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Transdiagnostic treatment of bipolar disorder and comorbid anxiety using the Unified Protocol for
Emotional Disorders: A pilot feasibility and acceptability trial

Kristen K. Ellard^{1*}, Emily E. Bernstein², Casey Hearing³, Ji Hyun Baek⁴, Louisa G. Sylvia¹, Andrew A.
Nierenberg¹, David H. Barlow⁵, Thilo Deckersbach¹

¹Department of Psychiatry, Massachusetts General Hospital, Boston, MA, USA

²Department of Psychology, Harvard University, Cambridge, MA, USA

³Department of Psychology, George Washington University

⁴Department of Psychiatry, Sungkyunkwan University Samsung Medical Centre, Gyeonggi-do, Korea

⁵Department of Psychology, Boston University, Boston, MA, USA

*Corresponding author. (K. Ellard) Bipolar Clinic and Research Program Massachusetts General Hospital
50 Staniford Street, Suite 580 Boston, MA 02114. kellard@mgh.harvard.edu

Abstract

Background

Comorbid anxiety in bipolar disorder (BD) is associated with greater illness severity, reduced treatment response, and greater impairment. Treating anxiety in the context of BD is crucial for improving illness course and outcomes. The current study examined the feasibility, acceptability and preliminary efficacy of the Unified Protocol (UP), a transdiagnostic cognitive behavioral therapy, as an adjunctive treatment to pharmacotherapy for BD and comorbid anxiety disorders.

Methods

Twenty-nine patients with BD and at least one comorbid anxiety disorder were randomized to pharmacotherapy treatment-as-usual (TAU) or TAU with 18 sessions of the UP (UP+TAU). All patients completed assessments every four weeks to track symptoms, functioning, emotion regulation and

temperament. Linear mixed-model regressions were conducted to track symptom changes over time and to examine the relationship between emotion-related variables and treatment response.

Results

Satisfaction ratings were equivalent for both treatment groups. Patients in the UP+TAU group evidenced significantly greater reductions over time in anxiety and depression symptoms (Cohen's d 's $>.80$).

Baseline levels of neuroticism, perceived affective control, and emotion regulation ability predicted magnitude of symptom change for the UP+TAU group only. Greater change in perceived control of emotions and emotion regulation skills predicted greater change in anxiety related symptoms.

Limitations

This was a pilot feasibility and acceptability trial; results should be interpreted with caution.

Conclusions

Treatment with the UP+TAU was rated high in patient satisfaction, and resulted in significantly greater improvement on indices of anxiety and depression relative to TAU. This suggests that the UP may be a feasible treatment approach for BD with comorbid anxiety.

Keywords: Bipolar disorder; anxiety disorders; transdiagnostic; cognitive behavioral therapy; emotion regulation

Introduction

Bipolar disorders (BD), including bipolar I, bipolar II, cyclothymia, “other specified” and “unspecified” bipolar and related disorders, affect approximately 4% of the population in the U.S. (Kessler et al., 2005) and 2% of the population worldwide (Merikangas et al., 2011). BD is characterized by the occurrence of (hypo)manic episodes and depressive mood episodes. While the mean duration of discrete mood episodes is about 13 weeks (Solomon et al., 2010), the majority of patients also have

persistent comorbid anxiety symptoms or anxiety disorders. Over 86% of patients with BD endorse a lifetime diagnosis of a comorbid anxiety disorder (Merikangas et al., 2007) with over a third of BD patients meeting diagnostic criteria for a current comorbid anxiety disorder that warrants treatment at any given time (Simon et al., 2004). The presence of comorbid anxiety has been identified as an independent marker of greater BD severity, and is associated with greater chronicity, reduced treatment response, and greater functional impairment (Deckersbach et al., 2014; Goldberg & Fawcett, 2012; J. H. Lee & Dunner, 2008; Otto et al., 2006). Thus, the reality of BD extends beyond traditionally emphasized discrete mood episodes and is often exacerbated by the presence of anxiety. This point is reinforced by the recent addition of an “anxious distress” specifier to BD in the revised Diagnostic and Statistical Manual, 5th Edition (DSM-5; APA, 2013). Anxiety in the context of BD therefore represents a crucial target for improving illness course and outcomes.

Existing treatments thus far do not adequately meet the need to address anxiety in the context of BD (Vazquez, Baldessarini, & Tondo, 2014). Although pharmacotherapy is the front-line treatment for BD, pharmacotherapy for the treatment of comorbid anxiety in BD faces significant challenges. Specifically, both SSRIs and benzodiazepines, the first-line pharmacological treatments for anxiety, may be contraindicated in the context of BD (El-Mallakh & Hollifield, 2008; Freeman, Freeman, & McElroy, 2002; Pacchiarotti et al., 2013; Sasson, Chopra, Harrari, Amitai, & Zohar, 2003). Though the negative effects of SSRIs in BD are under debate, there is evidence that they interact with mood stabilizers, aggravate side effects of other medications, and may trigger mania onset (Allain et al., 2016; Post et al., 2006; Tondo, Vazquez, & Baldessarini, 2010). Benzodiazepines carry the risk of developing dependence, which is particularly problematic for BD patients who show high incidences of comorbid substance use disorders (Brunette, Noordsy, Xie, & Drake, 2003). Cognitive-behavioral therapy (CBT), highly effective in the treatment of primary anxiety disorders, may offer a viable treatment alternative to pharmacotherapy for the treatment of anxiety in BD. Thus far, however, very few studies of CBT for anxiety in BD have been conducted, and those that do exist are limited to targeting a single specific anxiety disorder (Provencher, Hawke, & Thienot, 2011; Stratford, Cooper, Di Simplicio, Blackwell, & Holmes,

2015). This approach is problematic, as individuals with BD often present with multiple anxiety disorder diagnoses, begging the question of which specific anxiety disorder to target for treatment.

The current study aims to address the need for improved treatments for anxiety in the context of BD by testing the feasibility, acceptability and preliminary efficacy of the Unified Protocol for Transdiagnostic Treatment of Emotional Disorders (UP; Barlow et al., 2010a; Barlow et al., 2010b) as an adjunctive treatment to psychopharmacological treatment-as-usual (TAU) for BD and comorbid anxiety disorders. The UP is a transdiagnostic CBT treatment developed to address common core processes that underlie the full range of anxiety and mood disorders. Specifically, evidence from genetics, cognitive and affective neuroscience, and behavioral and physiological data shows that individuals across these disorder spectrums demonstrate a biological and psychological vulnerability towards increased affective lability relative to healthy controls, and exhibit a tendency to experience affective states as aversive, uncontrollable and unpredictable (Barlow, Sauer-Zavala, Carl, Bullis, & Ellard, 2014). These patterns are coupled with maladaptive and ineffective attempts to control, avoid or regulate emotional experiences. The UP specifically targets such deficits in emotion processing that are evident across mood and anxiety disorders including bipolar disorder.

The rationale for testing the UP for the treatment of BD and comorbid anxiety is twofold: First, given the high rates of comorbidity in BD referenced above, an approach that accounts for transdiagnostic processes offers greater parsimony. In addition to addressing symptoms of anxiety in BD, this approach may benefit other co-occurring disorders, such as substance dependence. Second, the UP specifically targets deficits in emotion regulation and emphasizes the adoption of more adaptive emotion regulation skills both through skills training and emotion exposures. BD are disorders particularly characterized by both emotion lability and the inability to adaptively manage or regulate emotional experiences, which are further intensified by anxiety symptoms (Heissler, Kanske, Schonfelder, & Wessa, 2014). Chronic emotion dysregulation can permeate every domain of functioning for individuals struggling with BD, and is linked to impulsive, risky or self-destructive behaviors, interpersonal problems, disruptions in work productivity, and even suicidality (Kessler et al., 2006; Muhtadie, Johnson, Carver, Gotlib, & Ketter,

2014; Samalin, de Chazeron, Vieta, Bellivier, & Llorca, 2016; Swann, Lijffijt, Lane, Steinberg, & Moeller, 2009; Van Rheeën, Murray, & Rossell, 2015). BD patients report investing more time and effort in trying to regulate their emotions than healthy controls, and engage maladaptive emotion regulation strategies such as rumination and suppression more frequently (Gruber, Harvey, & Gross, 2012; Thomas, Knowles, Tai, & Bentall, 2007; Van der Gucht, Morriss, Lancaster, Kinderman, & Bentall, 2009; Van Rheeën et al., 2015; Wolkenstein, Zwick, Hautzinger, & Joormann, 2014). Further, emotion dysregulation in BD is associated with worsened neuropsychological deficits (e.g. behavioral slowing, poor working memory, impaired executive control), worse subjective psychosocial functioning (Hoertnagl et al., 2011), more frequent mood episodes, and worse course of illness (Kanske, Heissler, Schonfelder, Forneck, & Wessa, 2013). It has been postulated that difficulties in regulating emotions underlie the chronic course of the illness (Phillips & Vieta, 2007; Wolkenstein et al., 2014). Thus, treatments that focus on targeting and improving emotion regulation skills may be particularly beneficial for individuals with BD.

Given the UP's focus on ameliorating emotion dysregulation using a transdiagnostic framework, we hypothesized that the UP may be particularly suited to address BD with comorbid anxiety. The UP has demonstrated efficacy in the treatment of a range of co-occurring anxiety and unipolar mood disorders (Barlow et al., submitted; Ellard, Fairholme, Boisseau, Farchione, & Barlow, 2010; Farchione et al., 2012), and preliminary data suggests efficacy for bipolar mood disorders as well (Ellard, Deckersbach, Sylvia, Nierenberg, & Barlow, 2012). The current study investigates the feasibility and acceptability of this approach as applied to the treatment of BD and comorbid anxiety disorders as an adjunctive treatment to standardized psychopharmacological treatment as usual (TAU). In addition, we evaluated the preliminary efficacy of this approach on improvement in bipolar mood and anxiety symptoms and psychosocial functioning, relative to pharmacological TAU alone.

Given the focus of the UP on targeting underlying emotion dysregulation as a transdiagnostic, trait-like factor affecting mood and anxiety symptoms, we additionally examined specific factors related to emotion regulation, perceptions of controllability of emotions, and temperamental variables related to

neuroticism and affective behavioral styles as a secondary, exploratory aim of this study, in order to better clarify potential treatment-related mechanisms of action. Specifically, we conducted exploratory analyses to determine whether baseline characteristics related to these factors predicted treatment response across treatment groups. Similarly, in order to begin to understand potential mechanisms of treatment effects, we examined whether treatment-related changes on these trait-like variables differentially predicted symptom change across treatment groups.

Methods

Participants

Participants were recruited from the Massachusetts General Hospital Bipolar Clinic and Research Program. The Massachusetts General Hospital Institutional Review Board approved the study protocol and participants provided written informed consent prior to the initiation of any study procedure. Psychiatric diagnoses were confirmed using the Structured Clinical Interview for DSM-IV (SCID-IV; First, Spitzer, Gibbon, & Williams, 1997) and mood episode severity was assessed using the Hamilton Depression Rating Scale (HAM-D; Hamilton, 1960) and Young Mania Rating Scale (YMRS; Young, Biggs, Ziegler, & Meyer, 1978). Eligible participants ($N = 29$, female = 17, $M_{\text{age}} = 43.72$, range 22-64) met criteria for bipolar disorder (BD-I, $n=27$; or BD-II, $n=2$), did not meet criteria for a major depressive or manic episode at study entry ($\text{HAM-D-17} \leq 16$ and $\text{YMRS} \leq 12$), and met criteria for at least one of the following anxiety disorders: generalized anxiety disorder ($n = 19$), panic disorder ($n = 14$), social phobia ($n = 18$). All participants were required to have at least 3 months of stability on their current dosage(s) of medication(s), and were asked to maintain this dosage throughout the study period. Stable maintenance pharmacotherapy was defined as maximum tolerated dosages according to Texas Implementation of Medication Algorithm (Suppes et al., 2005), as prescribed by a psychiatrist. Individuals were excluded if they endorsed current suicidal ideation; history of seizure disorder, brain injury, or neurological disease; met criteria for a psychotic disorder; reported psychotic symptoms; met criteria for a substance use disorder within the past 12 months, or had received electroconvulsive therapy (ECT) within the six months preceding study enrollment. Eligible participants were randomly assigned to either continued

psychopharmacological treatment as usual (TAU) or TAU plus 18 weekly sessions of the UP (UP+TAU). Individuals randomly assigned to the TAU group were offered 18 weekly individual treatment sessions with the UP at the completion of the study (month 6). This six-month wait period for commencement of UP sessions was comparable to the standard wait time for assignment to a CBT therapist at our clinic. Thirteen individuals were randomly assigned to the UP+TAU arm and 16 individuals to the TAU arm. See Figure 1 for a summary consort chart.

Procedure

All participants underwent a thorough baseline assessment, which included a combination of clinician-administered and self-report measures of mood and anxiety symptoms, functional impairment, personality, and emotion regulation (see Measures below). These assessments were repeated for all participants every four weeks for a period of six months. All assessments were conducted by blind independent evaluators (IE). IEs were masters-level doctoral students or doctoral-level clinicians trained to certification on all assessment measures. Certification procedures included attending a formal assessment training session and viewing and rating patient interviews. To certify, IEs were required to score within one point of an expert rater on clinical measures (T.D., K.E., or A.N.). To maintain IE blindness, monthly study assessments were scheduled on different days than therapy visits. Study IE's did not encounter study participants at any time other than during assessment visits.

TAU group

Participants randomized to TAU continued usual care under their treating psychiatrist, and were asked to refrain from psychotherapy for the duration of study participation (six months). Participants repeated clinician-administered and self-report assessments every four weeks (baseline through six months). Participants were closely monitored for worsening of symptoms or adverse events during this period. Medication usage, including any medication or dosage changes, was tracked and recorded during each assessment.

UP+TAU group

Participants randomized to UP+TAU continued care under their treating psychiatrist and completed clinician-administered and self-report assessments every four weeks (baseline through six months) following the same procedures as the TAU group. Additionally, they received 18 weekly one-hour treatment sessions with the UP. The UP intervention comprises 8 modules: (1) motivation enhancement, (2) psychoeducation, (3) present-focused awareness training, (4) cognitive appraisal and reappraisal, (5) emotion avoidance and emotion driven behaviors, (6) interoceptive awareness and exposure, (7) emotion exposure, and (8) relapse prevention. Participants were encouraged to complete weekly homework and to practice learned skills between sessions. In Module 1, patients identify concrete goals and personal markers of change for the treatment. Module 2 emphasizes the adaptive nature of emotions and their bidirectional relationships with behaviors, thoughts and physiological sensations. During Module 3, patients practice mindfulness skills aimed at shifting and focusing their attention to the present moment and noticing thoughts, physiological sensations and behaviors as they are occurring in real time. Emphasis is placed upon identifying automatic associations between specific thoughts, feelings and behaviors. Modules 4 through 6 focus on identifying maladaptive automatic emotion-related responses and modifying these responses towards more adaptive outcomes. Specifically, Module 4 introduces skills for modifying maladaptive, automatic emotion-related appraisals and core beliefs. Module 5 introduces skills for countering automatic, emotion-driven behaviors and behavioral avoidance. Module 6 focuses on identifying the connection between physiological, visceral states and specific thoughts and behaviors, and increasing awareness and tolerance of physiological sensations through interoceptive exposures. Module 7 focuses on integrating all skills learned in Modules 3 through 6 by conducting in- and between-session planned exposures to emotion-provoking scenarios in which patients practice applying skills from treatment. Finally, sessions ended in module 8 with the therapist and patient reviewing treatment concepts, differentiating between symptom recurrence and disorder relapse, and reflecting on how the practiced skills could continue to be implemented in the patient's life. For a more detailed description of the UP approach see Barlow et al., 2010; Ellard et al., 2010, 2012; Farchione et al., 2012. All treatment sessions were conducted by a doctoral-level psychologist (K.E.), a co-developer of the UP fully certified

in the treatment, with eight years of prior experience in CBT. Supervision of therapy sessions was provided weekly by a licensed clinical psychologist (T.D.).

Assessment Measures

Treatment feasibility/acceptability

Treatment feasibility and acceptability were tracked throughout the study. To track treatment feasibility in the UP+TAU group, the treating clinician rated treatment adherence at the end of each weekly in-person session using the Homework-Compliance Scale (HCS; Primakoff, Epstein, & Covi, 1986). Scores ranged from 1 (“the patient did not attempt assigned homework”) to 6 (“the patient did more of the assigned homework than was requested”). To track treatment acceptability, all participants completed the Client Satisfaction Questionnaire-8 (CSQ-8; Larsen, Attkisson, Hargreaves, & Nguyen, 1979) at each monthly assessment visit. The CSQ-8 is an eight-item, self-report measure developed to assess satisfaction with a specific healthcare or counseling service. Higher scores indicate greater satisfaction with treatment received. The CSQ-8 has demonstrated high internal consistency, and high correlation with treatment termination status and change in client-reported symptoms (Attkisson & Zwick, 1982).

Primary symptom outcomes

Changes in mood symptoms and functioning were monitored using semi-structured interviews and self-report questionnaires, in order to track concurrence between clinician-administered measures and patient subjective report.

Hamilton Depression Rating Scale, 17-item version (HAM-D-17; Hamilton, 1960)

Clinician-rated depressive symptoms were assessed monthly using 17-item HAM-D-17. The HAM-D-17 is a well-established clinician-rated structured interview with high reliability and validity, recently re-evaluated in a large meta-analysis (Trajković et al., 2011).

Quick Inventory of Depressive Symptomatology (QIDS-SR; Rush et al., 2003)

Self-report depressive symptoms were assessed monthly using the QIDS-SR, a 16-item measure designed to assess primary symptoms of depression. The QIDS-SR has been validated in chronic depression (Rush et al., 2003) as well as in outpatients with bipolar disorder (Trivedi et al., 2004).

Hamilton-Anxiety Rating Scale (HAM-A; Hamilton, 1959)

Clinician-rated anxiety was assessed using the HAM-A, a well-established 14-item structured interview used to assess anxiety-related symptoms. The HAM-A has consistently demonstrated high inter-rater reliability and validity (Bruss, Gruenberg, Goldstein, & Barber, 1994; Shear et al., 2001).

Anxiety Symptoms Questionnaire (ASQ; Pollack et al., 2011)

Self-report anxiety was assessed using the ASQ, a 17-item questionnaire, which measures both the intensity (ASQ-I) and frequency (ASQ-F) of psychological and somatic symptoms of anxiety.

Participants separately rated the intensity and frequency of each symptom on a scale of 0–10, from “none” to “frequently.” Higher total scores indicate greater anxiety. The ASQ has demonstrated good construct validity and test-retest reliability (Pollack et al., 2011).

Young Mania Rating Scale (YMRS; Young et al., 1978)

Clinician-rated (hypo)mania symptoms were assessed monthly using the YMRS. The 11-item YMRS is the most widely studied instrument for mania, and its reliability and validity are high (Young et al., 1978).

Altman Self-Rating Mania Scale (ASRM; Altman, Hedeker, Peterson, & Davis, 1997)

Self-reported symptoms of (hypo)mania were assessed using the ASRM, a 5-item instrument designed to assess presence and severity of manic symptoms. The ASRM has demonstrated high test-retest reliability and validity (Altman et al., 1997).

Longitudinal Interval Follow-up Evaluation - Range of Impaired Functioning Tool (LIFE-RIFT; Leon et al., 1999)

Overall functioning was described with the LIFE-RIFT, a brief measure designed to assess overall functioning and degree of symptom interference in functioning in patients with affective disorders. It has demonstrated good reliability and validity. Higher scores on the above measures indicate greater severity or impairment. The LIFE-RIFT has demonstrated good internal consistency, reliability and validity in bipolar patients (Leon et al., 2000).

Secondary and exploratory outcomes

At monthly visits, participants also completed self-report questionnaires developed to measure specific factors related to emotion regulation, perceptions and reactions to and controllability of emotions, and temperamental variables related to affective behavioral styles, in order to assess potential mechanisms of treatment with the UP.

Affective Control Scale (ACS; Williams, Chambless, & Aherns, 1997)

The ACS is a 42-item self-report measure designed to assess perceived controllability of emotions and fear of loss of control when experiencing strong affective states. ACS subscales expand on the construct of fear of fear, including fear of anxiety, fear of depression, fear of anger, and fear of strong positive affective states. The ACS has demonstrated acceptable internal consistency, test-retest reliability, and concurrent and divergent validity (Berg, Shapiro, Chambless, & Ahrens, 1998; Williams et al., 1997).

Anxiety Sensitivity Index (ASI; Reiss, Peterson, Gursky, & McNally, 1986)

The ASI is a 16-item, self-report measure developed to assess reactions to and perceptions of anxiety-related symptoms. The ASI has demonstrated good test-retest reliability and construct validity (Peterson & Heilbronner, 1987).

Difficulties in Emotion Regulation Scale (DERS; Gratz & Roemer, 2004)

The DERS is a 36-item, self-report measure developed to assess clinically relevant difficulties in emotion regulation, including 1) nonacceptance of emotional responses (Nonacceptance), 2) difficulties engaging in goal-directed behaviors (Goals), 3) impulse control difficulties (Impulse), 4) lack of emotional awareness (Awareness), 5) limited access to emotion regulation strategies (Strategies), 6) and lack of emotional clarity (Clarity). The DERS has demonstrated adequate internal consistency and adequate test-retest reliability (Fowler et al., 2014; Gratz & Roemer, 2004). Whereas replication of the original six-factor solution has been inconsistent in healthy samples (Bardeen, Fergus, & Orcutt, 2012; Lee, Witte, Bardeen, Davis, & Weathers, 2016; Snow, Ward, Becker, & Raval, 2013), a recent study in severe mental illness found an acceptable fit with the six-factor solution (Fowler et al., 2014).

Rumination Subscale of the Reflection-Rumination Questionnaire (RRQ; Trapnell & Campbell, 1999)

The RRQ was developed to differentiate between reflective versus ruminative self-focus. The RRQ Rumination subscale contains 12 items on a 5-point Likert-type scale (1= “strongly disagree, 5 = “strongly agree”). Previous studies have shown good test-retest reliability and convergent validity (Trapnell & Campbell, 1999).

Response Styles Questionnaire, Ruminative Responses Subscale (RSQ-RRS; Nolen-Hoeksema & Morrow, 1991)

The 22-item RRS subscale of the RSQ captures responses to negative mood, asking participants to indicate how often they engage in various self-focused thought patterns (e.g. "I think back to other times I have been depressed", "I think about how hard it is to concentrate", "I go away by myself and think about why I feel this way"). The RRS has demonstrated both internal consistency and construct validity as a stand-alone subscale (Nolen-Hoeksema & Morrow, 1991).

NEO Five-Factor Inventory (NEO-FFI; Costa & McCrea, 1992)

The NEO-FFI was developed to assess five domains of personality: (1) neuroticism (NEO-N), the tendency to experience negative emotions in response to stressors; (2) extraversion (NEO-E), the tendency towards increased sociability, positive emotionality, and general activity; (3) openness to experience (NEO-O), the tendency towards curiosity versus conservativeness; (4) agreeableness (NEO-A), the tendency towards altruistic and cooperative behavior; and (5) conscientiousness (NEO-C), the tendency towards thoughtful and deliberative planning and organization. The NEO-FFI contains 60 items rated on a 5-point Likert-type scale (1 = strongly disagree to 5 = strongly agree). Scores are used to derive five separate domain scores (12 items per domain). Each of the five domains of the NEO FFI has been found to possess adequate internal consistency and temporal stability (Costa & McCrea, 1992; Robins, Fraley, Roberts, & Trzesniewski, 2001).

Behavioral Inhibition/Behavioral Activation Scale (BIS/BAS; Carver & White, 1994)

The BIS/BAS was developed to measure behavioral inhibition (negative reactivity to aversive events) and behavioral activation (responsiveness to positive incentives and motivation and drive towards reward). It is comprised of 20 items with a 4-point Likert -type scale (1 = quite untrue of you; 4 = quite true of you).

Four subscales are derived consisting of Behavioral Inhibition (BIS), Reward Responsiveness (BAS-Reward), Drive (BAS-Drive) and Fun Seeking (BAS-Fun). The BIS/BAS has demonstrated good reliability and convergent validity in clinical samples, and the original factor structure (Carver & White, 1994) was replicated in patients with anxiety and mood disorders (Campbell-Sills, Liverant, & Brown, 2004).

Statistical Analyses

Descriptive data for the sample are presented as means with standard deviations (SD) for continuous variables and counts with proportions for categorical variables. We conducted chi-square analyses to evaluate group differences in gender, race, and ethnicity, and independent sample t-tests to evaluate baseline group differences in age, mood symptoms, functioning, emotion, and personality.

Primary outcomes

We conducted mixed-effects linear regression analyses to evaluate primary outcomes including treatment satisfaction, clinical symptoms, and functioning. Models included random intercept and slope over time and fixed effect for treatment. Treatment by time interactions were used to explore group differences in rates of change over time for outcome measures. Bonferroni corrections were applied. We used an intention-to-treat (ITT) analysis approach, which is based on participants' randomized assignments rather than their course during the study. Patients who completed at least one time point beyond randomization were included in the ITT analysis. The ITT approach aims to avoid artifacts such as non-random attrition that occurs during clinical trials. Additional mixed-effects linear regressions were modeled for treatment completers (i.e. completion of monthly assessments through month six for TAU group, completion of all 18 treatment sessions for UP+TAU group). Effect sizes are reported as Cohen's *d*.

Exploratory outcomes

Additional models were fit with baseline and change slopes for emotion regulation and personality measures as predictors of slope of mood and anxiety symptom change over the six months to explore the relationship between such process variables and symptom outcomes. Because we expect emotion-related variables to interact differently with each treatment approach, effects were computed separately for each

treatment arm. Therefore, given the resultant small sample size and thus limited power, these results should be interpreted with caution.

Results

Baseline characteristics of the sample are included in Table 1. At study entry, treatment groups did not differ in gender, race, ethnicity, age, education, or medication load, with the exception of psychostimulants: four patients in the TAU group were taking stable doses of psychostimulants, whereas no patients in the UP+TAU group were taking psychostimulants. No other significant differences in medication load were present. Treatment groups did not significantly differ on any clinical measure at baseline (p 's $>.05$) with the exception of the BIS, which was subsequently excluded from further analysis (Table 2).

Feasibility and Acceptability

Total attrition for all patients randomized to the study was 38% (11 out of 29 randomized; see Figure 1). Total attrition for patients who initiated treatment and completed at least one assessment timepoint (after four weeks of participation) was 25% (6 out of 24 treatment initiators). Attrition rates for the UP+TAU group were 38% of all randomized (5 out of 13), and 27% of treatment initiators (3 out of 11). Attrition rates for the TAU group were 38% of all randomized (6 out of 16), and 29% of treatment initiators (4 out of 14). For the UP+TAU group, reasons for dropout prior to treatment initiation were scheduling issues ($n=1$) and worsening of symptoms ($n=1$). Reasons for dropout after treatment initiation were discomfort with emotion exposures ($n = 1$), and unknown/lost to follow up ($n=2$). For the TAU group, reasons for dropout prior to treatment initiation were dissatisfaction with randomization assignment ($n=2$). Reasons for dropout after treatment initiation were non-adherence to criteria of abstinence from outside psychotherapy ($n=1$), and unknown/lost to follow up ($n=3$). Although client satisfaction ratings were slightly higher for UP+TAU, there were no significant differences in satisfaction ratings between treatment conditions (CSQ: Mean diff = -1.62, $t = -1.21$, $d = .51$, 95% CI: -1.20, 4.82). For the UP +TAU group, 3 participants dropped out after 3-4 treatment sessions; the remaining 8

completed all 18 treatment sessions. Mean homework compliance score (HCS) was 3.78 (± 1.49 , range 1.50-5.44), indicating on average patients completed “most but not all” of assigned homework.

Primary Symptom Change

Full results of linear mixed ITT models are presented in Table 3. Significantly greater linear reduction over time was found for the UP+TAU group in clinician rated anxiety scores (HAM-A: $M_{\text{diff}} = -5.91$, $t = 2.46$, $d = .88$, 95% CI: -10.82, -1.00) and both clinician and self-rated depression (HAM-D: $M_{\text{diff}} = -4.19$, $t = 2.36$, $d = .82$, 95% CI: -7.80, -0.58; QIDS: $M_{\text{diff}} = -3.75$, $t = 2.71$, $d = 1.06$, 95% CI: -6.60, -0.90). No significant group differences were found in linear change in self-reported anxiety (ASQ), clinician rated or self-report mania symptoms (YMRS, ASRM) or symptom interference in functioning (LIFE-RIFT; Table 3). Analysis of completer data, defined as TAU patients who completed all six monthly assessments and UP+TAU patients who completed all 18 treatment sessions, linear mixed models showed significantly greater linear reductions among UP+TAU patients relative to TAU patients in clinician-rated anxiety (HAM-A: $M_{\text{diff}} = -6.58$, $t = 2.30$, $d = 1.01$, 95% CI: -12.53, -0.63), both clinician and self-rated depression (HAM-D: $M_{\text{diff}} = -4.44$, $t = 2.66$, $d = 1.06$, 95% CI: -7.80, -0.58; QIDS: $M_{\text{diff}} = -5.19$, $t = 4.07$, $d = 1.67$, 95% CI: -7.82, -2.56), as well as symptom interference in functioning, although at trend level significance only (LIFE-RIFT: $M_{\text{diff}} = -2.01$, $t = 1.98$, $d = .86$, 95% CI: -4.10, 0.09).

Emotion Regulation and Temperament Variables

No significant differences in linear change over time between treatment groups were found for any emotion processing related measures, including measures of the emotion regulation (DERS), reaction to emotions (ACS), or anxiety sensitivity (ASI). In addition, no significant differences between treatment conditions were found for measures of temperament (NEO).

Exploratory Analyses: Relationship Between Symptom Change and Emotion Regulation Variables

Clinician-rated anxiety symptoms

Slope of change over time in clinician rated anxiety (HAM-A) scores was significantly negatively predicted by baseline measures of neuroticism (NEO-N), affective control (ACS), and emotion regulation

difficulties (DERS) in the UP+TAU group, but not TAU group (Table 4). Thus, greater baseline neuroticism, fear of emotions, and emotion regulation deficits predicted less reduction in anxiety symptoms for the UP+TAU group only. There were no significant baseline predictors of HAM-A change slopes for TAU group. Change over time in affective control (ACS) and emotion regulation skills (DERS) positively predicted change in HAM-A scores for the UP+TAU group only, such that the greater the reduction of fear of emotions and emotion regulation deficits over treatment, the greater the reduction in anxiety symptoms. By contrast, change in agreeableness (NEO-A) positively predicted change in HAM-A scores for the TAU group only, such that greater increases in agreeableness predicted greater reduction in anxiety symptoms (Table 5).

Self-report anxiety symptoms

The slope of change in self-report anxiety frequency (ASQ-F) was significantly negatively predicted by baseline measures of deficits in emotion regulation strategies (DERS Strategies) in the UP+TAU group only, with a trend towards significance for neuroticism (NEO-N) anxiety sensitivity (ASI), and emotion interference in goals (DERS Goals; Table 4). Change in emotion regulation difficulties (DERS Goals, Strategies, Clarity, Impulsivity), as well as rumination (RRQ, RRS) and anxiety sensitivity (ASI) uniquely predicted change in self-reported anxiety frequency (ASQ-F) for the UP+TAU group only, such that greater reductions in emotion regulation deficits, rumination and anxiety sensitivity predicted greater reductions in ratings of anxiety frequency. Change over time in acceptance of emotions (DERS Non-Acceptance) and affective control (ACS) significantly positively predicted change in self-report anxiety frequency for both treatment groups (Table 5), such that greater increases in acceptance of emotions and decreases in fear of emotions predicted greater reductions in anxiety frequency ratings.

Clinician-rated depression

Change in clinician-rated depression (HAM-D) over time was significantly negatively predicted by baseline measures of neuroticism (NEO-N), affective control (ACS), non-acceptance of emotions (DERS-Non-Acceptance subscale) and deficits in emotion regulation strategies (DERS Strategies subscale) for UP+TAU only. There were no significant baseline predictors of HAM-D change for TAU group. Both

groups showed a trend towards significance for the effect of baseline agreeableness (NEO Agreeableness) on clinician-rated depression symptom (HAM-D) change (Table 4). Change over time in Neuroticism (NEO-N), Behavioral Activation (BAS Drive), and rumination (RRQ) uniquely predicted change in HAM-D scores in the UP+TAU group, such that greater decreases in neuroticism and rumination, and greater increases in behavioral activation predicted greater reductions in depressive symptoms. For TAU, change in NEO Agreeableness uniquely predicted change in HAM-D. Both groups showed a trend towards significance for changes over time in emotion interference in goals (DERS Goals; Table 5).

Self-rated depression

Change in self-report depressive symptoms was negatively predicted at the trend level ($p = .06$) by baseline measures of Affective Control in UP+TAU group only. Baseline measures of NEO Agreeableness and Openness significantly positively predicted change in self-report depressive symptoms for TAU group, such that greater agreeableness and openness predicted greater change in depressive symptoms, with a trend towards significance for Behavioral Activation (Drive subscale; Table 4). Changes in NEO Agreeableness uniquely positively predicted change in self-report depressive symptoms for the TAU group (Table 5).

Symptom interference in functioning

Change in emotion regulation difficulties (DERS) significantly positively predicted change in symptom interference functioning (LIFE-RIFT) for the TAU group only, such that greater decreases in emotion regulation deficits predicted greater improvements in functioning (Table 4). There were no significant baseline predictors of change in symptom interference in functioning for either treatment group (Table 5).

Discussion

In the current study, we sought to determine the feasibility and acceptability of the UP, a transdiagnostic CBT treatment for emotional disorders, as applied to the treatment of BD with comorbid anxiety disorders. Results of this study suggest the UP is an acceptable treatment approach for individuals with BD and comorbid anxiety disorders. Patients rated their satisfaction with adjunctive treatment with the UP as equivalent to their satisfaction with pharmacotherapy treatment-as-usual, with a trend towards

greater satisfaction with the UP. This is notable given the increased frequency of visits required to receive adjunctive therapy with the UP relative to receiving pharmacotherapy alone (once weekly as opposed to once every three months as in standard care with pharmacotherapy alone), and the increased expectation of patient engagement through assigned homework and skills practice. Attrition rates did not differ between treatment groups, and a greater proportion of treatment drop-outs were due to dissatisfaction with treatment group assignment in the TAU group relative to the UP group, suggesting a preference for adjunctive CBT in this population. Three individuals dropped out of the UP+TAU condition after initiating treatment. One individual cited a discomfort with emotion exposures as a reason for discontinuation, whereas the other two discontinued for reasons unknown. One of these patients was attending college full-time and working part-time and had difficulty scheduling her sessions, and the other discontinued after accepting a full time nursing position. Therefore, the burden of attending weekly sessions may have been a factor for these patients, although both were unable to be re-contacted so this could not be confirmed. The remaining 11 patients attended all 18 treatment sessions. Patients were moderately compliant with assigned homework, on average completing most of the tasks assigned. This finding was also promising, as the added burden of homework compliance in the UP represents another potentially significant barrier to treatment acceptability and feasibility. Taken together, these results suggest the UP may be an acceptable treatment strategy for individuals with BD and comorbid anxiety, although the results here are in a relatively small sample and should be interpreted with caution.

Attrition rates for UP treatment initiators in this study (27%) were comparable to existing studies of adjunctive individual-based psychosocial treatments for bipolar disorder in adults. Average reported post-treatment attrition rates for individual-based psychosocial treatments are approximately 25% (median 27%, range 9%-41%; (Ball et al., 2006; Fava, Rafanelli, Tomba, Guidi, & Grandi, 2011; Frank et al., 2005; Jones et al., 2015; Meyer & Hautzinger, 2012; Miklowitz et al., 2007; Parikh et al., 2012; Reilly-Harrington et al., 2007; Scott et al., 2006; Swartz, Frank, & Cheng, 2012; Zaretsky, Lancee, Miller, Harris, & Parikh, 2008; for recent reviews, see Chatterton et al., 2017; Salcedo et al., 2016; Stratford et al., 2015; Swartz & Swanson, 2014). For example, Parikh et al (2012), Zaretsky et al (2008),

and Reilly-Harrington et al (2007) report acute post-treatment attrition rates of 29%, 28% and 40% respectively for adjunctive individual CBT treatment conditions in their studies. Although acute post-treatment (9-month) attrition rates are not reported, the multisite Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) trial reports one-year attrition rates of 41% for the CBT treatment condition, 27% for Family Focused Therapy (FFT) and 32% for Interpersonal Social Rhythm Therapy (IPSRT), all treatments delivered adjunctive to pharmacotherapy TAU and compared to clinical management alone. Other studies have shown more favorable attrition rates for individual CBT adjunctive to TAU at acute post-treatment, including 9% in a study of Recovery-Focused CBT (Jones et al., 2015), 17% for CBT (Scott et al., 2006), and 20% for CT (Ball et al., 2006). However, it should be noted that these studies do not provide information on comorbid anxiety disorders or anxiety symptom severity, whereas the previously referenced studies of adjunctive individual CBT report the presence of comorbid anxiety in approximately one-half to 100% of their samples (Parikh et al., 2012; Reilly-Harrington et al., 2007; Zaretsky et al., 2008). Therefore, comorbid anxiety may play a factor in higher relative attrition rates in studies of psychosocial treatment of BD, an area for further research.

In addition to feasibility and acceptability, we examined the efficacy of the UP in reducing depressive and anxious symptoms and improving functioning. Treatment with the UP plus pharmacotherapy resulted in greater reductions in clinician rated anxiety symptoms over time, and greater reductions in both clinician and self-report symptoms of depression over time, yielding large effect sizes. These findings held when using an ITT approach and when looking at treatment completers alone. It is interesting that treatment-related differences in self-rated depression symptoms were found, but no significant treatment-related difference in self-rated anxiety symptoms emerged, despite significant treatment-related differences in clinician-rated anxiety symptoms. This may be related to measurement artifact (the measure included in the current study only tracks frequency and intensity of anxiety symptoms, but not interference, hence there may be a ceiling effect), but might also be related to the relatively short time scale of this study. For many patients, physiological symptoms of anxiety are perceived as quite aversive, and therefore are particularly salient regardless of levels of interference.

Although gains may be made in emotion regulation skills and therefore changes in depression-related symptoms (i.e. guilty ruminations, feelings of self-worth, appetitive/vegetative changes) may be perceived, changes in reactions to anxiety-related symptoms may only be achieved through repeated exposure to anxiety symptoms over time, rather than during a brief study such as this. It should also be noted that in the present study, the explicit goal in the UP was not to eliminate anxiety but to change reactions to the experience of anxiety. Future studies should examine whether patients would endorse greater changes in self-reported frequency and intensity of anxiety over a longer-term follow up. Nevertheless, changes in clinician-rated anxiety suggest treatment with the UP decreased anxiety-related interference. Overall, preliminary results from this trial suggest that the UP may be a viable approach to addressing not only comorbid symptoms of anxiety, but also depression.

The paucity of existing trials examining the effects of psychosocial treatments on anxiety in BD, and in particular individual-based treatments, make it difficult to fully contextualize the results of the current trial. Of those that do exist, findings have been mixed. Reilly-Harrington et al. (2007) conducted an open trial of individual-based CBT with an additional module specifically targeting anxiety adjunctive to pharmacotherapy TAU. Results from this trial found significant reductions on anxiety ratings, yielding small effects. However, this trial did not include a control condition, and was intended to specifically target rapid-cycling bipolar disorder. Therefore, it is unclear if similar effects would have been found in non-rapid cycling bipolar patients, and additionally whether results would be superior to TAU. Fava et al. (2011) conducted a study of individual-based CBT plus Well-Being Therapy for subthreshold BD (cyclothymia) and anxiety, and found a significant post-treatment reduction in anxiety disorder comorbidity relative to TAU, with medium effects. Here again, however, the difference in BD population (cyclothymic as opposed to euthymic BD in the current study) makes it difficult to compare these results with the current trial. Trials of CBT for PTSD that have included BD patients have reported positive effects on reduction of PTSD symptoms overall (Mueser et al., 2008; Rosenberg, Mueser, Jankowski, Salyers, & Acker, 2004), however these studies do not report results separately for BD patients, therefore the specific effects on anxiety symptoms in BD are unknown. Reports of the effects of group-based

psychosocial treatments on anxiety symptoms have been mixed. Studies of Mindfulness-Based Cognitive Therapy (MBCT) have had varying results, yielding small treatment-related effect size reductions in anxiety relative to TAU in one study (Perich, Manicavasagar, Mitchell, Ball, & Hadzi-Pavlovic, 2013), and large treatment-related effect size reductions in anxiety in two others (Ives-Deliperi, Howells, Stein, Meintjes, & Horn, 2013; J. M. Williams et al., 2008). Studies of group CBT have also been inconclusive. Gonzalez-Isasi et al. (2012) found small treatment-related effect size differences in anxiety symptoms following group-based CBT relative to TAU. Da Costa et al. (2011) report significant within-group reductions in anxiety symptoms following group-based CBT, and no significant within-group reductions in anxiety symptoms following TAU. However, group comparisons are not reported, therefore specific treatment-related effects are unclear. Thus, there is a great need for further study of the effects of psychosocial treatments on anxiety in BD, which would allow the results of the current study to be more adequately contextualized.

The effects of adjunctive psychosocial treatments on depressive symptoms in BD have been more widely reported than anxiety, but trials are still sparse for individual-based treatments. Similar to the current study, moderate to large effect sizes for depression symptoms have been found with adjunctive, individual-based CBT relative to TAU (Ball et al., 2006; Jones et al., 2015), psychoeducation (Zaretsky et al., 2008), or clinical management (Fava et al., 2011; Miklowitz et al., 2007). Others have found no differences between CBT and TAU (Scott et al., 2012) or CBT and active psychosocial control conditions (group psychoeducation, Parikh et al., 2012; supportive psychotherapy, Meyer & Hautzinger, 2012). Effects of group-based treatments on depressive symptoms have been less robust. Medium effect size differences on depressive symptoms have been found relative to TAU for group-based CBT (Gonzalez Isasi, Echeburua, Liminana, & Gonzalez-Pinto, 2014), and CT (Lam et al., 2003), and MBCT relative to a waitlist control (J. M. Williams et al., 2008). Others have reported no difference between group-based CBT and TAU (Costa et al., 2011; Gomes et al., 2011), MBCT and TAU (Perich et al., 2013), MBCT and waitlist (Ives-Deliperi et al., 2013), or a Dialectic Behavior Therapy (DBT) skills-based group treatment and waitlist (Van Dijk, Jeffrey, & Katz, 2013). Thus, by comparison, the current study appears to be

comparable to previously reported individual adjunctive psychosocial treatments in reducing symptoms of depression relative to pharmacotherapy TAU. However, the UP may also confer an added benefit by simultaneously ameliorating symptoms of anxiety.

In order to better understand potential mechanisms of action of the UP in BD with anxiety, we sought to examine how variables related to emotion processing, emotion regulation and temperament predicted symptom change in an additional, exploratory analysis. Analyses of these variables revealed intriguing differences in the interaction between emotion- and temperament-related variables and outcomes in each treatment condition. The efficacy of treatment with the UP was influenced by baseline levels of neuroticism, perceived affective control, and emotion regulation ability. These variables affected the impact of the UP on both anxiety- and depression-related symptoms. This finding was surprising given the UP's specific focus on targeting underlying neuroticism and improving emotion regulation skills; the findings here suggest that, for the UP to be most effective, individuals may need to meet a certain threshold level of emotion regulation ability, and may need to exhibit a threshold level of neuroticism. The promising effects of the UP on anxiety and depressive symptoms on aggregate in this study suggests the UP is a viable treatment approach for individuals with BD and comorbid anxiety, however the interaction with emotion regulation and neuroticism-related variables suggest for a subset of individuals, in particular those with more severe emotion dysregulation and neurotic temperament, the beneficial effects may be out of reach. Anecdotally, individuals who exhibited greater emotional lability in session, and subsequently demonstrated greater psychosocial and functional instability between sessions, responded less well to treatment. These individuals tended to be less homework compliant, have more disruptive life circumstances between sessions, and have greater difficulty consolidating treatment concepts from one session to the next. These individuals also demonstrated a greater difficulty with the heavily didactic nature of the treatment, as evidenced by decreased homework compliance and greater difficulty comprehending key treatment concepts. Future studies are needed to determine whether adjustments to treatment delivery (e.g. intensive didactic sessions followed by repeated weekly exposure practice) or increasing baseline emotion regulation capacity through alternate intervention strategies (e.g.

transcranial magnetic stimulation, transcranial direct current stimulation, attention or cognitive bias training) might improve the ability to benefit from treatment with the UP.

For the UP+TAU group only, greater change in perceived control of emotions and emotion regulation skills predicted greater change in anxiety related symptoms, endorsed by both clinician ratings and self-report, and greater changes in neuroticism and rumination predicted greater change in depressive symptoms. These findings, although requiring cautious interpretation, are promising in terms of purported mechanisms of action of the UP. The UP was developed to specifically target maladaptive emotion processing, both in terms of perceptions and regulation of emotions, deficits in both being related to an underlying temperament of increased neuroticism (Barlow et al., 2014). Results of the current trial suggest a significant relationship between changes in these variables and changes in symptoms related to treatment with the UP. This suggests the UP may be effective in ameliorating emotion dysregulation and accompanying neurotic symptoms in patients with BD and comorbid anxiety, although perhaps only for a subset of patients as discussed above. Changes in acceptance of emotions and perceived control of emotions significantly predicted self-rated frequency of anxiety for both treatment groups, suggesting that how people perceive and react to their anxious experiences influences how pervasive they view anxiety to be in their lives.

Although not a direct aim of this study, incidental findings of the relationship between temperamental and emotion regulation variables and pharmacological treatment-as-usual outcomes are intriguing. For the pharmacotherapy treatment-as-usual group alone, change over time in the temperamental measure of agreeableness significantly predicted clinician-rated changes in anxiety and depression-related symptoms. Further, changes in conscientiousness and openness also predicted change in depressive symptoms. One hypothesis for these results is perhaps greater agreeableness, openness and conscientiousness correlates with greater medication compliance, an area for further inquiry.

Surprisingly, treatment groups did not differ in change over time on any secondary measure of emotion regulation, reactions to emotions, or temperament. This may be reflective of the more global, trait-like characteristics of these measures, which may be less sensitive to change over brief periods of

time. Future studies are needed to understand potential longitudinal effects of the UP on these more static, emotion processing-related variables over time.

There are several limitations to consider when interpreting the results of this study. First, this was a small pilot feasibility and acceptability trial; therefore, the small sample size does not afford sufficient statistical power to detect anything less than a large effect size. The results should be considered exploratory and preliminary, with the intention of generating further testing of this approach. Second, as our intention was to test the feasibility and acceptability of the UP as an adjunctive treatment to pharmacotherapy TAU, we opted to preserve the TAU condition as close to clinical TAU as possible. Specifically, we wished to determine whether the adjunctive UP+TAU approach would be feasible and acceptable in this comorbid population given the added burden of weekly visits and homework. However, we cannot rule out that the additional clinician face-time received in the UP+TAU condition relative to TAU (weekly as opposed to monthly) may account for some differences in treatment response between conditions. We attempted to address this limitation in part by including assessments of purported treatment mechanisms of action (e.g. emotion regulation skills). However, the difference in equipoise between treatments should nevertheless be considered as a limitation. Third, a single therapist conducted all treatment sessions for the UP+TAU group; therefore, we are unable to isolate effects of therapist from treatment effects, which limits the generalizability of the results. Fourth, in order to investigate more broadly the feasibility of this treatment approach as applied to a general treatment seeking population of patients with BD and anxiety, we opted for a heterogeneous bipolar sample including both bipolar I and bipolar II diagnoses. Although the sample included primarily patients with bipolar I (93%), given the small sample size in the current study we are unable to determine specific effects of treatment with the UP on discrete categories of BD patients. Finally, although attempts were made to maintain IE blindness to treatment condition, we cannot rule out the possibility that not all IE assessments were fully independent.

Conclusion

The current study sought to investigate the feasibility, acceptability, and preliminary efficacy of the UP as an adjunctive approach to pharmacotherapy treatment-as-usual in a population of BD patients

struggling with comorbid anxiety symptoms. Results of this study are promising – patients in the UP group found the treatment no less satisfactory than pharmacotherapy alone, were relatively homework compliant, and improved on indices of anxiety and depression. This suggests that weekly sessions with the UP are tolerable in this population, and there is a reasonable expectation that patients will be able to engage in treatment-related homework assignments between sessions. However, this study also suggests that not all patients benefit equally from the UP. Specifically, patients higher in baseline emotion dysregulation and levels of neuroticism fared less well in the current trial than those lower on these variables. Future studies are needed to determine a) alternate treatment delivery options for those patients who are more severely dysregulated at baseline; and b) whether alternate methods to enhance emotion regulation capacity, such as neuromodulation, attention training, or bias modification training used prior to a course of treatment with the UP might enhance UP treatment outcomes in this population. Overall, results from this study provide a helpful first step in determining the efficacy of a transdiagnostic CBT approach in addressing comorbid anxiety in the context of BD.

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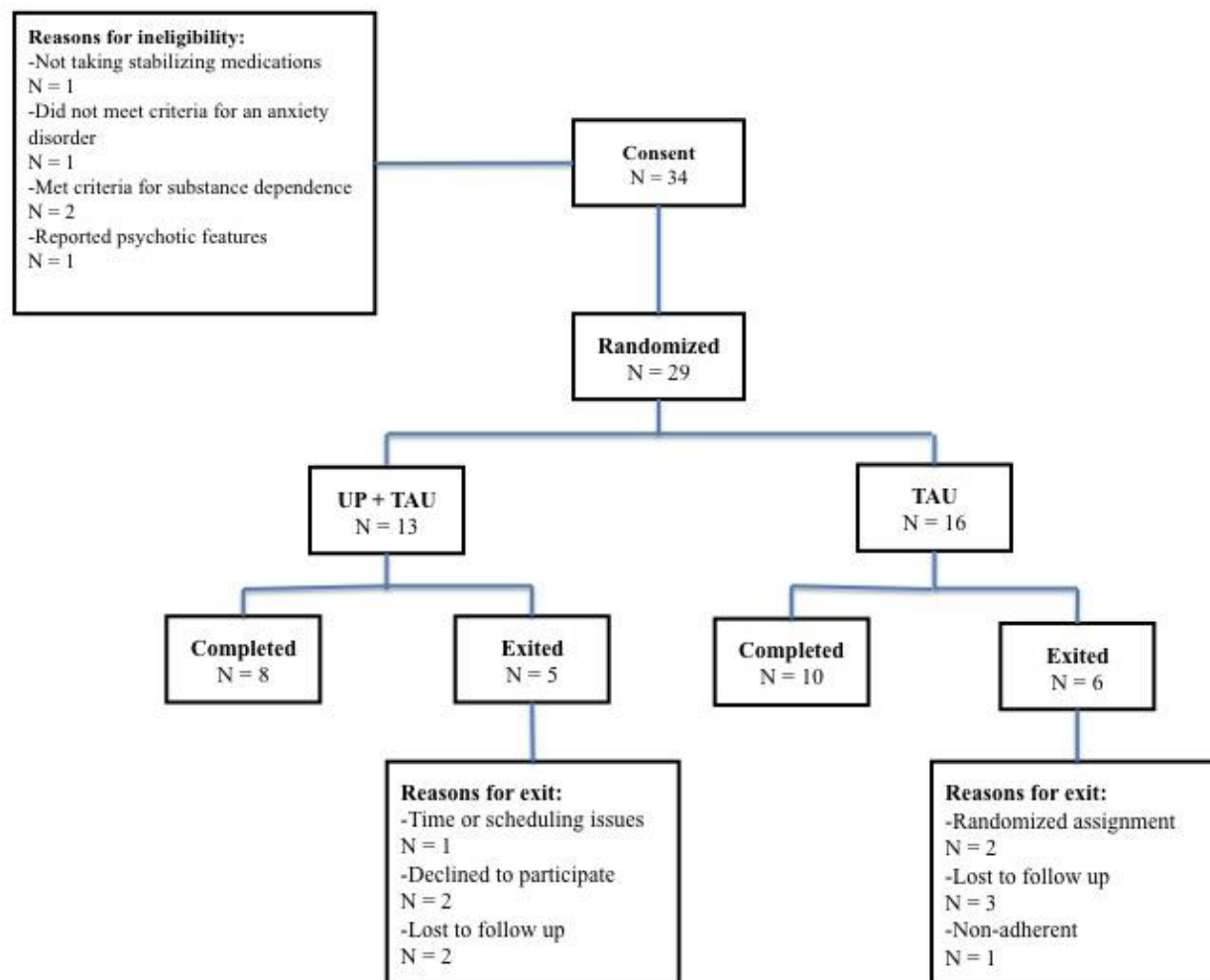


Fig 1. CONSORT diagram

Table 1. Baseline demographics.

Measure	Whole Sample N (%)	UP + TAU N (%)	TAU N (%)	Sig.
<i>Gender</i>				0.46
Male	12 (41.38)	6 (46.15)	6 (37.5)	
Female	17 (58.62)	7 (53.85)	10 (62.5)	

<i>Age</i>		43.72 ± 13.84	43.08 ± 13.84	44.25 ± 14.27	0.83
<i>Race</i>					0.82
	White	24 (82.76)	11 (84.62)	13 (81.25)	
	Black	2 (6.90)	1 (7.69)	1 (6.25)	
	Other or unreported	3 (10.34)	1 (7.69)	2 (12.5)	
<i>Ethnicity</i>					1.00
	Hispanic/Latino	1 (3.44)	1 (7.69)	0 (0.00)	
	Not Hispanic/Latino	26 (89.66)	11 (84.62)	15 (93.75)	
	Unreported	2 (6.90)	1 (7.69)	1 (6.25)	
<i>Education</i>					0.29
	Graduate School	8 (27.59)	5 (38.46)	3 (18.75)	
	College Graduate	12 (41.38)	5 (38.46)	7 (43.75)	
	Partial College	7 (24.14)	2 (15.38)	5 (31.25)	
	High School Graduate	2 (6.90)	1 (7.69)	1 (6.25)	
<i>Bipolar Diagnosis</i>					0.91
	BP-I	27 (93.10)	12 (92.31)	15 (93.80)	
	BP-II	2 (6.90)	1 (7.70)	1 (6.30)	
<i>Medication Load</i>					
	Anticonvulsants	29 (100.00)	13 (100.00)	16 (100.00)	1.00
	Antipsychotics	14 (48.28)	8 (61.54)	6 (37.50)	0.08
	Benzodiazepines	16 (55.17)	5 (38.46)	9 (56.25)	0.87
	SSRI	4 (13.79)	1 (7.69)	4 (25.00)	0.73
	SNRI	1 (3.45)	1 (7.69)	0 (0.00)	0.45
	Atypical				
	Antidepressants	5 (17.24)	1 (7.69)	3 (18.75)	1.00
	Psychostimulants	4 (13.79)	0 (0.00)	4 (25.00)	0.05*
	Hypnotics	2 (6.90)	2 (15.38)	1 (6.25)	0.66

Note: * $p=.053$.

Table 2. Baseline clinical characteristics.

Measure	UP + TAU (M±SD)	TAU (M±SD)	<i>t</i>	Sig.
<i>Symptoms/Functioning</i>				

HAM-A	13.15 (7.20)	18.06 (6.7)	1.90	0.08
ASQ-I	4.48 (1.52)	4.78 (2.07)	0.45	0.66
ASQ-F	4.09 (2.33)	4.68 (2.15)	0.69	0.49
HAM-D	9.62 (6.21)	12.63 (5.51)	1.38	0.18
QIDS	11.40 (5.34)	12.27 (4.34)	0.41	0.68
ASRM	3.11 (3.26)	3.58 (2.91)	0.35	0.73
YMRS	3.08 (2.53)	2.94 (3.04)	0.13	0.90
LIFE-RIFT	11.69 (3.30)	12.25 (2.43)	0.11	0.61
<i>Treatment Satisfaction</i>				
CSQ-8	28.33 (3.57)	27.25 (3.82)	0.66	0.52
<i>Emotion Processing</i>				
ACS	4.09 (0.58)	3.91 (0.52)	0.85	0.41
ASI	31.50 (9.06)	25.63 (14.30)	0.17	0.22
BIS	16.50 (1.45)	14.63 (2.80)	2.11	0.05*
BAS-Drive	8.08 (2.53)	6.44 (3.53)	1.40	0.17
BAS-Fun	6.92 (3.14)	7.93 (2.86)	0.91	0.37
BAS-Reward	12.54 (2.33)	11.25 (2.38)	1.47	0.16
DERS	3.02 (0.49)	2.88 (.35)	0.67	0.42
NEO -Neuroticism	16.92 (2.25)	16.00 (2.80)	0.96	0.35
NEO-Agreeableness	19.96 (4.01)	20.56 (5.03)	0.35	0.72
NEO-Openness	18.74 (4.33)	19.06 (3.19)	0.48	0.63
NEO-Conscientiousness	13.68 (2.65)	13.56 (2.76)	0.12	0.91
RRS	58.73 (12.79)	59.88 (12.79)	0.30	0.77

Note: HAM-A = Hamilton Anxiety Rating Scale; ASQ-I = Anxiety Sensitivity Questionnaire, Intensity Subscale; ASQ-F = Anxiety Sensitivity Questionnaire, Frequency Subscale; HAM-D = Hamilton Depression Rating Scale; QIDS = Quick Inventory of Depressive Symptoms; ASRM = Altman Self-Rated Mania Scale; YMRS = Young Mania Rating Scale; LIFE-RIFT = Longitudinal Interval Follow-Up Evaluation Range of Impaired Functioning Tool; CSQ-8 = Client Satisfaction Questionnaire; ACS = Affective Control Scale; ASI = Anxiety Sensitivity Index; BAS= Behavioral Activation Scale; DERS = Difficulties in Emotion Regulation Scale; NEO = NEO Five Factor Inventory of Personality; RRS = Ruminative Response Scale. * $p < .05$.

Table 3. Primary symptom outcomes.

ITT	Treatment Completers
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		(N=28)						(N=18)					
		Mean Difference (UP vs. TAU)	<i>t</i>	Sig.	Cohen's <i>d</i>	95% Confidence Interval for Difference		Mean Difference (UP vs. TAU)	<i>t</i>	Sig.	Cohen's <i>d</i>	95% Confidence Interval for Difference	
						Lower Bound	Upper Bound					Lower Bound	Upper Bound
<i>Treatment Acceptability</i>													
CSQ		1.62	1.21	NS	0.51	-1.16	4.40	1.81	1.27	NS	0.62	-1.20	4.82
<i>Anxiety</i>													
HAMA		-5.91	2.46	0.02	0.88	-10.82	-1.00	-6.58	2.30	0.03	1.01	-12.53	-0.63
ASQ-F		-1.08	1.62	NS	0.62	-2.44	0.29	-1.39	1.92	0.07	0.87	-2.90	0.12
ASQ-I		-1.05	1.73	NS	0.66	-2.29	0.20	-1.18	1.68	NS	0.78	-2.65	0.30
<i>Depression</i>													
HAMD		-4.19	2.36	0.02	0.82	-7.80	-0.58	-4.44	2.66	0.01	1.06	-7.80	-0.58
QIDS		-3.75	2.71	0.01	1.06	-6.60	-0.90	-5.19	4.07	<.001	1.67	-7.82	-2.56
<i>Mania</i>													
YMS		-1.76	1.24	NS	0.41	-4.62	1.11	-2.01	1.19	NS	0.48	-5.51	1.48
ASRMS			1.10	NS	0.35	-1.51	0.44	-0.45	0.86	NS	0.30	-1.53	0.63
<i>Symptom Interference in Functioning</i>													
LIFE-RIFT		-1.23	1.31	NS	0.48	-3.15	0.69	-2.01	1.98	0.06	0.86	-4.10	0.09

Table 4. Baseline predictors of symptom change.

	Anxiety				Depression				Functioning	
	Clinician-rated		Self-report		Clinician-rated		Self-report		Clinician-rated	
	(HAM-A)		(ASQ-F)		(HAM-D)		(QIDS)		(LIFE-RIFT)	
	UP+T AU	TA U	UP+T AU	TA U	UP+T AU	TAU	UP+T AU	TA U	UP+T AU	TA U
	Beta	Beta	Beta	Beta	Beta	Beta	Beta	Beta	Beta	Beta
<i>Temperament</i>										
NEO										
Neuroticism	-0.72**	0.47	-0.67*	0.35	-0.84**	0.37	-0.31	0.25	-0.65*	0.51
Agreeableness	0.40	0.41	0.38	0.22	0.77**	0.59*	-0.19	.66**	0.36	0.45
Openness	0.39	0.56*	0.63*	0.05	0.50	0.55*	-0.38	.69**	0.11	0.54
Extraversion	-0.15	0.16	-0.59	0.31	0.00	0.16	0.02	0.19	0.14	0.15
Conscientiousness	-0.28	0.17	-0.33	0.32	0.00	0.21	-0.01	0.03	-0.17	0.20
<i>Rumination</i>										
RRS	-0.04	0.29	0.14	0.33	0.21	-0.15	0.01	0.22	-0.27	0.08
RRQ	0.18	0.24	-0.16	0.06	0.06	0.40	0.41	0.37	0.38	0.55
<i>Inhibition/Activation</i>										
BAS-Drive	-0.07	0.44	-0.06	0.49	-0.30	0.79**	0.52	0.56*	-0.07	0.54
BAS-Fun	0.26	0.05	0.35	0.00	0.07	0.23	0.58	0.13	0.14	0.03
BAS-Reward	0.31	0.22	0.23	0.02	0.23	0.08	0.61	0.03	0.29	0.06
<i>Affective Control</i>										
ACS										
Total	-0.77**	0.02	-0.51	0.15	-0.53	-0.03	-0.57	0.01	-0.52	0.35
Anger	-0.61	0.14	-0.23	0.11	-0.27	-0.10	-0.68*	0.12	-0.53	0.22
PA	-0.53	0.37	-0.41	0.12	-0.21	0.23	-0.47	0.37	-0.21	0.51
Depression	-	-	-0.45	-	-0.62	-0.46	-0.47	-	-0.47	-

		0.72**	0.3		0.3			0.4		0.0
			4		0			1		4
		-	-		-			-		-
Anxiety	0.87**	0.1	-0.56	0.3	0.89**	0.05	-0.52	0.1	-	0.1
	*	4		7	*			5	0.76**	5
<i>Anxiety Sensitivity</i>										
ASI	-0.37	0.0	-0.67*	0.0	-0.15	0.20	-0.20	0.1	0.01	0.1
		6		6				2		3
<i>Emotion Regulation Skills</i>										
DERS										
Total	-	0.1	-0.55	0.1	-0.60	0.19	-0.34	0.1	-0.53	0.5
	0.76**	8		5				4		3
Non-Acceptance	-	0.2	-0.57	0.1	-0.71*	0.05	-0.45	0.2	-0.64*	0.4
	0.83**	4		2				4		1
Goal-Interference	-	-	-0.66*	-	-0.39	-0.09	-0.62	-	-0.59	-
	0.79**	0.3		0.1				0.4		0.2
		8		2				6		7
Impulsivity	-0.59	0.1	-0.49	0.1	-0.42	0.60*	-0.27	0.3	-0.24	0.4
		0		4				9		6
Awareness	-0.20	0.2	0.20	0.2	-0.04	0.14	-0.15	0.1	-0.30	0.3
		8		1				4		4
Strategies	-	0.1	-	0.1	-	-0.46	-0.19	0.4	-0.55	0.0
	0.80**	9	0.73**	3	0.75**			0		5
Clarity	-0.48	0.4	-0.54	0.0	-0.43	0.41	-0.01	0.5	-0.24	0.4
		1		3				0		7

Table 5. Change in temperament and emotion regulation variables as predictor of change in symptoms.

	Anxiety				Depression				Functioning	
	Clinician-rated		Self-report		Clinician-rated		Self-report		Clinician-rated	
	(HAM-A)		(ASQ-F)		(HAM-D)		(QIDS)		(LIFE-RIFT)	
	UP+T	TA	UP+T	TAU	UP+T	TAU	UP+T	TAU	UP+T	TAU
	AU	U	AU		AU		AU		AU	
	Beta	Beta	Beta	Beta	Beta	Beta	Beta	Beta	Beta	Beta
<i>Temperament</i>										
NEO										
Neuroticism	-0.61	0.15	-0.29	-0.19	0.87**	0.36	-0.20	0.18	-0.59	0.41
					*					
Agreeableness	0.02	0.75**	-0.34	0.60*	0.21	0.56*	0.02	0.77*	0.35	0.55
								*		
Openness	0.31	-	0.47	-0.44	0.27	-0.19	-0.29	0.03	0.22	-0.19
		0.12								
Extraversion	-0.39	-	-0.51	-0.37	0.05	-0.27	-0.62	-0.19	0.00	-0.34
		0.49								
	-0.44	0.01	-0.58	0.26	-0.43	0.28	-0.24	0.19	-0.03	0.19

Conscientious											
Rumination											
RRS	0.64*	0.52	0.84**	0.35	0.49	0.46	-0.04	0.66*	0.31	0.23	
RRQ	0.77**	0.26	0.94**	0.10	0.69*	0.12	0.12	0.36	0.38	-0.08	
Inhibition/Activation											
BIS	0.74**	-0.11	0.55	-0.05	0.85**	-0.15	0.00	-0.09	0.67*	-0.44	
BAS-Drive	0.19	-0.22	0.12	-0.29	0.07	-0.11	0.39	-0.22	0.20	-0.49	
BAS-Fun	-0.23	0.06	-0.48	-0.44	-0.16	-0.29	-0.01	0.00	0.17	-0.11	
BAS-Reward	-0.15	-0.20	0.03	-0.35	-0.42	-0.60*	-0.22	-0.48	-0.15	-0.43	
Affective Control											
ACS											
Total	0.69*	0.69**	0.83**	0.63*	0.49	0.28	0.39	0.47	0.23	0.61*	
Anger	0.58	0.52	0.39	0.31	0.28	0.10	0.79**	0.32	0.30	0.46	
PA	0.48	0.23	0.64*	0.20	0.27	0.11	0.39	0.01	0.03	0.02	
Depression	0.51	0.23	0.79**	0.33	0.36	0.52	0.18	0.43	-0.02	0.46	
Anxiety	0.84**	0.33	0.95**	0.29	0.73**	0.00	0.29	0.27	0.50	0.38	
Anxiety Sensitivity											
ASI	0.64*	0.19	0.81**	0.21	0.58	-0.13	0.44	0.13	0.32	0.15	
Emotion Regulation Skills											
DERS											
Total	0.69*	0.66**	0.86**	0.61*	0.59	0.85**	0.15	0.69*	0.23	0.82**	
Non-Acceptance	0.64*	0.45	0.32	0.91**	0.54	0.81	0.22	0.25	0.16	0.55*	
Goal-Interference	0.66*	0.53	0.89**	0.25	0.66*	0.59*	-0.12	0.81**	0.31	0.62*	
Impulsivity	0.65*	0.55*	0.14	0.10	0.41	0.48	0.24	0.23	0.24	0.31	
Awareness	0.27	-0.10	0.00	-0.31	0.60	0.03	-0.04	0.05	0.26	0.29	
Strategies	0.70*	0.19	0.91**	0.34	0.59	0.38	0.17	0.35	0.23	0.31	

Clarity	0.53	0.47	0.72**	0.42	0.33	0.49	0.15	0.54	0.07	0.61*
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Highlights

- Examines a transdiagnostic CBT approach to treating anxiety in bipolar disorder (UP).
- Treatment with the UP demonstrated feasibility and acceptability.
- The UP adjunctive to medication TAU resulted in greater reductions in anxiety.
- The UP adjunctive to TAU also resulted in greater reductions in depression.
- UP adjunctive to TAU was a viable approach to treating anxiety in bipolar disorder.