Comparing the Effectiveness of Imagery Focussed Cognitive Therapy to Group Psychoeducation for Patients with Bipolar Disorder: A Randomised Trial

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This study was registered with ClinicalTrials/gov (Identifiier NCT03750305) and supported by a subsidy by Rino Zuid clinical training course in support of first authors PhD.

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Background: Bipolar disorder is a severe, chronic mental disorder. Treatment options are limited, with pharmacological approaches continuing to dominate. However, relapse rates remain high. Several adjunctive psychosocial interventions, mostly psychoeducation (PE) and cognitive behavioural therapy (CBT), have been trialled, but treatment innovation is still needed. In the past, brief group PE has proven as beneficial as longer individual CBT in reducing levels of depression and increasing self-management strategies. We compared the relative effectiveness of group PE to an imagery focussed cognitive behavioural therapy (ImCT). Study design: This was a randomised parallel group study with both daily and weekly measures. A total of 62 adult patients were randomly allocated to either ImCT or group PE. Daily, weekly and pre-and post-intervention measures were used to assess impact on (i) mood instability, (ii) overall levels of depression, anxiety and mania, and (iii) general functioning, hopelessness and imagery characteristics. A four-week baseline and 16-week follow-up period were included.

Results: Mood instability reduced in both conditions after intervention. Levels of mania, depression and anxiety also reduced in both conditions, but on the daily measures, depression and anxiety significantly more so in the ImCT condition. Compared with the PE condition, the ImCT condition additionally showed reduced hopelessness, and a decrease in intrusive, problematic imagery.

Limitations: These findings need to be replicated in a larger trial.

Conclusions: Findings suggest that ImCT is a promising new avenue for management of bipolar disorder, an area in which treatment development is urgently needed.

Key words

Mental Imagery

Bipolar Disorder

Psychoeducation

Mood instability

Cognitive behavioural therapy

Introduction

Bipolar disorder (BD) is a chronic, severe mental disorder typically characterised by recurring episodes of depression and (hypo)mania (APA, 2013). Prevalence has been estimated at 1-4% of the general population (Kroon et al., 2013). BD has the highest rate of suicide of all psychiatric disorders, with recent estimates suggesting that of individuals with BD will attempt complete suicide (Miller & Black, 2020). BD is also co-morbid with a number of other mental disorders, notably anxiety and alcohol and substance misuse (Merikangas et al., 2007), which make diagnosis and treatment more challenging. Unsurprisingly, BD has substantial associated healthcare costs (Ketter, 2010) and a marked impact on quality of life for individuals (Rademacher et al., 2007), and caregivers (Perlick et al., 2001). There is an urgent need for treatment development in BD. This introduction first sets out the limitations of current approaches to treatment of BD and then describes a novel psychological intervention aimed at improving mood instability and anxiety in BD via focusing on maladaptive mental imagery processes. Mental imagery impacts on emotion, motivation and behaviour and contributes to mood dysregulation and instability in a transdiagnostic manner (see Ji et al., 2019 for a review), thereby holding potential as an innovative treatment target in BD.

Pharmacological approaches to BD have predominated for many years, with all international guidelines recommending that BD be managed primarily by medication, such as Lithium (APA, 2002, 2013; NICE, 2018). However, frequent relapse remains common (Perlis et al., 2006) and the side effect burden of such medications can be high, leading to difficulties with compliance. Psychological treatments may offer particular scope for benefit as they bypass challenges associated with pharmacotherapy: for instance, administration of antidepressant medication can induce a ‘manic switch’ (Pacchiarotti et al., 2013). Psychological treatments are currently recommended as an adjunct to medication by

international guidelines (APA, 2002; NICE, 2018), specifically to prevent relapse or target inter-episodic mood symptoms. In addition, it is recommended that psychoeducation become an integral part of good clinical practice for all individuals diagnosed with BD (Goodwin et al., 2016; NICE, 2018). Family therapy interventions, inter-personal and social rhythms therapy, and cognitive behavioural therapy (CBT) have all been evaluated in rigorous clinical trials. Unfortunately, the evidence-base for the effectiveness of psychological interventions for BD remains mixed (Jauhar et al., 2016). Given the limitations of current pharmacological and psychological treatment options for BD, it is clear that innovation is urgently needed.

As highlighted above, one potential treatment target which has been gathering interest in psychological research is maladaptive mental imagery. In contrast with verbal cognition, which takes the form of words, mental imagery "occurs when perceptual information is accessed from memory, giving rise to seeing with the mind's eye, hearing with the mind's ear and so forth" (Kosslyn et al., 2001). Mental imagery recruits similar neural circuitry to perception (Pearson et al., 2015) and so is experienced 'as if' reality. In BD, Holmes and colleagues (Holmes et al., 2008) proposed that imagery acts as an amplifier for mood states (depression, mania, anxiety), fuelling approach or avoidance behaviour. A burgeoning evidence-base lends support to this theory. For example, in a naturalistic study Holmes et al. (2011) found that in patients with bipolar disorder, high levels of intrusive imagery were associated with greater mood instability. In phenomenological studies, individuals with BD have been shown to report vivid, affect-laden mental imagery across a variety of mood states (Di Simplicio et al., 2016; Hales et al., 2011; Ivins et al., 2014). In community samples, individuals at high risk of BD demonstrate a greater tendency to use mental imagery in everyday life and a greater emotional impact of prospective (future-oriented) imagery (Ng et al., 2016). Therefore, in the context of BD, targeting maladaptive imagery-based cognitions

may prove beneficial and provide much needed treatment innovation. However, further controlled clinical studies to test mental-imagery focussed interventions in BD are needed.

To date, much of the focus of psychological and pharmacological approaches to BD has been on prevention and treatment of full-blown mood episodes. However, there are neglected features of the BD experience that require further investigation. One such feature is chronic subsyndromal inter-episodic mood instability (Henry et al., 2008) which impacts on functioning (Marangell et al., 2009) and is associated with worse prognosis (Altshuler et al., 2006). As highlighted, mental imagery has been proposed to have a role in driving unstable mood (Holmes et al., 2008; Holmes et al., 2011). For example, people with BD can experience vivid negative future-oriented mental imagery (e.g. of being rejected socially or experiencing a relapse) which amplify expectation of future threat, causing anxiety or low mood and thereby contributing to mood instability (Holmes et al., 2011). Vivid positive mental imagery (e.g. of exciting experiences or achieving personal goals) has also been shown to elevate mood in at-risk of bipolar samples (O' Donnell et al., 2017). Thus, targeting maladaptive mental imagery may improve mood stability. As noted previously, a key unmet need in BD is management of co-morbid anxiety, which worsens treatment outcome and heightens risk of suicide (Simon et al., 2004). Anxiety provoking mental imagery has been highlighted in clinical guidelines as a potential target in BD that requires further consideration (Goodwin et al., 2016).

Holmes and colleagues (Hales et al., 2018; Holmes et al., 2016; Holmes et al., 2019) developed an imagery based cognitive therapy (ImCT) treatment for BD targeting mood instability and anxiety, also known as the Mood Action Psychology Programme; MAPP. This manualised treatment consists of an extended, four session assessment resulting in a focussed imagery micro-formulation; 4-6 treatment sessions using one or more of four distinct

imagery-based techniques to target the formulated maladaptive imagery symptom; and two consolidation sessions in which a visual blueprint (record) of the treatment is made.

In a controlled case series study, Holmes et al. (2016) demonstrated that the ImCT, or MAPP treatment, improved mood instability in 11 of 14 patients, and led to a significant reduction in mean depression and anxiety post-intervention scores. A trial of ImCT against standard care has been conducted in the UK (Trial registration: ISRCTN16321795) (Steel et al., 2020) with results as yet unpublished.

In this study, we compare the effectiveness of ImCT against psychoeducation in an adequately powered sample of patients. PE is one of the most commonly applied psychosocial interventions for BD and recommended in international clinical guidelines (Kupka et al., 2015; NICE, 2014). In a previous randomised controlled trial, six sessions of PE were found to be almost as efficacious as 20 sessions of CBT in terms of symptom burden and likelihood of relapse (Parikh et al., 2012). In addition, we also sought to collect data on acceptability and feasibility, as assessed via rates of completion of self-report measures and overall treatment retention rates.

Specifically, we hypothesised that, compared with PE, ImCT would result in greater reductions in: (i) mood instability (the primary outcome variable), quantified as the measure-by-measure variability on daily Likert-scales of mania, depression and anxiety as well as weekly questionnaires measuring anxiety, depression and levels of mania; (ii) symptoms of depression, mania and anxiety (secondary outcome variables), as measured by mean daily and weekly measures as before and (iii) levels of hopelessness, daily functioning and affect lability at end of intervention and at follow-up. Moreover, we expected that the ImCT group would have a larger reduction in problematic imagery measured both weekly and at fixed time points during the study.

Methods

Study design

This was a randomised, parallel group study using a case series design, comparing two types of psychosocial interventions for patients with bipolar disorder (BD): either twelve 1-hour sessions of ImCT or six 2-hour sessions of group psychoeducation. Both groups received standard care as required, which could include any of the following: adjunctive medication, supportive sessions with a specialised mental health nurse, a single session with a family therapist, and crisis management interventions. The 26-month study, during the period October 2018 until December 2020, used daily and weekly online self-report measures and blinded outcome assessors. It was conducted in a specialised community mental health team for BD using a shared case load system, situated within a large psychiatric hospital in the Netherlands. Participants completed four weeks of daily and weekly online baseline monitoring of mood and before being randomly assigned to one of the two intervention groups. Daily and weekly self-report data was collected during the intervention period and completed at five face-to-face assessments: at intake, pre-treatment, post- treatment, and at 8 and 16-weeks follow-up. All measures were deemed feasible and realistic in the afore-mentioned small-scale studies (Hales et al., 2018; Holmes et al., 2016), with high data adherence from participants. Mood monitoring is a core and integral part of management of symptoms in bipolar disorder recommended by NICE (NICE, 2014). Indeed, mood monitoring alone can improve mood stability in patients with bipolar II disorder (Bopp et al., 2010). Both daily and weekly mood monitoring required little time; daily not more than a few minutes, weekly not more than 15 minutes.

Based on the parameters of previous studies investigating ImCT with similar methodologies (Hales et al., 2018; Holmes et al., 2016) the study aimed to include 60 participants for sufficient power to test the primary and secondary hypotheses. This trial was

pre-registered at Clinicaltrials.gov (identifier NCT03750305). Ethical approval was given by METC azM/UM (NL64193.068.18/METC183005).

Participants

Participants were recruited by internal advertisement using online and paper information leaflets and posters in waiting rooms. Full details of the recruitment, screening and exclusion criteria are provided in the Supplementary Materials. At referral to the service, all patients had received a diagnosis of BD type I or II after a comprehensive interview with a psychiatrist and specialised nurse, and a multidisciplinary consensus meeting using DSM 5 criteria (APA, 2013).

Interventions:

ImCT:

Thirty participants attended 12 1-hour sessions of Imagery Focussed CBT (ImCT), which included assessment, active treatment and consolidation sessions. The mean duration of ImCT was 12.83 weeks (*sd* = 1.60; range = 12-19 weeks). ImCT consisted of an in-depth assessment or mapping phase (4 sessions), followed by an active treatment phase (6 sessions), and a consolidation phase (2 sessions). The treatment followed a published manual developed by Holmes et al. (2019). The in-depth assessment included identifying problematic imagery, for example imagery that contributed to mood instability or anxiety. Subsequently a micro-formulation was co-constructed with the participant to understand the triggers for problematic imagery, the content of imagery and associated emotions and appraisals, and maintenance factors. The micro-formulation provided a jointly agreed target for the subsequent imagery-based interventions. The active intervention consisted of using one or more of the following imagery strategies to target problematic imagery: metacognitive imagery interventions, rescripting of imagery, promoting positive imagery or competing imagery tasks. Metacognitive imagery techniques aimed to help participants to view the

image as just a mental representation (for example to change the image so that the participant learns that 'an image is just an image'), rescripting focussed on changing problematic imagery into positive or benign images with updated associated appraisals. Positive imagery techniques consisted of creating positive, soothing or mood-enhancing imagery. Imagery competing tasks helped to reduce problematic imagery by use of concurrent visuospatial task. The final two sessions consisted of a consolidation phase in which participant were guided to make a film or image(s) recorded on their cell phone which reminded them of helpful imagery strategies they had learned that could contribute to relapse prevention.

The ImCT intervention was delivered by four therapists, all experienced clinical psychologists or psychotherapists with more than 8 years post-qualification experience. Three therapists had prior experience working with BD, one with schema therapy and personality disorders. Therapists delivering ImCT received two days training in ImCT and weekly group supervision from developers of the original ImCT manual and intervention (SH; MdS) during which all participants in treatment were discussed. One of the recurring items on the agenda was adherence to protocol. Supervision did not indicate any adherence violations.

All sessions were recorded, and 10% of sessions were rated by an independent research assistant using a bespoke protocol checklist to assess adherence to ImCT protocol. A high fidelity to protocol was demonstrated.

Psychoeducation:

Participants assigned to the group psychoeducation intervention received six sessions of 2 hours duration over 6 consecutive weeks, following a well-known manual distributed since 2015 by the Dutch knowledge centre for BDs (KenBis) and evaluated as effective by Zyto (Zyto et al., 2020). In the first three sessions patients received information on BD, symptoms, prevalence, aetiology and mood stabilisers. The remaining sessions focussed on (early) recognition of mood variations, and management or coping strategies. Finally,

medication adherence strategies and relapse strategies were discussed, resulting in an individual relapse prevention plan. The PE group was supported by easily accessible online information on the topics covered in the PE, consisting of written and video material. The psychoeducation groups were delivered by qualified mental health nurses, all with more than 10 years' experience in BDs care facilities. All were trained in the psychoeducation method by KenBis in 2015 and received regular continuing professional development in group psychoeducation and had monthly group coaching. [1]

Materials:

Mood measures daily

National Institute of Mental Health Life Chart Methodology (NIMHLCM) measured changes in mood (Denicoff et al., 2000). Participants rated their mood (mania and depression separately) on a 9-point Likert scale, ranging from -4 (severe depression, admission required due to severe dysfunction) to 0 (stable mood) to +4 (severe mania, admission required due to severe dysfunction). The NIMHLCM was validated by Denicoff and colleagues (Denicoff et al., 2000) demonstrating a high correlation between the life chart method ratings and ratings on the Inventory of Depressive Symptomatology, (r = -0.87, p < .001), on the Young Mania Rating Scale (r = 0.66, p < 0.001), and Global Assessment of Functioning (GAF scores) (r = 0.73, p < .001).

Likert scale for anxiety: Daily levels of anxiety were measured using a 11-point Likert scale, ranging from 0, 'no anxiety at all', to 10, 'severe anxiety'.

Mood measures weekly

[1] Due to Covid-restriction during the last months of the trial, the last PE group (with 6 participants participating in the study) and the last 3 ImCT treatments were entirely online. One ImCT treatment was partially online (4 out of 12 sessions).

Altman Self-Rating Mania scale (ASRM) is a self-report measure of mania symptom severity, often used in research on BD. The ASRM consists of five items, each scored on a 5-point Likert scale with answers ranging from 0 ("not more than usual") to 4 ("more than usual most of the time"). Previous research showed good psychometric properties and good test-retest reliability for the ASRM (Altman et al., 1997).

Quick Inventory of Depressive Symptomatology, Self-report (QIDS-SR) is a 16-item self-report measure of depression covering the nine DSM 5 symptoms. Answers are scored on a four-point Likert scale, with answers ranging from 0 ("no change in my usual") to 3 ("great difficulty with"). The QIDS-SR total score correlates highly (r = .86) with the Hamilton Rating Scale of Depression and has a high internal consistency (Cronbach alpha = .92) (Rush et al., 2003).

Beck Anxiety Inventory (BAI; (Osman et al., 1993) is a 21-item self-report questionnaire used for measuring the severity of anxiety. Answers are rated on a 4-point Likert scale with answers ranging from 0 ("not at all") to 3 ("very much"). The BAI has a high reliability (Cronbach alpha .95) and high test re-test reliability (r = .65, p < .05).

Pre and post measures (at start baseline, start intervention, end intervention, 8- and 16-week follow-up):

Mood instability: Affect Lability Score Short Version (ALS-18): The ALS-18 (Oliver & Simons, 2004) is an 18-item self-report scale measuring lability in affect. Ratings are made on a 4-point scale with a maximum score of 72. Scores range from 1 ("very characteristic of me"), to 4 ("very uncharacteristic of me"). Higher scores are associated with lower affect lability. The ASL-18 has high reliability (Cronbach alpha a = .87) (Look et al., 2010) and appears significantly associated with concurrent measures of depression and difficulties in emotion regulation (*rs* between .90 - .92) (Contardi et al., 2018).

Level of general functioning and coping: Longitudinal Interval Follow up Evaluation – Range of Impaired Functioning Tool (Life-Rift): Participants rated their level of functioning using the Life-Rift (Leon et al., 1999) a 9-item scale for people with affective disorders measuring four different functional areas (employment, interpersonal relations, satisfaction and recreation) on a 5-point Likert scale (low rating implies higher functioning). There is a high inter-rater reliability (r = .94) and high internal consistency (Cronbach alpha between .78 and .84) (Leon et al., 1999).

Level of hopelessness: Beck Hopelessness Scale (BHS): The BHS (Beck et al., 1997) Beck, Brown, & Steer, 1997) is a 20 item self-report scale measuring hopelessness. Answers are rated "yes" or "no". Beck and colleagues (Beck et al., 2006) found that a score of 9 or higher predicted 16 of 17 (94.2%) psychiatric patients who later died by suicide. The BHS demonstrates good internal consistency (Cronbach alpha a = .93) and has high reliability in psychiatric samples (Beck et al., 1997). Higher scores are associated with higher hopelessness.

Imagery characteristics:

Weekly measure: The Visual Analogue Scales of Imagery Characteristics (VAS-Imagery): Four imagery questions tailored to BD populations (Holmes et al., 2016). These were: "How often did you experience intrusive imagery over the last week?", "How much did these influence your daily life?", "How much control did you experience over these images?" and "How unpleasant were these images?", rated on a 11-point VAS-scale, ranging from 0 ("not at all") to 11 ("all the time or very much").

Mental Imagery and Coping with BD Questionnaire (MICQ-BD): is a 14 item self-report instrument developed in the UK and used in prior studies on ImCT (Hales et al., 2018; Holmes et al., 2016). It assesses patient responses to, and ability to cope with problematic mental imagery, e.g. "When an unhelpful mental image popped up, I could disengage from

it", Ratings were on a 5-point scale from "not at all" to "a lot". Holmes et al. (2016) calculated the internal consistency (Cronbach alpha *a* = .70) to be satisfactory. Higher scores are associated with more perceived control over problematic mental imagery.

Results

Insert Figure 1

In total 76 participants expressed an interest in participating from which a total of 62 participants were included. An overview of participants and attrition is presented in Figure 1. Adherence to treatment was high in both conditions, with one drop-out in each condition. Except for the higher number of admissions in the ImCT group, there were no significant differences between the groups for demographic and clinical characteristics.

Insert Table 1

Changes in Mood Instability

First, we estimated changes in mood instability. We computed the measure-by-measure variability of scores on the daily mania, depression and anxiety measures and weekly ASRM, QIDS-SR and BAI scores. Rather than use measures of variability that ignore the order of the measures (e.g. variance, standard deviation, or entropy), a measure-by-measure change score was computed based on the absolute difference between subsequent

measures. So, for example, a participant with the (ordered) scores: 1, 5, 2, 7 would have mean measure-by-measure change values of: 4 (abs(1-5)),3 abs(5-2)), and 5 abs(2-7)). Table 2 shows the mean and standard deviation of the measure-by-measure scores for each group.

Insert Table 2

Participants in both groups experienced more stability in symptoms of mania, depression and anxiety on the daily measures after the intervention (30-55% reductions). On the weekly measures of mania (ASRM), depression (QIDS-SR) and anxiety (BAI) a similar reduction in variability was found after intervention for both groups. The largest reduction in both groups was in variability of mania and anxiety scores (both daily and weekly).

Results of mixed-effects linear modelling of measure-by-measure change (mbm_value) scores are shown in Table 3. First, the effect of phase (baseline before intervention and follow-up afterwards) is tested by comparing a model containing a fixed effect of Phase [effects structure: (mbm_value ~ phase + (1 | subjectID))] to a random-effect-only model (Null) [effects structure: (mbm_value ~ + (1 | subjectID))] for each measure. Second, a model containing an interaction between phase and condition was compared to the phase-only model [effects structure: (score ~ phase + phase:condition + (1 | subjectID))] to test for an interaction between phase and treatment condition. No main effect of intervention condition was included because there was no theoretical reason to assume a significant difference between conditions before random assignment. The interaction models should be interpreted with caution because the detection of group effects in pre-post designs is most appropriately tested with an ANCOVA analysis (Clifton & Clifton, 2019) (these analyses are included in Table S1 and generally agree with the mixed-effects results). All comparisons were done with a chi squared test and no correction for multiple comparisons was made. All

models used a maximum likelihood estimation with the lmer() function from the R package lme4 (version 4.1) (Bates et al., 2015).

Insert Table 3

Results show a significant effect of phase for all six measure-by-measure variability scores. However, no significant interaction between phase and treatment condition were found, indicating, no evidence in support of a larger reduction of mood instability in the ImCT group.

To evaluate the stability of these changes by comparing these measures between the first follow-up phase (first 8 weeks post intervention) and the second follow-up phase (the subsequent 8 weeks i.e. weeks 9-16) the mixed-effects models were slightly different. Specifically, since differences between treatment conditions were expected, the phase plus interaction model was replaced with two models: a phase and condition model [effects structure: (score ~ phase + condition + (1 | subjectID))] and a full model [effects structure: (score ~ phase + condition + phase:condition + (1 | subjectID))]. Few, if any, significant differences on these measures were seen between the first and second follow-up phases, indicating the changes were relatively stable 16 weeks after treatment concluded (see Table S3 in the supplementary materials for details).

Changes in Levels of Mania, Depression and Anxiety

Second, we calculated if there were significant differences between the raw scores on measures of mania, depression and anxiety, both daily and weekly. Table 4 shows the mean

and standard deviation of each score for each group. Nearly all measures show a large decrease in mean score from baseline to post-intervention follow-up phase.

Insert Table 4

Insert Table 5

As before, effects of phase as well as an interaction between phase and intervention condition were tested using linear mixed-effects models. Both groups experienced significantly less mania, depression and anxiety symptoms at follow-up compared to baseline (Table 5). The models including the interaction term indicate the ImCT group experienced a significantly greater reduction in levels of depression and anxiety than the PE group on the daily, but not on the weekly measures, and mania did not differ for daily or weekly. The effects after intervention seem relatively stable for anxiety and depression measures (no significant difference between the first eight weeks post-intervention and the second eight weeks) but a significant reduction (~50%) in the improvement for both daily and weekly mania scores (see Table S4 in the supplementary materials).

Changes in Affect Lability, Level of Functioning and Hopelessness

Affect lability (ALS), level of functioning (Life-Rift), hopelessness (BHS) were measured at various stages of the study with scores summarised in Table 6. The critical scores were measured directly before intervention and after the intervention concluded.

Insert Table 6

Again, mixed-effects linear modelling was used to test if scores differed directly before the intervention started and directly after the intervention ended (phase of the study) and if phase interacted with treatment condition. The results are summarised in Table 7. There was a significant reduction in affect lability (ALS) with no significant interaction with treatment condition. Similarly, there was a significant overall decrease in levels of hopelessness (BHS) but that effect showed an interaction with treatment condition -- suggesting that the decrease was larger in the ImCT group. There were no significant differences or interactions for the measure of level of functioning (Life-Rift).

Similar analysis compared the scores directly after the intervention to scores 8 weeks after intervention. A main effect of phase was only seen for the Life-Rift measure (continued reduction in scores), and a main effect of condition for BHS, indicating lower scores for the ImCT group (see Table S5 in the supplementary materials).

Insert Table 7

Changes in Problematic Imagery

Problematic imagery was measured by the weekly VAS-imagery scale (VAS-IM). The mean scores are shown in Table 4. When compared using linear mixed-effects modelling, there was a significant main effect of phase with no interaction with treatment

condition (Table 5). Both treatment groups showed a reduction in levels of problematic mental imagery. A subsequent comparison of stability in the follow-up phases (Table S4) indicate no main effects but a significant interaction.

A measure of problematic imagery was also included with the time locked measures (MICQ-BD, mean scores shown in Table 6). Linear mixed-effects modelling showed a significant effect of phase and an interaction between phase and treatment condition (Table 7). The change in scores after the intervention appears to be driven by an increase in scores for people in the ImCT condition (higher scores correspond to less problematic imagery). Subsequent measures (comparing 8 weeks after intervention to directly after intervention) indicate the difference between treatment conditions remains without significant evidence of decreasing (Table S5).

Discussion

This study explored the effects of imagery focussed cognitive therapy (ImCT) vs group psychoeducation (PE) on mood instability and anxiety in bipolar disorder. Mood instability reduced in both treatment conditions after intervention. Levels of mania, depression and anxiety also reduced in both treatment conditions, but on the daily measures of depression and anxiety significantly more so in the ImCT than the PE condition. Compared with the PE condition, the ImCT condition additionally showed reduced hopelessness, and a decrease in intrusive, problematic imagery. Below, these findings are discussed in more detail.

First, we found that mood instability decreased significantly for both the ImCT and PE groups, with no significant differences between conditions. This effect was particularly large in the daily measurements, where a reduction of between 30 and 50% was found in

mood variation on the daily measurements, and maintained 16-weeks post intervention. This is important as inter-episodic mood instability is associated with poor long term prognosis (Birmaher et al., 2014) and negative impact on daily functioning (McElroy et al., 2001). Furthermore, these findings support earlier ones that ImCT can improve mood instability (Hales et al., 2018; Holmes et al., 2016).

The finding that reductions in mood instability were particularly strong in the daily measures is noteworthy, and could suggest that daily measurements of mood and anxiety might be more sensitive than weekly measures in detecting inter-episode mood instability in patients with BD. As this inter-episodic mood instability is predictive of possible pending relapse into mania or depression (Patel et al., 2015) and reduced functioning (Grunze & Born, 2020) targeting this specifically in a treatment such as ImCT could potentially reduce rates of relapse.

Second, we found that both groups had significantly lower levels of depression, anxiety and mania during the 16 weeks following the intervention, compared to four weeks baseline. In a previous randomised controlled trial, twenty sessions of standard cognitive behavioural therapy (CBT) were found to be no more superior than 6 sessions of PE (Parikh et al., 2012). In our trial however, ImCT decreased levels of both depression and anxiety significantly more than PE. This was evident on the daily measures, though not the weekly measures. However, it has been argued that daily measurements of mood have more ecological validity than retrospective questionnaires and are less prone to memory and mood biases than longer time intervals in BD (Verhagen et al., 2016). Moreover, levels of mania reduced significantly in both groups in the first 8-weeks follow-up. This is promising, as to date the impact of psychosocial interventions on mania has been mixed (Chiang et al., 2017).

With respect to the remaining study outcomes, both ImCT and PE groups had a significant reduction in levels of hopelessness after intervention, with the ImCT group

improving significantly more than the PE group on scores of hopelessness. This is highly relevant as BD confers the highest risk of suicide of all psychiatric disorders (Miller & Black, 2020) and hopelessness is associated with an increased risk (Valtonen et al., 2009). In addition, both groups experienced significantly less affect lability, and no significant changes in level of functioning.

As expected, the ImCT group experienced significantly more control over their problematic imagery after intervention than the PE group. This is in line with findings from earlier pilot studies on ImCT (Hales et al., 2018; Holmes et al., 2019) and suggests that the intervention has indeed changed problematic imagery as intended.

Drop-out rates were very low in both groups, which suggests that both interventions were acceptable and valid to patients. ImCT participants reported that the imagery interventions gave them more confidence in managing mood instability, and that the imagery focussed approach better suited their way of thinking and "felt like speaking the same language".

It has been suggested that the limited impact of standard CBT for BDs may be due in part to the lack of consensus regarding the underlying theoretical model for the disorder (Parikh et al., 2012). This is in contrast to CBT for unipolar depression, where a robust model exists and response rates in therapy are higher. The novel focus of ImCT on problematic mental imagery, a previously neglected symptom in BDs which has been shown to strongly drive mood instability and anxiety, may offer much needed treatment innovation based on a solid experimental evidence base (Holmes et al., 2011). In addition, neither anxiety nor hopelessness are the focus of standard psychosocial interventions for BD, but in ImCT imagery relating to these symptoms can be targeted if formulated as a priority in the assessment ('mapping') phase of the intervention (Holmes et al., 2019). This flexible approach may be particularly useful as the experience of BD is highly variable between

individuals, with anxiety and suicidality frequently co-occurring but lacking effective interventions in this population.

The PE group intervention had much lower drop-out rates than earlier studies (3% vs 20%) (Buizza et al., 2019). Previously reported positive outcomes of group PE include greater adherence to medication, higher levels of functioning, and an increase in knowledge in both patients and their carers (Batista et al., 2011), with some studies also reporting a reduction in levels of depression but not in mania (Zyto et al., 2020). Possibly, the effects of ImCT in this trial may be under-estimated in comparison with a standard PE package. The effectiveness of this PE package versus standard PE could be usefully tested in future studies. The high compliance despite high levels of depression, mania and anxiety also suggests there is no need to exclude patients who are currently manic or depressed from research trials.

There are a few limitations to this study. First, the sample is relatively small and drawn from one regional patient population, a larger replication that includes broader sampling from less specialised services would improve the generalizability of the results. Second, our results indicate the daily measures were the most sensitive at detecting change. Given this, in future studies it would be useful to include a daily mental imagery measure (in addition to the weekly measure) to allow a fine-grained analysis of the relationship between mood and imagery variables. Finally, one aspect of this study that makes interpreting the results more difficult is the marked efficacy of the group PE condition, which also showed improvement on many key measures. The PE treatment is standard care at this facility but differs from the ImCT condition on the number of sessions and the inclusion of group therapy. Future studies attempting to quantify the impact of ImCT could more closely align control conditions with the ImCT protocol as well as include a control group that is wait-listed and not actively receiving.

In summary, our study found that ImCT was as effective as PE at reducing mood instability and levels of mania, and was significantly better in reducing daily levels of anxiety, depression, hopelessness and problematic imagery over the course of the intervention. Although these results warrant further replication, this study suggests that ImCT is a helpful addition to standard care for patients with BD, offering much needed treatment innovation for this population.

References

Altman, E. A., Hedekker, D., & Peterson, J. L. (1997). The Altman Self-rating Mania Scale. *Biological Psychiatry, 42*(10), 948-955.

Altshuler, L. L., Post, R. M., Black, D. O., Keck, P. E., Jr., Nolen, W. A., Frye, M. A., Suppes, T., Grunze, H., Kupka, R. W., Leverich, G. S., McElroy, S. L., Walden, J., & Mintz, J. (2006). Subsyndromal depressive symptoms are associated with functional impairment in patients with bipolar disorder: Results of a large, multisite study. *Journal of Clinical Psychiatry, 67*(10), 1551-1560. https://doi.org/10.4088/jcp.v67n1009

APA. (2002). Practice guideline for the treatment of patients with bipolar disorder (revision). *American Journal of Psychiatry, 159*(4 Suppl), 1-50.

APA. (2013). *Diagnostic and Statistical Manual of mental disorders (5th ed.)*. Arlington: American Psychiatric Association. https://doi.org/10.1176/appi.books.9780890425596

Bates, D., Mächler, M., Bolker, B., & Walker, S. (2015). Fitting linear mixed-effects models using lme4. *Journal of Statistical Software, 67*(1). https://doi.org/10.18637/jss.v067.i01

Batista, T. A., Von Werne Baes, C., & Juruena, M. F. (2011). Efficacy of psychoeducation in bipolar patients: Systematic review of randomized trials. *Psychology & Neuroscience, 4*(3), 409-416. https://doi.org/10.3922/j.psns.2011.3.014

Beck, A. T., Brown, G. K., Berchick, R. J., Steward, B. L., & Steer, R. A. (2006). Relationship between hopelessness and ultimate suicide: A replication with psychiatric outpatients. *Focus, IV*(2), 291 - 296. https://doi.org/https://doi.org/10.1176/foc.4.2.291

Beck, A. T., Brown, G. K., & Steer, R. A. (1997). Psychometric characteristics of the scale for suicide ideation with psychiatric outpatients. *Behaviour Research and Therapy, 35*(11), 1039-1046.

Birmaher, B., Gill, M. K., Axelson, D. A., Goldstein, B. I., Goldstein, T. R., Yu, H., Liao, F., Iyengar, S., Diler, R. S., Strober, M., Hower, H., Yen, S., Hunt, J., Merranko, J. A., Ryan, N. D., & Keller, M. B. (2014). Longitudinal trajectories and associated baseline predictors in youths with bipolar spectrum disorders. *Americal Journal of Psychiatry 171*(9), 990-999. https://doi.org/10.1176/appi.ajp.2014.13121577

Buizza, C., Candini, V., Ferrari, C., Ghilardi, A., Saviotti, F. M., Turrina, C., Nobili, G., Sabaudo, M., & de Girolamo, G. (2019). The long-term effectiveness of psychoeducation for bipolar disorders in mental health services. A 4-year follow-up study. *Frontiers in Psychiatry, 10*, 873. https://doi.org/10.3389/fpsyt.2019.00873

Bopp, J., Miklowitz, D., Goodwin, G., Stevens, W., Rendell, J., & Geddes, J. (2010). The longitudinal course of bipolar disorder as revealed through weekly text messaging: a feasibility study. *Bipolar Disorders*, 12(3), 327–334.

Chiang, K. J., Tsai, J. C., Liu, D., Lin, C. H., Chiu, H. L., & Chou, K. R. (2017). Efficacy of cognitive-behavioral therapy in patients with bipolar disorder: A meta-analysis of randomized controlled trials. *PLoS One, 12*(5), e0176849. https://doi.org/10.1371/journal.pone.0176849

Clifton, L., & Clifton, D. A. (2019). The correlation between baseline score and post-intervention score, and its implications for statistical analysis. *Trials, 20*(1), 43. https://doi.org/10.1186/s13063-018-3108-3

Contardi, A., Imperatori, C., Amati, I., Balsamo, M., & Innamorati, M. (2018). Assessment of affect lability: Psychometric properties of the ALS-18. *Frontiers in Psychology, 9*, 427. https://doi.org/10.3389/fpsyg.2018.00427

Denicoff, K. D., Leverich, G. S., Nolen, W. A., Rush, R., A. J., McElroy, S. L. A., Keck, P. E., Suppes, P. E., Altshuler, L. L., Kupka, F. W., Frye, M. A., Hatef, J., Brotman, M. A., & Post, R. M. (2000). Validation of the Prospective NIMH-Life-Chart Method (NIMH-LCM-P) for longitudinal assessment of bipolair illness. *Psychological Medicine, 30*, 1391-1397. https://doi.org/Https://www.cambridge.org/core/product/8E493183C6D28841E09B01C3A

Di Simplicio, M., Renner, F., Blackwell, S. E., Mitchell, H., Stratford, H. J., Watson, P., Myers, N., Nobre, A. C., Lau-Zhu, A., & Holmes, E. A. (2016). An investigation of mental imagery in bipolar disorder: Exploring "the mind's eye". *Bipolar Disorders, 18*(8), 669-683. https://doi.org/10.1111/bdi.12453

O' Donnell, C., Di Simplicio, M., Brown, R., Holmes, E. A., & Burnett Heyes, S. (201). The role of mental imagery in mood amplification: An investigation across subclinical features of bipolar disorders. *Cortex*. https://doi.org/10.1016/j.cortex.2017.08.010

Goodwin, G. M., Haddad, P. M., Ferrier, I. N., Aronson, J. K., Barnes, T., Cipriani, A., Coghill, D. R., Fazel, S., Geddes, J. R., Grunze, H., Holmes, E. A., Howes, O., Hudson, S., Hunt, N., Jones, I., Macmillan, I. C. M.-W., H., Miklowitz, D. R., Morris, R., Mufano, M., Paton, C., Shaharkian, B. J. S., K., Sinclair, J., Taylor, D., Vieta, E., & Young, A. H. (2016). Evidence-based guidelines for treating bipolar disorder revised third edition recommendations from the British Journal of Psychopharmacology. *Journal of Psychopharmacology, 30*(6), 495-553. https://doi.org/0.1177/0269881116636545

Grunze, H., & Born, C. (2020). The impact of subsyndromal bipolar symptoms on patient's functionality and quality of life. *Frontiers in Psychiatry, 11*, 510. https://doi.org/10.3389/fpsyt.2020.00510

Hales, S. A., Deeprose, C., Goodwin, G. M., & Holmes, E. A. (2011). Cognitions in bipolar affective disorder and unipolar depression: Imagining suicide. *Bipolar Disorders, 13*(7-8), 651-661. https://doi.org/10.1111/j.1399-5618.2011.00954.x

Hales, S. A., Di Simplicio, M., Iyadurai, L., Blackwell, S. E., Young, K., Fairburn, C. G., & Geddes, J. R. (2018). Imagery-focused cognitive therapy (ImCT) for mood instability and anxiety in a small sample of patients with bipolar disorder: A pilot clinical audit. *Behavioural and Cognitive Psychotherapy*. https://doi.org/10.1017/S1352465818000334

Henry, C., Van den Bulke, D., Bellivier, F., Roy, I., Swendsen, J., M'Baïlara, K., Siever, L. J., & Leboyer, M. (2008). Affective lability and affect intensity as core dimensions of bipolar disorders during euthymic period. *Psychiatry Research, 159*(1-2), 1-6. https://doi.org/10.1016/j.psychres.2005.11.016

Holmes, E. A., Bonsall, M. B., Hales, S. A., Mitchell, H., Renner, F., Blackwell, S. E., Watson, P., Goodwin, G. M., & Di Simplicio, M. (2016). Applications of time-series analysis to mood fluctuations in bipolar disorder to promote treatment innovation: A case series. *Translational Psychiatry, 6*, e720. https://doi.org/10.1038/tp.2015.207

Holmes, E., Hales, S. A., Young, K., & Di Simplicio, M. (2019). *Imagery-based cognitive therapy for bipolar disorder and mood instability*. The Guilford Press.

Holmes, E. A., Deeprose, C., Fairburn, C. G., Wallace-Hadrill, S. M., Bonsall, M. B., Geddes, J. R., & Goodwin, G. M. (2011). Mood stability versus mood instability in bipolar disorder: A possible role for emotional mental imagery. *Behaviour Research and Therapy, 49*(10), 707-713. https://doi.org/10.1016/j.brat.2011.06.008

Holmes, E. A., Geddes, J. R., Colom, F., & Goodwin, G. M. (2008). Mental imagery as an emotional amplifier: Application to bipolar disorder. *Behaviour Research and Therapy, 46*(12), 1251-1258. https://doi.org/10.1016/j.brat.2008.09.005

Ivins, A., Di Simplicio, M., Close, H., Goodwin, G. M., & Holmes, E. (2014). Mental imagery in bipolar affective disorder versus unipolar depression: Investigating cognitions at times of 'positive' mood. *Journal of Affective Disorders, 166*, 234-242. https://doi.org/10.1016/j.jad.2014.05.007

Jauhar, S., McKenna, P. J., & Laws, K. R. (2016). NICE guidance on psychological treatments for bipolar disorder: Searching for the evidence. *Lancet Psychiatry, 3*(4), 386-388. https://doi.org/10.1016/s2215-0366(15)00545-3

Ji, J. L., Kavanagh, D. J., Holmes, E. A., MacLeod, C., & Di Simplicio, M. (2019). Mental imagery in psychiatry: Conceptual and clinical implications. *CNS Spectrums, 24*(1), 114-126. https://doi.org/10.1017/S1092852918001487

Ketter, T.A. (2010). Diagnostic features, prevalence, and impact of bipolar disorder. *Journal of Clinical Psychiatry, 71*(6), 14-18. https://doi.org/10.4088/JCP.8125tx11c

Kosslyn, S. M., Ganis, G., & Thompson, W. L. (2001). Neural foundations of imagery. *Nature Reviews Neuroscience, 2*(9), 635-642. https://doi.org/https://doi.org/10.1038/35090055

Kroon, J. S., Wohlfarth, T. D., Dieleman, J., Sutterland, A. L., Storosum, J. G., Denys, D., de Haan, L., & Sturkenboom, M. C. (2013). Incidence rates and risk factors of bipolar disorder in the general population: A population-based cohort study. *Bipolar Disorders, 15*(3), 306-313. https://doi.org/10.1111/bdi.12058

Kupka, F. W., Goossens, P., van Bendegem, M., Daemen, P., Daggenvoorde, T., Daniels, A., Dols, A., Hillegers, M., Hoogelander, A., ter Kulve, E., Peetoom, T., Schulte, R., Stevens, A., & van Duin, D. (2015). Multidisciplinaire richtlijn bipolaire stoornissen.

Leon, A. C., Solomon, D. A., Mueller, T. I., Turvey, C. L., Endicott, J., & Keller, M. B. (1999). Range of Impaired functioning tool (Life-Rift): A brief measure of functional impairment. *Psychological Medicine, 29*, 869-878.

Look, A. E., Flory, J. D., Harvey, P. D., & Siever, L. J. (2010). Psychometric properties of a short form of the affective lability scale (ALS-18). *Personality and Individual Differences, 49*(3), 187-191. https://doi.org/10.1016/j.paid.2010.03.030

Marangell, L. B., Dennehy, E. B., Miyahara, S., Wisniewski, S. R., Bauer, M. S., Rapaport, M. H., & Allen, M. H. (2009). The functional impact of subsyndromal depressive symptoms in bipolar disorder: Data from STEP-BD. *Journal of Affective Disorders, 114*(1-3), 58-67. https://doi.org/10.1016/j.jad.2008.07.006

McElroy, S. L. A. A., L. L., Suppes, P. E., Keck, T., Frye, M. A., Denlcoff, K. D., Nolen, W. A., Kupka, F. W., Leverich, G. S., Rochussen, J., Rush, R., A. J., Post, R. M. A., Altshuler, L. L., Suppes, P. E., Keck, T., Frye, M. A., Denlcoff, K. D., Nolen, W. A., Kupka, F. W., Leverich, G. S., Rochussen, J., Rush, R., A. J., & Post, R. M. (2001). Axis I psychiatric comorbidity and its relationship to historical illness variables in 288 patients with bipolar disorder. *American Journal of Psychiatry, 158*(3), 420-426.

Merikangas, K. R., Akiskal, H. S., Angst, J., Greenberg, P. E., Hirschfeld, R. M. A., Petukhova, M., & Kessler, R. C. (2007). Lifetime and 12-month prevalence of bipolar spectrum disorder in the national comorbidity survey replication. *Archives of General Psychiatry, 64*(5), 543-552. https://doi.org/10.1001/archpsyc.64.5.543

Merikangas, K. R., Jin, R., He, J. P., Kessler, R. C., Lee, S., Sampson, N. A., Viana, M. C., Andrade, L. H., Hu, C., Karam, E. G., Ladea, M., Medina-Mora, M. E., Ono, Y., Posada-Villa, J., Sagar, R., Wells, J. E., & Zarkov, Z. (2011). Prevalence and correlates of bipolar spectrum disorder in the World Mental Health Survey initiative. *Archives of General Psychiatry, 68*(3), 241-251. https://doi.org/10.1001/archgenpsychiatry.2011.12

Miller, J. N., & Black, D. W. (2020). Bipolar disorder and suicide: A review. *Current Psychiatry Reports, 22*(2), 6. https://doi.org/10.1007/s11920-020-1130-0

Ng, R. M., Heyes, S. B., McManus, F., Kennerley, H., & Holmes, E. A. (2016). Bipolar risk and mental imagery susceptibility in a representative sample of chinese adults residing in the community. *International Journal of Social Psychiatry, 62*(1), 94-102. https://doi.org/10.1177/0020764015597951

National Collaborating Centre for Mental Health (UK). (2014). *Bipolar Disorder: The NICE Guideline on the Assessment and Management of Bipolar Disorder in Adults, Children and Young People in Primary and Secondary Care*. The British Psychological Society and The Royal College of Psychiatrists.

National Institure for Health and Care Excellence. (2018). *Bipolar disorder assessment and management (NICE Guideline NG 185).* https://www.nice.org.uk/guidance/cg185/evidence/full-guideline-pdf-4840895629

Oliver, M. N. I., & Simons, J. S. (2004). The Affective Lability Scales: Development of a short-form measure. *Personality and Individual Differences, 37*(6), 1279-1288. https://doi.org/10.1016/j.paid.2003.12.013

Osman, A., Barrios, F. X., Aukes, D., Osman, J. R., & Markway, K. (1993). The Beck Anxiety Inventory: Psychometric properties in a community population. *Journal of Psychopathology and Behavioral Assessment, 15*(4).

Pacchiarotti, I.,, Bond, D.J.M.D.,, Baldessarini R.J., W.A.., N., Grunze H., Licht R.W., Post R.M., Berk M., Goodwin G.M., Sachs G.S., Tondo L., Findling R.L., Youngstrom E.A., Tohen M., Undurraga J., González-Pinto A., Goldberg J.F., Yildiz A., Altshuler L.L., Calabrese J.R., Mitchell P.B, Thase M.E., Koukopoulos A., Colom F., Frye M.F., Malhi G.S., Fountoulakis K.N., Vázquez G., Perlis R.H., Terence A. Ketter, M.D. ,, Cassidy F., Akiskal H., Azorin J.M., Valentí M., Mazzei D.H., Lafer B., Kato T., Mazzarini L., Martínez-Aran A., Parker G., Souery D., Özerdem A., McElroy S.L., Girardi P., Bauer M., M.D.,, Yatham L.N., Zarate C.Z., Nierenberg A.A.,

Birmaher B., Kanba S., M.D.,, El-Mallakh R.S., Serretti A., Rihmer Z., H., A., Young A.H., Kotzalidis G.D., MacQueen G.M., Bowden C.L., Ghaemi S.N., Lopez-Jaramillo C., Rybakowski J., Ha K., Perugi G., Kasper S., Amsterdam J.D., Hirschfeld R.M., Kapczinski F., & Vieta E. (2013). The international society for bipolar disorders (ISBD) task force report on antidepressant use in bipolar disorders. *American Journal of Psychiatry, 170*(11), 1249-1262. https://doi.org/10.1176/appi.ajp.2013.13020185

Parikh, S. V., Zaretsky, A., Beaulieu, S., Yatham, L. N., Young, L. T., Patelis-Siotis, I., Macqueen, G. M., Levitt, A., Arenovich, T., Cervantes, P., Velyvis, V., Kennedy, S. H., & Streiner, D. L. (2012). A randomized controlled trial of psychoeducation or cognitive-behavioral therapy in bipolar disorder: A Canadian network for mood and anxiety treatments (CANMAT) study [CME]. *The Journal of clinical psychiatry, 73*(6), 803-810. https://doi.org/10.4088/JCP.11m07343

Patel, R., Lloyd, T., Jackson, R., Ball, M., Shetty, H., Broadbent, M., Geddes, J. R., Stewart, R., McGuire, P., & Taylor, M. (2015). Mood instability is a common feature of mental health disorders and is associated with poor clinical outcomes. *BMJ Open, 5*(5), e007504. https://doi.org/10.1136/bmjopen-2014-007504

Pearson, J., Naselaris, T., Holmes, E. A., & Kosslyn, S. M. (2015). Mental imagery: Functional mechanisms and clinical applications. *Trends in Cognitive Sciences, 19*(10), 590-602. https://doi.org/10.1016/j.tics.2015.08.003

Perlick, D. A., Rosenheck, R. R., Clarkin, J. F., Raue, P., & Sirey, J. (2001). Impact of family burden and patient symptom status on clinical outcome in bipolar affective disorder. *Journal of Nervous and Mental Disease, 189*(1), 31-37. https://doi.org/10.1097/00005053-200101000-00006

Perlis, R. H., Ostacher, M. J., Patel, J. K., Marangell, L. B., Zhang, H., Wisniewski, S. R., Ketter, T. A., Miklowitz, D. J., Otto, M. W., Gyulai, L., Reilly-Harrington, N. A., Nierenberg, A. A., Sachs, G. S., & Thase, M. E. (2006). Predictors of recurrence in bipolar disorder: Primary outcomes from the systematic treatment enhancement program for bipolar disorder (STEP-BD). *American Journal of Psychiatry, 163*(2), 217-224. https://doi.org/10.1176/appi.ajp.163.2.217

Rademacher, J., DelBello, M. P., Adler, C., Stanford, K., & Strakowski, S. M. (2007). Health-related quality of life in adolescents with bipolar I disorder. *Journal of Child and Adolescent Psychopharmacology, 17*(1), 97-103. https://doi.org/10.1089/cap.2006.0049

Rush, A. J., Trivedi, M. H., Ibrahim, H. M., Carmody, T. J., Arnow, B., Klein, D. N., Markowitz, J. C., Ninan, P. T., Kornstein, S., Manber, R., Thase, M. E., Kocsis, J. H., & Keller, M. B. (2003). The 16-item Quick Inventory of Depressive Symptomatology (QIDS), Clinician Rating (QIDS-C), and Self-Report (QIDS-SR): A psychometric evaluation in patients with chronic major depression. *Biological Psychiatry, 54*(5), 573-583. https://doi.org/10.1016/s0006-3223(02)01866-8

Simon, N. M., Otto, M. W., Wisniewsky, S. R. F., M., Sagduyu, K., Frank, E., Sachs, G. S., Nierenberg, A., Thase, M. E., & Pollack, M. H. (2004). Anxiety disorder comorbidity in bipolar disorder patients: Data from the first 500 partcicipants in the systematic treatment enhancement program for bipolar disorder (STEP-BD). *American Journal of Psychiatry 161*(12), 2222-2229.

Steel, C., Wright, K., Goodwin, G., Simon, J., Morant, N., Taylor, R., Brown, M., Jennings, S., Hales, S., & Holmes, E. (2020). The IBER study: Study protocol for a feasibility randomised controlled trial of imagery based emotion regulation for the treatment of

anxiety in bipolar disorder. *Pilot and Feasibility Studies, 6*(1), 83. https://doi.org/10.1186/s40814-020-00628-8

Valtonen, H. M., Suominen, K., Haukka, J., Mantere, O., Arvilommi, P., Leppamaki, S., & Isometsa, E. T. (2009). Hopelessness across phases of bipolar I or II disorder: A prospective study. *Journal of Affective Disorders, 115*(1-2), 11-17. https://doi.org/10.1016/j.jad.2008.06.013

Verhagen, S. J. W., Hasmi, L., Drukker, M., van Os, J., & Delespaul, P. (2016). Use of the experience sampling method in the context of clinical trials. *Evidence Based Mental Health, 19*(3), 86-89. https://doi.org/https://dx.doi.org/10.1136%2Febmental-2016-102418

Zyto, S., Jabben, N., Schulte, P. F. J., Regeer, E. J., Goossens, P. J. J., Kupka, R. W., & Task Force Psychotherapy of the Dutch Foundation for Bipolar, D. (2020). A multi-center naturalistic study of a newly designed 12-sessions group psychoeducation program for patients with bipolar disorder and their caregivers. *International Journal of Bipolar Disorders, 8*(1), 26. https://doi.org/10.1186/s40345-020-00190-5