.10, 0.78)	**0.45 (0.00, 0.89)**	0.10 (−0.34, 0.55)
	SDP $n = 36$	5.09 (3.46)	4.77 (3.61)	4.74 (3.22)	5.55 (3.79)	4.55 (2.99)	4.47 (3.36)	4.90 (3.38)							
ODSIS	UP $n = 44$	3.08 (3.67)	3.36 (4.37)	3.21 (3.89)	4.33 (4.50)	3.96 (4.47)	3.93 (4.36)	3.18 (4.01)	-0.02 (−0.46, 0.42)	0.13 (−0.31, 0.57)	0.15 (−0.29, 0.59)	0.17 (−0.27, 0.61)	**0.46 (0.02, 0.91)**	**0.52 (0.07, 0.97)**	0.22 (−0.22, 0.66)
	SDP $n = 36$	3.14 (3.37)	2.82 (3.73)	2.66 (3.38)	3.59 (3.89)	2.03 (3.69)	1.87 (3.31)	2.28 (4.10)							

Note. ADIS CSR = Clinical Severity Rating from the Anxiety and Related Disorders Interview Schedule for DSM-5. CGI-S = Clinical Global Impression-Severity. CGI-I = Clinical Global Impression-Improvement. SIGH-A = Structured Interview Guide for the Hamilton Anxiety Scale. SIGH-D = Structured Interview Guide for the Hamilton Depression Scale. OASIS = Overall Anxiety Severity and Interference Scale. ODSIS = Overall Depression Severity and Interference Scale. WSAS = Work and Social Adjustment Scale. Positive effect sizes denote an increase in scores and negative effect sizes denote a decrease in scores. Bold values represent statistically significant change ($p < .05$).

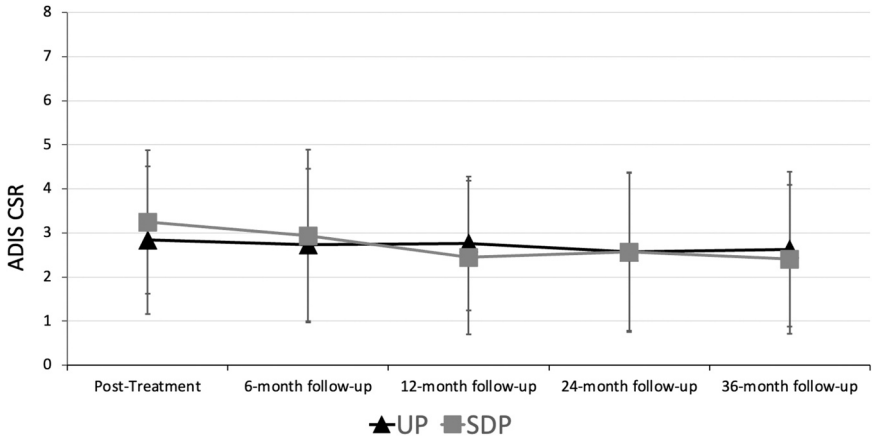

Fig. 2. Principal Diagnosis ADIS CSR Score Trajectories Across Follow-Up, Note: ADIS CSR = Clinical Severity Rating for principal diagnosis obtained from Anxiety and Related Disorders Interview Schedule for DSM-5. SDP = Single Disorder Protocol. UP = Unified Protocol for Transdiagnostic Treatment of Emotional Disorders.

Table 4
Treatment Response Across Follow-Up.

Outcome	Time point	Treatment response	
		UP	SDP
Principal diagnosis	Post-Tx	67.8	49.5
	6MFU	67.6	49.7
	12MFU	68.2	63.9
	24MFU	63.8	71.0
	36MFU	61.6	73.2
Any emotional disorder	Post-Tx	64.1	36.4
	6MFU	55.6	32.4
	12MFU	62.8	52.8
	24MFU	52.9	63.3
	36MFU	52.9	48.6

Note. Treatment response is defined as the percentage of participants in each condition who no longer met diagnostic criteria at each assessment (i.e., CSR<4). "Any emotional disorder" refers only to the disorders for which participants met diagnostic criteria at baseline (i.e., CSR >= 4 at baseline), as these were the only disorders that were re-assessed at subsequent time points.

completers from a randomized equivalence trial and therefore was not powered to test clinical equivalence between conditions. As a result of the small sample size, we were unable to conduct LGMs due to issues with model convergence and fit. Given this significant limitation, effect size magnitudes are reported and should be considered in addition to statistical significance, as it is possible that there were meaningful differences in outcomes between conditions that we were unable to detect. Next, this study reports on cross-sectional outcomes that reflect participant functioning at discrete time periods; reference windows for assessment measures ranged from one week to one month. These outcomes are therefore only reflective of participant functioning during that moment in time and consequently may conceal other periods of worse functioning or meaningful symptom fluctuation over the course of the follow-up period. Furthermore, outcomes for each treatment condition are presented in aggregate and individual patterns of response during follow-up are thus obscured. It is possible that a more idiographic analysis of individual participant response would reveal significant symptom reoccurrence between follow-up assessments. However, given that many participants were in remission at 36-month follow-up, it is also possible that participants were better equipped to cope with symptom fluctuations following a course of CBT.

Although treatment seeking behavior was assessed at each clinical interview, it is possible that rates of treatment were underreported. Moreover, due to our small sample size and missing data, it was not possible to systematically quantify the effect of treatment seeking on outcomes. While rates of additional CBT or therapy and medication use for anxiety and/or depression did not significantly differ between the UP and SDPs at any timepoint, it is interesting that at 36-month follow-up a greater proportion of participants who reported additional psychotherapy were in the UP condition and a greater proportion of participants who reported current medication use were in the SDP condition. The UP promotes acceptance of intense emotions and focuses on changing the ineffective action tendences associated with them, with a module focused on how emotions are adaptive and serve an important function. Future research on patient preferences for treatment should explore whether the UP produces greater willingness to experience uncomfortable emotions, if that influences decisions about what type of treatment to pursue if symptoms reoccur, and at what symptom threshold.

Importantly, given our small sample size, it is unclear given whether receipt of additional treatment (either psychotherapy or medication use) differentially impacted outcomes in either treatment condition. In particular, due to incomplete longitudinal data across timepoints, it was not possible to characterize how psychotropic medication use changed over the follow-up period. Since psychotropic medication usage data were limited to a dichotomous variable reflecting presence or absence, it is unknown whether medication use at follow-up timepoints represents an increase or decrease in medication dosage, which may obscure important differences between groups for this outcome. Since receipt of additional treatment is rarely reported in psychotherapy outcome studies, it would be informative for future studies to collect more precise data on psychotropic medication usage and motivations for seeking further treatment. For example, it is noteworthy that a considerable proportion of the sample were still on psychotropic medication or engaged in psychotherapy for anxiety or depression when average scores on clinical outcomes were below threshold or mild.

While retention among enrolled participants was moderate (i.e., ranging from approximately 64–86% across the various time points) and comparable to other studies, only 57% of participants eligible for the long-term follow-up study were enrolled. It is reassuring that among eligible participants, there were no difference between those who enrolled and those who did not on any key demographic variables, treatment condition, or clinical severity. Additionally, although we limited study participation to treatment completers, our sample of completers who enrolled in the long-term follow-up study did not differ on any key demographic or clinical variables from the intent-to-treat sample. However, it is still possible that these two groups differed from one another in other ways that limit generalizability. Other aspects of the study sample, namely lack of racial diversity and high educational attainment, may also impact the generalizability of findings. These limitations should be addressed in future studies by recruiting more diverse samples across a range of identities.

Strengths of the study include the use of a high-quality randomized

clinical equivalence trial to recruit participants. There were substantial therapist and intervention quality assessments, two active treatment conditions, clinician-rated and self-reported outcomes, and minimal exclusion criteria to maximize external validity. Clinical interviews were conducted by independent evaluators blinded to participant treatment assignment to protect against differential assessment of outcomes. These aspects of study design facilitate greater confidence in the validity of study findings and the effect size estimates for the long-term efficacy of CBT for anxiety disorders across both treatment conditions, in contrast to existing RCTs for long-term efficacy of CBT, which tend to be less methodologically rigorous [10].

Given the chronic nature of anxiety disorders, longer follow-up periods will be necessary to further characterize the maintenance of treatment gains and better inform efforts to preserve treatment gains. For example, there may be optimal times to reinforce treatment gains and skill usage among treatment responders to protect against full disorder reoccurrence and maximize the return-on-investment of CBT interventions for participants and healthcare systems alike. In the present study, even though average symptom scores remained subclinical or in the mild range, most participants reported receiving additional treatment at some point during the follow-up period. It would be helpful to better understand the motivation behind additional treatment seeking as an avenue for the augmentation of existing interventions or the development of booster session protocols.

Nevertheless, it is promising that up to three years post-treatment, approximately two-thirds of participants remained in remission from their primary anxiety disorder diagnosis across both CBT treatment conditions. The UP continues to demonstrate comparable effectiveness to existing gold-standard diagnosis-led CBT protocols, which further supports its utility as one cost-effective, evidence-based protocol that can be utilized with a broad range of clinical presentations. Although the UP has the potential to mitigate implementation barriers within healthcare systems by minimizing the training burden on providers, it is necessary to first establish that outcomes are at least comparable to existing first-line diagnosis-led protocols at both acute and long-term outcome.

Findings from the present study represent a substantial contribution to the evidence base for the utility of the UP as a vehicle for increasing access to and the impact of evidence-based mental health treatments for the most commonly occurring psychological disorders. It will be important for future studies to assess the ease of training providers in the UP and the ability of providers to deliver the UP with sufficient fidelity to determine whether transdiagnostic protocols are able to fully deliver on their promise.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: David H. Barlow reports financial support was provided by National Institute of Mental Health. Jacqueline R. Bullis reports financial support was provided by Barlow Research Foundation. Dr. Barlow reported receiving royalties from Oxford University Press (which includes royalties for all 5 treatment manuals included in this study), Guilford Publications Inc, Cengage Learning, and Pearson Publishing; receiving grants from the National Institute of Mental Health, the National Institute of Alcohol and Alcohol Abuse, and Colciencias (Government of Columbia Initiative for Science, Technology, and Health Innovation); serving as a consultant for and receiving honoraria from the Agency for Healthcare Research and Quality, the Foundation for Informed Medical Decision Making, the Department of Defense, the Renfrew Center, the Chinese University of Hong Kong, Universidad Católica de Santa Maria (Arequipa, Peru), New Zealand Psychological Association, Hebrew University of Jerusalem, Mayo Clinic, and various American universities. Dr. Farchione reported receiving royalties from Oxford University Press for one of the treatment manuals included in this study. The other authors have no conflicts of interest to declare.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.xjmad.2023.100024.

References

[1] Kessler RC, Aguilar-Gaxiola S, Alonso J, Chatterji S, Lee S, Ormel J, Wang PS. The global burden of mental disorders: an update from the WHO World Mental Health (WMH) surveys. Epidemiol Psichiatr Soc 2009;18(1):23–33. https://doi.org/10.1017/s1121189×00001421.

[2] Aderka IM, Hofmann SG, Nickerson A, Hermesh H, Gilboa-Schechtman E, Marom S. Functional impairment in social anxiety disorder. J Anxiety Disord 2012;26(3):393–400. https://doi.org/10.1016/j.janxdis.2012.01.003.

[3] Barrera TL, Norton PJ. Quality of life impairment in generalized anxiety disorder, social phobia, and panic disorder. J Anxiety Disord 2009;23(8):1086–90. https://doi.org/10.1016/j.janxdis.2009.07.011.

[4] Whiteford HA, Ferrari AJ, Degenhardt L, Feigin V, Vos T. The global burden of mental, neurological and substance use disorders: an analysis from the Global Burden of Disease Study 2010. PLoS One 2015;10(2):e0116820. https://doi.org/10.1371/journal.pone.0116820.

[5] Carpenter JK, Andrews LA, Witcraft SM, Powers MB, Smits JAJ, Hofmann SG. Cognitive behavioral therapy for anxiety and related disorders: a meta-analysis of randomized placebo-controlled trials. Depress Anxiety 2018;35(6):502–14. https://doi.org/10.1002/da.22728.

[6] Hofmann SG, Smits JA. Cognitive-behavioral therapy for adult anxiety disorders: a meta-analysis of randomized placebo-controlled trials. J Clin Psychiatry 2008;69(4):621–32. https://doi.org/10.4088/jcp.v69n0415.

[7] Fava GA, Grandi S, Rafanelli C, Ruini C, Conti S, Belluardo P. Long-term outcome of social phobia treated by exposure. Psychol Med 2001;31(5):899–905. https://doi.org/10.1017/s0033291701004020.

[8] Fava GA, Rafanelli C, Grandi S, Conti S, Ruini C, Mangelli L, Belluardo P. Long-term outcome of panic disorder with agoraphobia treated by exposure. Psychol Med 2001;31(5):891–8. https://doi.org/10.1017/s0033291701003592.

[9] Scholten WD, Batelaan NM, van Balkom AJ, Wjh Penninx B, Smit JH, van Oppen P. Recurrence of anxiety disorders and its predictors. J Affect Disord 2013;147(1–3):180–5. https://doi.org/10.1016/j.jad.2012.10.031.

[10] van Dis EAM, van Veen SC, Hagenaars MA, Batelaan NM, Bockting CLH, van den Heuvel RM, Engelhard IM. Long-term outcomes of cognitive behavioral therapy for anxiety-related disorders: a systematic review and meta-analysis. JAMA Psychiatry 2020;77(3):265–73. https://doi.org/10.1001/jamapsychiatry.2019.3986.

[11] Barlow DH, Farchione TJ, Bullis JR, Gallagher MW, Murray-Latin H, Sauer-Zavala S, Cassiello-Robbins C. The unified protocol for transdiagnostic treatment of emotional disorders compared with diagnosis-specific protocols for anxiety disorders: a randomized clinical trial. JAMA Psychiatry 2017;74(9):875–84. https://doi.org/10.1001/jamapsychiatry.2017.2164.

[12] Barlow DH, Farchione TJ, Fairholme CP, Ellard KK, Boisseau CL, Allen LB, Ehrenreich-May J. Unified protocol for transdiagnostic treatment of emotional disorders: Therapist guide. Oxford University Press; 2011.

[13] Barlow DH, Ellard KK, Sauer-Zavala S, Bullis JR, Carl JR. The origins of neuroticism. Perspect Psychol Sci 2014;9(5):481–96. https://doi.org/10.1177/1745691614544528.

[14] Barlow DH, Sauer-Zavala S, Carl JR, Bullis JR, Ellard KK. The nature, diagnosis, and treatment of neuroticism: Back to the future. Clin Psychol Sci 2014;2(3):344–65. https://doi.org/10.1177/2167702613505532.

[15] Bullis JR, Boettcher H, Sauer-Zavala S, Farchione TJ, Barlow DH. What is an emotional disorder? A transdiagnostic mechanistic definition with implications for assessment, treatment, and prevention (https://doi.org/) Clin Psychol: Sci Pract 2019;26(2):e12278. https://doi.org/10.1111/cpsp.12278.

[16] Carlucci L, Saggino A, Balsamo M. On the efficacy of the unified protocol for transdiagnostic treatment of emotional disorders: a systematic review and meta-analysis. Clin Psychol Rev 2021;87:101999. https://doi.org/10.1016/j.cpr.2021.101999.

[17] Cassiello-Robbins C, Southward MW, Tirpak JW, Sauer-Zavala S. A systematic review of Unified Protocol applications with adult populations: facilitating widespread dissemination via adaptability. Clin Psychol Rev 2020;78:101852. https://doi.org/10.1016/j.cpr.2020.101852.
[18] Sakiris N, Berle D. A systematic review and meta-analysis of the Unified Protocol as a transdiagnostic emotion regulation based intervention. Clin Psychol Rev 2019; 72:101751. https://doi.org/10.1016/j.cpr.2019.101751.
[19] Longley, S.L., & Gleiser, T.S. (202). Efficacy of the Unified Protocol: A systematic review and meta-analysis of randomized controlled trials. *Clinical Psychology: Science and Practice, 30* (2), 208–221. https://doi.org/10.1037/cps0000141.
[20] Sauer-Zavala S, Fournier JC, Jarvi Steele S, Woods BK, Wang M, Farchione TJ, Barlow DH. Does the unified protocol really change neuroticism? Results from a randomized trial. Psychoogical Med 2021;51(14):2378–87. https://doi.org/10.1017/S0033291720000975.
[21] Stump, N.E., Southward, M.W., & Sauer-Zavala, S. Assessing theories of state and trait change in neuroticism and symptom improvement in the Unified Protocol. *Behavior Therapy,* In Press. https://doi.org/10.1016/j.beth.2023.05.005.
[22] McManus F, Shafran R, Cooper Z. What does a transdiagnostic approach have to offer the treatment of anxiety disorders? Br J Clin Psychol 2010;49(4):491–505. https://doi.org/10.1348/014466509×476567.
[23] Dalgleish T, Black M, Johnston D, Bevan A. Transdiagnostic approaches to mental health problems: Current status and future directions. J Consult Clin Psychol 2020; 88(3):179–95. https://doi.org/10.1037/ccp0000482.
[24] Eustis EH, Gallagher MW, Tirpak JW, Nauphal M, Farchione TJ, Barlow DH. The Unified Protocol compared with diagnosis-specific protocols for anxiety disorders: 12-month follow-up from a randomized clinical trial. Gen Hosp Psychiatry 2020; 67:58–61. https://doi.org/10.1016/j.genhosppsych.2020.08.012.
[25] Bullis JR, Fortune MR, Farchione TJ, Barlow DH. A preliminary investigation of the long-term outcome of the unified protocol for transdiagnostic treatment of emotional disorders. Compr Psychiatry 2014;55(8):1920–7. https://doi.org/10.1016/j.comppsych.2014.07.016.
[26] Hope DA, Heimberg RG, Turk CL. Managing social anxiety: a cognitive-behavioral therapy approach: therapist guide. Oxford University Press,; 2006.
[27] Foa EB, Yadin E, Lichner TK. Exposure and response (ritual) prevention for obsessive-compulsive disord. er: Therapist guide. Second ed. Oxford University Press; 2012.
[28] Zinbarg RE, Craske MG, Barlow DH. Mastery of your anxiety and worry: Therapist guide. Second ed. Oxford University Press; 2006.
[29] Craske MG, Barlow DH. Mastery of your anxiety and panic: Therapist guide. Fourth ed. Oxford University Press; 2007.
[30] Brown TA, Barlow DH. Anxiety and related disorders interview schedule for DSM-5 - Lifetime version. Oxford University Press; 2014.
[31] Di Nardo PA, Brown TA, Barlow DH. Anxiety Disorders Interview Schedule for DSM-IV:Lifetime Version (ADIS-IV-L). Oxford University Press; 1994.
[32] Brown TA, Di Nardo PA, Lehman CL, Campbell LA. Reliability of DSM-IV anxiety and mood disorders: implications for the classification of emotional disorders. J Abnorm Psychol 2001;110(1):49–58. https://doi.org/10.1037//0021-843x.110.1.49.
[33] Guy W. S. Department of Health, Education, and Welfare. ECDEU Assess Man Psychopharmacol U 1976.
[34] Berk M, Ng F, Dodd S, Callaly T, Campbell S, Bernardo M, Trauer T. The validity of the CGI severity and improvement scales as measures of clinical effectiveness suitable for routine clinical use. J Eval Clin Pract 2008;14(6):978–83. https://doi.org/10.1111/j.1365-2753.2007.00921.x.
[35] Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol 1959;32 (1):50–5. https://doi.org/10.1111/j.2044-8341.1959.tb00467.x.
[36] Hamilton M. A rating scale for depression. J Neurol, Neurosurg, Psychiatry 1960; 23(1):56–62. https://doi.org/10.1136/jnnp.23.1.56.
[37] Shear MK, Vander Bilt J, Rucci P, Endicott J, Lydiard B, Otto MW, Frank DM. Reliability and validity of a structured interview guide for the Hamilton Anxiety Rating Scale (SIGH-A). Depress Anxiety 2001;13(4):166–78. https://doi.org/10.1002/da.1033.abs.
[38] Williams JB. A structured interview guide for the Hamilton Depression Rating Scale. Arch Gen Psychiatry 1988;45(8):742–7. https://doi.org/10.1001/archpsyc.1988.01800320058007.
[39] Carrozzino D, Patierno C, Fava GA, Guidi J. The hamilton rating scales for depression: a critical review of clinometric properties of different versions. Psychother Psychosom 2020;89(3):133–50. https://doi.org/10.1159/000506879.
[40] Norman SB, Cissell SH, Means-Christensen AJ, Stein MB. Development and validation of an overall anxiety severity and impairment scale (OASIS). Depress Anxiety 2006;23(4):245–9. https://doi.org/10.1002/da.20182.
[41] Bentley KH, Gallagher MW, Carl JR, Barlow DH. Development and validation of the overall depression severity and impairment scale. Psychol Assessessment 2014; 26(3):815–30. https://doi.org/10.1037/a0036216.
[42] Marks IM, Connolly J, Hallam RS. Psychiatric nurse as therapist. Br Med J 1973;3: 156–60. https://doi.org/10.1136/bmj.3.5872.156.
[43] Mundt JC, Marks IM, Shear MK, Greist JH. The work and social adjustment scale: a simple measure of impairment in functioning. Br J Clin Psychol 2002;180:461–4. https://doi.org/10.1192/bjp.180.5.461.
[44] Zahra D, Qureshi A, Henley W, Taylor R, Quinn C, Pooler J, Byng R. The work and social adjustment scale: Reliabiltiy, sensitivity and value. Int J Psychiatry Clin Pract 2014;18(2):131–8. https://doi.org/10.3109/13651501.2014.894072.
[45] Muthén LK, Muthén BO. Mplus user's guide: Statistical analysis with latent variables. Seventh ed. Muthén & Muthén; 1998.
[46] Matza LS, Morlock R, Sexton C, Malley K, Feltner D. Identifying HAM-A cutoffs for mild, moderate, and severe generalized anxiety disorder. Int J Methods Psychiatr Res 2010;19(4):223–32. https://doi.org/10.1002/mpr.323.
[47] Zimmerman M, Martinez JH, Young D, Chelminski I, Dalrymple K. Severity classification on the Hamilton Depression Rating Scale. J Affect Disord 2013;150 (2):384–8. https://doi.org/10.1016/j.jad.2013.04.028.
[48] Craske MG. Transdiagnostic treatment for anxiety and depression. Depress Anxiety 2012;29(9):749–53. https://doi.org/10.1002/da.21992.
[49] Steele SJ, Farchione TJ, Cassiello-Robbins C, Ametaj A, Sbi S, Sauer-Zavala S, Barlow DH. Efficacy of the Unified Protocol for transdiagnostic treatment of comorbid psychopathology accompanying emotional disorders compared to treatments targeting single disorders. J Psychiatr Res 2018;104:211–6. https://doi.org/10.1016/j.jpsychires.2018.08.005.