The feasibility and acceptability of a novel Anxiety in Bipolar Disorder (AIBD) intervention compared to treatment as usual: A randomised controlled trial

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Background: Comorbid anxiety is common in bipolar disorder (BD) and associated with worse clinical outcomes including increased suicidality. Despite effective psychological treatments for anxiety, research into treating anxiety in BD is underdeveloped. This paper describes a novel psychological intervention to address Anxiety in context of Bipolar Disorder (AIBD).

Methods: Adults with BD and clinically significant anxiety symptoms were randomised to AIBD plus treatment as usual (TAU) or TAU alone. AIBD offered 10 sessions of psychological therapy using a formulation-based approach. Feasibility and acceptability was evaluated through recruitment, retention, therapy attendance, alliance, fidelity and qualitative feedback. Clinical outcomes were assessed at baseline, 16, 48 and 80 weeks: interim assessments of relapse at 32, 64 weeks.

Results: Seventy-two participants were recruited with 88% retention to 16 and 74% to 80 weeks (similar between arms). Therapy participants attended $\bar{x}$ 7.7 (*SD* 2.8) sessions. Therapeutic alliance and therapy fidelity were acceptable. Qualitative interviews indicated participants valued integrated support for anxiety with BD, and coping strategies. Some suggested a longer intervention period. Clinical outcomes were not significantly different between arms up to 80 weeks follow-up.

Conclusions: AIBD is feasible and acceptable but lack of impact on clinical outcomes indicates adaptations are required. These are discussed in relation to qualitative feedback and recent literature published since the trial completed.

1.INTRODUCTION

Comorbid anxiety is common in BD (12-month prevalence 32- 53%; McIntyre et al. 2006, Otto et al. 2006): lifetime 60- 90%; Merikangas et al. 2007, Sala et al. 2012) and linked to worse clinical outcomes, including higher relapse, worse medication side- effects, poorer psychosocial function and higher suicidality (Otto, Simon et al. 2006, Simon et al. 2007, Goes et al. 2012, Goldeberg and Fawcett 2012, Sala, Goldstein et al. 2012).

Despite the importance of anxiety in BD, development of effective psychological treatment is limited. Two systematic reviews concluded there is preliminary evidence for structured psychological interventions but still a pressing need for specific treatment protocols for anxiety in BD (Provencher et al. 2011, Stratford et al. 2015). A promising initiative in this area has been an investigation of feasibility and acceptability of the Unified Protocol for Emotional Disorder (UP: Barlow, Ellard, et al., 2010; Barlow, Todd et al., 2017) for individuals with BD and at least one comorbid anxiety disorder (Ellard, Bernstein et al., 2017). Although UP was not specifically developed with individuals with BD, it was argued that its focus on emotional dysregulation was likely to make it appropriate for this group. Ellard and colleagues randomised 29 individuals to receive either UP+TAU or TAU alone, with approximately 62% retention to end of treatment follow-up (6 months) and similar treatment satisfaction in both groups. Greater change over time was reported UP+TAU for clinician-reported anxiety and both self- and clinician-reported depression.

A key question in developing treatment approaches to anxiety comorbidity is whether to target anxiety diagnoses or symptoms. The latter was chosen here for 3 reasons: i) anxiety disorders tend to be highly comorbid, especially in BD (Provencher, Hawke et al. 2011) and multiple separate interventions for specific anxiety disorders would be inefficient. ii) Anxiety-related distress in BD often doesn't fit neatly within an anxiety diagnostic category (Provencher, Hawke et al. 2011, Hampshire 2014). iii) Anxiety disorders typically share key elements, including interference with functioning and subjective feelings of anxiety, worry and tension (Barlow et al. 2010).

The aim of this study was to test the feasibility and acceptability of the Anxiety in Bipolar Disorder (AIBD) intervention using an RCT design.

2. METHODS

This study was preregistered (ISRCTN: 84288072), reviewed and approved by UK NHS Ethics (REC ref: 10/H1015/83) with a published research protocol (Jones et al. 2013).

2.1 Trial design

A rater-blind individually randomised controlled trial comparing <=10 sessions of integrated CBT for anxiety in BD (AIBD), plus treatment as usual (TAU), compared with TAU alone: conducted across seven NHS trusts in the North West of England. A nested qualitative study explored feasibility and acceptability.

Participants were randomised by an independent clinical trials unit (MAHSC CTU 9) with randomly-sized permuted blocks minimised on gender, number of previous mood episodes (depression and mania: <7, 8-19 or >20) and current anxiety (HAM-A score: 0-17, 18-24 or >25).

To ensure blindness, researchers were housed separately from therapists and had no involvement in randomisation or post-randomisation data. Trial participants were instructed to avoid disclosing treatment arm. Unblindings were recorded and an alternate blind RA allocated.

2.2 Recruitment

Participants were recruited (June 2011-May 2012) from NHS mental health and primary care services and voluntary groups. Advertisements in local media, and at NHS and non-NHS sites aimed to maximise participant access. All participants provided written informed consent.

2.3 Inclusion/exclusion criteria

Inclusion criteria: i) DSM-IV (SCID) verified BD diagnosis (First et al. 1997); ii) Current significant anxiety (HADS-A >= 8; Zigmond and Snaith 1983)); iii) Ability to provide informed consent; iv) > = 18 years.

Exclusion criteria: i) Current mood mixed episode (or last four weeks); ii) Current suicidal ideation with intent.

2.4 Intervention

AIBD development was informed by thematic analysis of individual qualitative interviews (n=21) and 3 focus groups (n=21) with individuals with experience of BD and anxiety. These both focussed

on what type of support people wanted in relation to their experiences of anxiety. Key themes and topics with illustrative quotes are presented in Table 1. In line with the results of these interviews and focus groups, AIBD was developed to be sensitive to the potential impact of anxiety and to offer information and structured psychological support to address collaboratively agreed personalised therapy goals. AIBD was offered flexibly in terms of location (client's home or clinical setting according to client preference) and session duration, with sessions supported by client workbooks including client therapy record and anxiety recovery plans, lived experience accounts of anxiety and BD and information about additional resources and support. Specific CBT strategies were drawn from best practice guidance from NICE in relation anxiety and BD available during the period of AIBD development (2010-2011 NICE 2004, 2005a,b, 2006).

Important AIBD elements include flexible engagement, reviewing of positive experiences and coping as well as difficulties, and a flexible formulation-driven approach to individual therapy plan development. The individualised formulation-driven approach took into account level of engagement and motivation and explored links between anxiety and bipolar experiences, including issues around functioning, to elicit personally valued treatment goals. On the basis of this information, consideration was given to the client's key anxiety concerns and which of these to target as goals within therapy. The specific intervention plan in each case was guided by the individual formulation, and incorporated appropriate cognitive behavioural strategies focussed on addressing anxiety experiences and consequent behaviour. This included CBT to facilitate adaptive approaches to dealing with anxiety and where appropriate addressing the impact of depressed or elevated mood on these issues as well. Typically the CBT approach included learning more about the nature of their anxiety symptoms and developing coping strategies for dealing with them using CBT techniques including graded exposure/interoceptive exposure, relaxation and breathing techniques, cognitive restructuring, behavioural experiments, thought monitoring/challenge and adaptive problem solving. Where it was clear that mood instability and relapse were strongly associated with anxiety difficulties, mood-monitoring techniques, detection of early warning signs for problematic mood changes and coping strategies in relation to these early warning signs regularisation of routine and mood related problem-solving strategies were also a feature of therapy. The information from all phases was finally drawn into an anxiety recovery plan highlighting key challenges for the client and which techniques they have selected to be useful in addressing them (including strategies already successfully used by the client and new strategies developed in therapy). The relative emphasis between anxiety and mood strategies varied between clients based on their individual goals and formulation. Table 2 provides a brief summary of therapy progress for two illustrative clients. This approach differs from UP in being specifically developed for, and with, individuals with bipolar disorder, with a strong focus on individual formulation, a flexible personalised approach to relative emphasis of the intervention stages, incorporation of mood relapse prevention approaches if required and omission of mindfulness as an intervention strategy (as this is not currently recommended by NICE in relation anxiety or depression).

(Table 2 AIBD phases; relative emphasis depended on individual goals and formulation).

2.5 Therapists

AIBD was delivered by three therapists; all met BABCP accreditation criteria, trained in AIBD and received weekly clinical supervision from SJ.

2.6 Primary Feasibility and Acceptability Outcomes

Feasibility and acceptability of AIBD were evaluated in terms of levels of recruitment into the trial, retention of participants in both arms of the study, treatment fidelity, assessed by the Cognitive Therapy Scale-Revised version (CTS-R; Blackburn et al. 2001) and the AIBD Fidelity Scale (available from authors on request), therapeutic alliance (Work Alliance Inventory, WAI-S ; Tracey and Kokotovic 1989) and therapy attendance and client evaluation.

2.7 Qualitative interviews

A nested qualitative study was conducted with 17 therapy participants (purposively sampled on age and gender, HADS-A score at recruitment, number of sessions attended, previous relapse history) to explore subjective experiences of AIBD.

2.8 Clinical Outcomes

Face-to-face assessments were conducted at initial interview (to confirm diagnosis), baseline, 16, 48 and 80 weeks: interim telephone assessments 32 and 64 weeks. Observer-ratings were obtained at each assessment. Self-report measures not obtained at interim assessments.

Primary clinical outcome was impact of AIBD on observer- and self-reported anxiety (Hamilton Anxiety Rating Scale, HAM-A; Hamilton 1959, Shear et al. 2001: State-Trait Anxiety Inventory, STAI; Spielberger 1983), time to relapse and symptoms of mania and depression (SCID for DSM-IV Longitudinal Interval Follow-up Evaluation, SCID LIFE; Keller et al. 1987, First, Spitzer et al. 1997); Hamilton Depression Rating Scale (Hamilton 1960) and Bech-Rafaelsen Mania Scale, MAS (Bech et al. 1978).

Additional clinical outcomes were personal recovery (Bipolar Recovery Questionnaire, BRQ; Jones et al. 2013); Quality of Life (Quality of Life in Bipolar Disorder Scale, QoL.BD; Michalak et al. 2010), and functioning (Personal and Social Performance Scale, PSP; Morosini et al. 2000).

2.9 Data analysis

Primary outcome information on recruitment and retention levels, therapy fidelity, alliance, acceptability and completion were all summarised with descriptive statistics. Sample characteristics including baseline mood and anxiety were reported.

The clinical and functional outcome measures were analysed using the methods that would be employed in a full trial. The intention-to-treat principle was employed throughout. For the time to relapse survival analyses, covariates were treatment arm, gender, number of previous bipolar episodes (8-20 and more than 20, both versus 1-7) and baseline HAM-A total in a cox regression model.

A two level linear mixed model was fitted with time as a discrete covariate and an unstructured covariance matrix at level 2 using the *mixed* procedure in Stata (2015). This model corresponds to a

repeat measure model but allows for missing data at some time points, enabling subjects with incomplete data to be included in the analysis. The normality assumption of these models was checked using a normal probability plot of model residuals. A model with a discrete time by treatment interaction was fitted to estimate the treatment effect and the 95% confidence interval at each follow-up time point (Model 1). If there was no interaction at the 5% level based on a Wald test, the interaction term was omitted and the overall treatment effect was estimated from this simpler model (Model 2). The same covariates described above were used for these models, additionally adjusting for baseline value of the outcome. A baseline response by discrete time interaction term was also included.

Qualitative interviews were audio-recorded, transcribed verbatim and thematically analysed to explore participants' experiences of AIBD (Braun and Clarke 2006). Themes were compared against the data using a constant comparative approach by a multidisciplinary panel (CH, SP, LR, SJ, RL). Interviews were conducted until thematic saturation was achieved.

3 RESULTS

3.1 Participants

Participants were mainly white British females with a chronic course of BD, (>70% had over 20 mood episodes at baseline, Table 3) aged over 40 years (AIBD $\bar{x}$= 45.5, *SD* = 10.7; TAU $\bar{x}$= 42.9, *SD* = 16.6).

The majority had a Bipolar I diagnosis (*n* = 62, 86%), were either divorced or never married (*n* = 48, 67%) and parents (*n* = 42, 58%). Although most participants had at least commenced further education (*n* = 55, 76%), only a minority were in employment (*n* = 28, 39%). Of those not in work, the majority were in receipt of sickness/disability benefits (*n* = 23 of 44, 52%). Comparing AIBD with TAU the only substantial differences were in relationship status (twice as many married or cohabiting in AIBD), employment (approximately 10% more AIBD participants in work) and referral source (two-thirds of referrals in AIBD were self-referrals compared with one third of TAU).

At baseline, consistent with HADS-A screening, 85% of participants met criteria for at least one current anxiety disorder; Generalised Anxiety Disorder (GAD) and social phobia were the most common (Table 2). More AIBD participants met criteria for two or more anxiety disorders (59% vs. 40%).Rates of Social Phobia, Agoraphobia, Post-Traumatic Stress Disorder(PTSD), Panic ± Agoraphobia, and Specific Phobia were all numerically higher in AIBD versus TAU.

STAI-S and STAI-T scores at baseline (Table 6) were elevated compared with general populations and anxiety group norms[1] (Spielberger 1983): HAM-A scores were in the normal range.

Observer-rated measures scores (indicated very mild depression HAM-D(Hamilton 1960)) (Zimmerman et al. 2013) and extremely low mania scores (MAS) (Bech 2012) at baseline, both arms.

[1] General population (means; STAI-S, 35.88-36.03; SD, 10.52-11.07: STAI-T 35.03-35.06; SD, 8.88-9.31) and diagnosed anxiety group (without BD) (STAI-S: *M* = 49.023, SD = 11.62: STAI-T *M* = 48.08, SD = 10.65) Spielberger, C. D. (1983). *State-Trait Anxiety Inventory (Form Y)*. S. Palo Alto, CA, US, Consulting Psychologists Press.

Personal recovery scores were higher at baseline than in a previous RCT for BD (Jones et al. 2015). Quality of life (QoL-BD) is similar to that reported in the measure development paper (Michalak, Murray et al. 2010), personal and social functioning (PSP) indicates no more than mild impairment in functioning (Morosini, Magliano et al. 2000).

3.2 Primary Outcomes

3.2.1 Feasibility and acceptability

Figure 1 presents recruitment and retention rates according to CONSORT criteria (Schulz et al. 2010). Of 122 people screened, 14 declined, 9 were uncontactable and 27 did not meet study inclusion criteria. Of 72 randomised participants, 32 (44%) were recruited by clinician referral. Twenty-five AIBD participants came via self-referral (62.5%), compared to 15 (37.5%) TAU (see Table 3).

Recruitment target was met (n = 72; 59% of those screened for eligibility). Retention was 88% (*n* = 63) to end of therapy (16 weeks), 78% (*n* = 56) to 32-week follow-up, 75% (*n* = 54) to 48- and 64-week follow-up, and 74% (*n* = 53) to 80-week follow-up (feasibility target 75% ± 10% to 80 weeks (Jones, McGrath et al. 2013). Retention rates at least as high in TAU as in AIBD (Figure 1). Measure completion rates for retained participants varied from 97% at baseline to 79% at 80 weeks (Table 4).

Single unblindings were reported in seven AIBD and four TAU participants: an alternate blinded-RA was allocated in each case. Two participants lost to follow-up died during the final follow-up period for reasons unrelated to the trial.

Mean AIBD attendance was 7.7 (SD = 2.8); two participants attended zero session, 84% (*n* = 31) attended >=4 sessions and 59% (*n* = 22) attended 9-10 sessions.

Adherence to the therapy protocol and CTS-R were independently assessed for 26 randomly selected therapy recordings across early (sessions 1-2), mid (sessions 4-5) and late (sessions 7-10) phases. Adherence to the treatment protocol was 77.65% (SD 10.33) across the above phases. CTS-R mean was 47.1 (*SD* = 5.03); above threshold criteria for CBT competence of 36 (Keen and Freeston 2008) and consistent across sessions; early, $\bar{x}$ =47.5,*SD* = 5.74, mid, $\bar{x}$ =47.4 *SD* = 5.24,late, $\bar{x}$ =46.1 *SD* = 3.76).

Therapeutic alliance was assessed after sessions 3 and 10 with complete data from 23 clients at session 3 ($\bar{x}$ =71.22, *SD* 9.20) and 16 at session 10 ($\bar{x}$= 72.88*, SD* 9.62): therapist ratings were obtained for 23 clients at session 3 (Mean 65.78, SD 7.52) and 15 at session 10 ($\bar{x}$ = 70.89, *SD* 6.45). Ratings at both stages were higher than reported in previous psychological intervention studies of complex psychological problems including BD (Davidson et al. 2006, Jones, Smith et al. 2015)

3.2.1.1. Client ratings of therapy

AIBD clients rated therapy on two 0–10 scales. Firstly, how helpful they thought the therapy was 0 (not at all) to 10 (extremely); secondly, whether they would recommend it to someone with similar problems 0 (definitely not) to 10 (definitely yes). Data was available for 21 participants: experience of therapy averaged 9.14 (*SD* 0.55); likelihood of recommending the therapy averaged 9.26 (*SD* 0.70).

3.2.1.2 Qualitative interview findings (see Table 5 for illustrative quotes)

Participants indicated they valued the intervention in contrast with previous forms of support received. They identified benefits of treating anxiety and BD together in contrast with previous experiences of having these problems addressed separately. AIBD is relatively brief; several participants found this helpful in providing a clear structure and personally-identified targets. However, others wished therapy had been longer, although without specifying omissions from therapy as delivered. Coping strategies learnt in AIBD were helpful in: i) overcoming anxiety-based social isolation and functional limitations; and ii) increasing confidence in dealing with BD.

3.3 Secondary self- and observer-reported outcome measures

Key clinical outcomes were anxiety symptoms, sub-syndromal mood symptoms, (see Table 6-7) and time to relapse (Figures 2-4). The treatment by time interaction was significant for STAI-State but not STAI-Trait, with the lower scores at weeks 16 and 48, in AIBD vs TAU, although not by week 80.

Observer-rated anxiety (HAM-A), depression (HAM-D) and mania (MAS) remained low throughout in both arms; significant treatment by time effects for MAS only with higher score at 48 weeks and lower at 80 weeks for AIBD.

37% (n=13) of TAU and 43% (n=16) of AIBD had a relapse of either mania or depression by 48-week follow-up, and 49% (n =17) of TAU and 59% (n=22) of AIBD by 80 weeks. Neither these nor differences for mania or depression alone were significant.

There were trends toward significant interactions between time and treatment group for personal recovery (BRQ) and personal and social performance (PSP) but not quality of life (QoL.BD): patterns suggested improvements in in AIBD at 16 weeks versus TAU for BRQ and to 48 weeks for QoL.BD.

Effect sizes for all comparisons are small-medium.

4 DISCUSSION

This paper reports the first RCT feasibility study of a novel psychological intervention for anxiety in BD. The approach is feasible: 59% of screened participants were randomised to feasibility trial which compares well with previous CBT for BD trials (Lam et al. 2005, Scott et al. 2006, Jones, Smith et al. 2015). Retention rate to 80 weeks was 72%, within the target of 75% ± 10% and comparable to other CBT trials in BD: 67% follow-up to 15 months (Jones, Smith et al. 2015); 75% to 18 months follow-up(Scott, Paykel et al. 2006) . Furthermore, retention was broadly balanced across arms, indicating absence of resentful demoralisation (Brewin and Bradley 1989). No trial-related adverse events were reported. The arms did differ in referral route with more participants in the therapy being recruited through self-referral. However both arms were similar in terms of demographic characteristics except for the larger proportion of the therapy arm who had >=2 anxiety disorders.

Participants were over 40 years old, and over two-thirds had at least 20 prior episodes; more than those reported in some specific relapse prevention trials (Lam, Hayward et al. 2005, Meyer and Hautzinger 2012). Only a third of the participants were in work, with most others in receipt of sickness/disability benefits.

85% of participants met criteria for anxiety disorders. Mood symptoms were low throughout and participants were relatively high functioning on personal recovery, quality of life and personal and social functioning measures. Participants attended 77% of AIBD sessions offered, indicating a significant commitment to AIBD. Several previous BD therapy trials didn't specify attendance rates (Lam et al. 2003, Scott, Paykel et al. 2006). Meyer reported 14.5% of therapy participants attended < 80% of sessions, the majority whom attended < 50% (Meyer and Hautzinger 2012). More specific data indicated individual recovery therapy attendance of 78% of sessions (Jones, Smith et al. 2015). Thus, AIBD attendance rates are comparable with the published literature. Acceptable therapeutic alliance and therapy fidelity were achieved. Client ratings of therapy usefulness and likelihood of recommending therapy were high (average >9/10 in both cases) but available for only 21 of 37 AIBD participants and so not definitive. In-depth qualitative interviews indicated the participants valued AIBD, linked to improvements in both symptoms and functioning in a number of clients. Some participants wanted a longer intervention, although others were happy with it as delivered.

The trial was not powered to test impact of AIBD on clinical outcomes and effect size estimates were imprecise and largely non-significant. Self-reported anxiety (STAI-S) indicated potential improvements in anxiety to 48, but not 80 weeks post-baseline. In contrast, observer-rated anxiety (HAM-A) was low throughout the trial. This discrepancy is potentially important for further trial development. Based on the screening data, the reports of therapy clients and the self-report measurements, it seems possible HAM-A underestimated perceived anxiety.

Observer measures indicated low depression (HAM-D) and mania (MAS) consistent with recruitment of euthymic participants and remained throughout follow-up.

Personal recovery (BRQ) but not personal and social functioning (PSP) improved more rapidly for participants in AIBD during therapy, whilst Qol.BD was numerically improved to 48 weeks but gains were not sustained at later follow-up.

Mood relapse rate was lower than that reported by Meyer (64.5% at 80 weeks; (Meyer and Hautzinger 2012) and Lam (75% at 30 months; Lam, Hayward et al. 2005) and comparable to Scott et al (52% at 18 months; Scott, Paykel et al. 2006). Although numerically higher in AIBD arm, the hazard ratio did not approach statistical significance.

Overall the current findings support the feasibility and acceptability of the trial design and the AIBD intervention. However it is important to acknowledge the lack of signal overall for the trial based on current findings. This suggests building on evidence for the importance of the integrated approach to anxiety in BD with an intervention revised to address potential factors impacting on efficacy, as indicated by qualitative feedback and by the wider literature emerging since completion of the trial. The most obvious trial for comparison with the present study is that of Ellard and colleagues, given their specific focus on addressing anxiety in BD through the use of UP (Ellard, Bernstein et al., 2017). There are several factors that may account for the difference in outcome findings. Although both have more female and predominantly white participants, it is not possible to compare clinical severity with respect to prior mood episodes or current anxiety disorders as these were not reported by Ellard. The present study had broader inclusion criteria and therefore did not exclude potential participants on evidence of psychotic symptoms, substance use issues or suicidal ideation without intent, in contrast to Ellard. It is therefore possible that in our study participants had more severe and complex clinical issues. Our analytic approach used time as a discrete variable in contrast to

Ellard for which it was a continuous variable. The advantage of the discrete time approach is that it provides estimates of the treatment effect at each assessment point adjusted for baseline covariates and is superior to separate analysis of covariance at each time-point, as information is shared across time-points supporting a missing at random assumption. Finally, it is unclear from their description whether the baseline assessment is included as a predictor or a response in their model.

Our findings can also be usefully interpreted in light of outcomes from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) STEP-BD study which explored the impact of lifetime anxiety disorder comorbidity on outcome from structured psychological therapy. In particular whether this moderated the relationship with clinical recovery in response to structured psychotherapy (cognitive behaviour therapy, family focussed therapy or interpersonal and social rhythm therapy) compared to a three session control condition of collaborative care for depressed BD participants (Deckersbach, Peters et al. 2014). Participants with one lifetime anxiety disorder showed greater improvement in response to structured therapy compared to collaborative care. This difference was not apparent for those with no lifetime history or with more than one lifetime anxiety diagnosis. This moderation affect appeared to be linked with the much poorer response of those with lifetime anxiety to the collaborative care intervention compared to those with no lifetime history (49% vs 62% recovery) rather than a differential response to structured psychotherapy (66% vs 64% recovery). This report did not indicate anything about responses patterns in relation to anxiety symptomatology or functional outcomes. These findings with respect to participants with BD and current depression require further prospective exploration including study of wider samples including those outside current mood episodes. A review of the effectiveness in general of psychological therapy for anxiety in bipolar spectrum disorders concluded that CBT including anxiety components may improve anxiety symptoms in cyclothymia among other bipolar spectrum conditions but that development of both psychological models and treatment protocols specific to anxiety in bipolar disorder are a priority (Stratford, Cooper et al., 2015).

There is accumulating evidence that individuals with BD typically respond to psychological therapy better when delivered earlier in the course of their disorder. This has been reported in relation to CBT and group psychoeducation and is consistent with recent positive outcomes for a trial of recovery focused therapy for recent onset BD (Jones, Smith et al. 2015; Scott, Paykel et al., 2006) It is therefore possible that focussing the intervention in the future more clearly on individuals with more recent BD onset might lead to stronger clinical effects. Although we considered post-hoc additional exploratory analysis of the relationships between severity and outcome in the current sample, we concluded that this would be inappropriate with relatively small participant group, consistent with recent CONSORT guidance (Eldridge, Chan et al, 2016).

Strengths included comprehensive participant assessment, extensive follow-up post-intervention and use of mixed methods to explore participants' therapy experiences.

The trial was successful in demonstrating feasibility and acceptability of selection, recruitment and intervention procedures. People took therapy when offered, and retention was acceptable. Secondary clinical data present a mixed picture, with most promising outcomes in self-reported anxiety and quality of life. RCTs of CBT for anxiety typically report follow-up period up to 48 weeks, which may be appropriate for a future AIBD trial (Covin et al. 2008). Although AIBD was generally well received, some participants wanted more sessions. Extending AIBD to 12-15 sessions, would be

consistent with NICE guidance interventions for anxiety (NICE 2011). More robust clinical outcomes might be obtained by opting for more restrictive inclusion criteria particularly with respect to duration of BD course. If successful, a definitive trial employing a revised version of the AIBD intervention would provide a timely addition to therapeutic options for BD consistent with the importance of anxiety in NICE BD guidelines (NICE 2014).

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Table 1. Summary treatment development information from individual interviews and focus groups

Individual interviews	Issues	Quotes
Therapy experiences	Recognition of the impact anxiety can have. Collaborate to personalise individual therapy goals	"the GP understands nothing about anxiety.. . ., tells them there's something else wrong with them . . .. Or gives them the wrong medication er . . . doesn't realise how serious the anxiety is so doesn't recommend them to a psychiatrist or a psychologist." AA018 "I felt worried more ….. and more … and I felt more unable to disclose information, because I didn't know if they were on my side you know. So I think it's very important to establish a bit of trust . . .A054
'I just want to know why': Knowledge as power	Importance of specific information about the nature of anxiety and relationships to mood experiences	".. I always think knowledge is, knowledge is power. And, and the more I know, the more better able I am to handle a situation which is not within my control" AA018
Limitations of drug treatment	Drug treatments for anxiety seen as sometimes unhelpful and even worsening anxiety. Strong support for psychological approaches.	"… medication is needed but medication alone doesn't do anything for anxiety, and it is just not active at all." AA054 "they tried me on a, a mixture of medication . . . and the first one actually made me . . . a damn sight worse…." AA008
Cognitive and behavioural strategies	importance of having effective approaches to deal with anxiety related thoughts and behaviour Awareness that these approaches are difficult to identify or apply without structured support	"When you are dealing with emotions like I was dealing with, it's hard enough just to cope with that, never mind trying to analyse yourself, because there is not many people can do that, it's the hardest analysation there is." AA022
Focus Groups		

Content	Information and support in relation to both BD and anxiety Recognition of the positive emotions associated with overcoming challenging situations and providing support to address these Genuine collaboration around treatment targets and potential outcomes Opportunities for family or key clinician to attend key sessions to support change	"If a therapist is aware of the bipolar running alongside the anxiety erm they'll probably get less frustrated, and there might be tools that they can help . . ." P006 "There'd be nothing wrong in you saying 'this is how I want this to go'. And someone else might want it to go a different way and they'd be able to negotiate it at that time rather that it being built." P001 "Yeah. But it has to be my set of goals. Not you coming in and saying 'Right I want you to be mood free . . . in 6 weeks' time'." P002
Support materials	Flowcharts/work sheets to self-monitor progress in therapy and as a post therapy resource Engaging support materials including lived experience accounts and links to other resources/organisations	"…and the worksheets as well, you know, when I was in the mood, even though a couple of weeks later it might not felt like it was working again, you can . . . keep going back to it". P004 "But in a manual you can go back in to tap in and tap out of, I think it's a good idea. …. So if you can keep going back to it 'cause we don't always get the computer up". P005
Barrier and facilitators	Importance of timely access to therapy Support for time limited approach deliverable by a range of disciplines to minimise waiting lists.	"Yes, getting through the GP to get the referrals there is not an awful lot of places now and waiting lists are ridiculously long." P004 "We'd want you to be able to quantify it at the end of your 10 weeks or whatever and say well this is what you expected to get out of it. Did you or didn't you?" P007 I think it would be really important for anyone

	delivering the programme, which sounds really good, you know, if you can get social workers and nurses and everyone to learn a package or whatever" P001

Table 2. Phases of Treatment of AIBD

Phase	Focus/Content	'Sarah'	'James'
1	Introducing the anxiety approach	Psychoeducation regarding thoughts feelings and behaviour links relevant to anxiety and bipolar disorder	Psychoeducation regarding thoughts feelings and behaviour links relevant to anxiety and bipolar disorder
2	Collecting information about current and historical anxiety/mood and functioning	10 year history of BD starting at University, 3 year history of panic attacks	27 year history of BD starting with major depression and overdose following relationship break down, 6 year history GAD and social phobia symptoms
3	Identifying anxiety related therapy goals	Primary goal reduction in panic attacks	Primary goal to improve management of anxiety and improve social life
4	Initial formulation of relationships between anxiety/mood experiences and progress towards recovery goals	Had isolated herself to avoid triggers of mania and became more anxious about leaving home. Panic triggered on seeing an ex-colleague when had seen her when ill. Began to recur without obvious triggers. At first sign of panic symptoms would return home and lie down.	Increasingly avoidant of social contact and relationships. Although feels lonely much of the time he found social activities anxiety provoking and was concerned this will would escalate uncontrollably and cause a mood episode. Believed mood fluctuations always likely to lead to mood episode.
5	Identifying and applying CBT techniques to facilitate positive coping with anxiety	Examination of thoughts, feelings and behaviours linked to leaving feared situations provided rationale for graded exposure and behavioural experiments.	Trained in relaxation and breathing techniques, applied in situ in social situations outside the home. Record of anticipated vs actual outcomes and impact of this on anxiety related cognitions and mood
6	Identification and application where appropriate of CBT techniques enabling positive coping with mood instability	Amended early warning signs and coping plan to remove avoidance items	Psychoeducation about normal mood variation vs early warning signs of episodes

7	Development and completion of anxiety recovery plan	Progressed through hierarchy from being able to view old colleagues on facebook to visiting her old work place and meeting an ex-colleague for a cup of tea. Anxiety recovery plan summarised key messages from therapy and longer term plans for self-management	Improved understanding of mood variation and confidence in managing anxiety. This led to increased social activities with a plan that includde key messages from therapy and longer term plans for self-management
8	Sharing lessons from therapy with key stakeholders (clinician and/or carer)	Anxiety recovery plan shared in joint session with Sarah and her family	Anxiety recovery plan shared with James's care coordinator

Table 3. Baseline sociodemographic and clinical characteristics of clinical sample

Characteristic	AIBD, N = 37 No. (%)	TAU, N = 35 No. (%)
Gender		
Male	13 (35.1)	10 (28.6)
Female	24 (64.9)	25 (71.4)
Ethnicity		
White British	33 (89.2)	32 (91.4)
Other white	0	1 (2.9)
Asian other	0	1 (2.9)
British Asian	2 (5.4)	1 (2.9)
Not stated	2 (5.4)	0
Number of previous episodes		
≤7	4 (10.8)	3 (8.6)
8-19	7 (18.9)	6 (17.1)
20+	26 (70.3)	28 (74.3)
Bipolar Status		
Bipolar I	31 (83.8)	31 (88.6)
Bipolar II	6 (16.2)	4 (11.4)
Marital Status		
Married or cohabiting	17 (45.9)	7 (20.0)
Divorced/annulled/separated	9 (24.3)	13 (37.1)
Never married	11 (29.7)	15 (42.9)
Number of children		
0	15 (40.5)	15 (42.9)
1	7 (18.9)	4 (11.4)
>= 2	15 (41.0)	16 (45.7)

Education		
Year 7-11 (No GCSE)	3 (8.1)	0
GCSEs or equivalent	6 (16.2)	8 (22.9)
Further or higher education not completed	7 (18.9)	4 (11.5)
Further/ higher or postgraduate education completed	21 (56.7)	23 (65.7)
Working		
No	21 (56.8)	23 (65.7)
Yes	16 (43.2)	12 (34.3)
Source of referral		
NHS	12 (37.5)	20 (62.5)
Self	25 (62.5)	15 (37.5)
No. current anxiety disorders		
0	5 (13.5)	6 (17.1)
1	10 (27.0)	15 (42.9)
>= 2	22 (59.4)	14 (40.0)
Current anxiety disorders		
Social Phobia	12 (32.4)	9 (25.7)
Agoraphobia	6 (16.2)	4 (11.4)
GAD	19 (51.4)	18 (51.4)
PTSD	10 (27.0)	7 (20.0)
Panic +/- Agoraphobia	9 (24.3)	6 (17.1)
OCD	5 (13.5)	6 (17.1)
Specific Phobia	9 (24.3)	6 (17.1)

Table 4. Completion of measures by trial arm and assessment timepoint

Treatment arm	Baseline[a] (0 weeks), No. (SD)	16 weeks, No. (SD)	48 weeks, No. (SD)	80 weeks, No. (SD)
AIBD	36 (97.3)	28 (90.3)	20 (74.1)	20 (76.9)
TAU	34 (97.1)	27 (84.4)	22 (84.6)	22 (84.6)

[a]No. and % presented of those with primary outcome data

Table 5. Post Therapy qualitative interview findings

Theme	Illustrative quote
Intervention value	*'And it is the only therapy I have had in all my... I have had anxiety since I was what, about 15 and that is the only thing that worked for me was that CBT [SIC] therapy.'* (AN003)
Benefits of treating anxiety and BD together	*'Normally people do them separately and trying to put them together when you are ill is just... not easy at all… if you have got them separate it's like skirting round each issue, but putting them together …….. a person that deal with them all, and will go slowly over everything so you know what to expect, it is so much better, definitely.'* (AN007)
Treatment duration	*'it was 10 sessions, and that were it, but the 10 sessions meant that the goals that were laid out at session one, those were the goals that were worked at, and those were the goals that were achieved by the end and that is a far better way of working.'* (AN001) *'I remember thinking I didn't want them to come to an end. But I couldn't have told you, or couldn't have probably pinpointed aspects that I needed more to cover I think I was just... gaining so much that I kind of felt maybe there was more to gain as well you know if I had carried on.'* (AN008) "it's good when you have the sessions but once they finish you feel, I felt like lost, and CBT is ok during treatment but long term, putting it into practice day to day, you know it's difficult to remember instantly all the tips, and that." (AN006)
Benefits of coping strategies	*'it has been crippling for me over the years. I have had a number of breakdowns, and each time it's always been the anxiety that has kept me prisoner in my own home, it has stopped me from socialising, and progressing so this time, I have healed better and with coping strategies that have allowed me to do things, a lot quicker than before.' (AN008)* *'prior to becoming part of this study I thought my bipolar disorder owned me... and was in control of me and I had no control over*

	it... and through this study, now I own it and I control it... I... through this study and through the work that I did with [research assistant] and [therapist] it give me, renewed belief and… made me take control of my life again." (AN001)

Table 6. Summary of Continuous Clinical Outcome Measures by time in AIBD and TAU groups

Measure		AIBD			TAU		
	Week	Mean	SD	n	Mean	SD	n
STAI-State	0	47.1	11.2	36	48.0	15.1	35
	16	44.3	14.3	30	47.7	11.0	31
	48	40.8	12.2	23	44.5	14.2	24
	80	48.7	15.0	24	41.7	15.1	24
STAI-Trait	0	53.7	8.2	37	53.4	11.3	35
	16	51.5	11.4	30	52.6	9.9	31
	48	47.9	12.6	23	50.3	10.9	24
	80	49.6	11.2	24	46.3	13.1	23
HAM-D	0	8.7	5.1	37	8.0	5.5	35
	16	10.1	7.8	31	10.5	7.7	31
	32	9.2	7.5	25	8.9	7.6	27
	48	8.7	7.9	24	7.9	6.3	25
	64	9.8	7.0	26	7.4	8.6	23
	80	9.1	7.0	27	8.7	8.0	26
HAM-A	0	9.1	6.1	37	9.8	7.8	35
	16	10.3	9.2	31	11.0	7.7	31
	32	9.7	8.1	25	10.8	9.9	27
	48	10.2	9.1	24	10.8	8.8	25
	64	11.6	8.1	26	11.1	11.4	23
	80	12.3	9.1	27	11.3	10.6	26
MAS	0	2.2	2.4	37	2.5	2.9	35

	16	2.1	2.5	31	2.2	2.1	31
	32	1.5	2.9	25	2.6	4.1	27
	48	3.4	5.0	24	2.0	3.0	25
	64	2.9	3.3	26	3.7	4.9	23
	80	2.4	3.7	27	4.8	5.8	26
BRQ	0	2,107	374	36	2,161	405	34
	16	2,248	411	31	2,146	401	27
	48	2,326	374	21	2,351	480	23
	80	2,318	379	20	2,398	497	23
PSP	0	73.16	10.13	37	71.77	12.40	35
	16	73.68	12.64	31	71.52	12.02	31
	48	74.91	14.95	23	72.83	15.20	24
	80	71.12	13.56	25	78.14	16.02	22
QoL BD	0	142.6	28.4	36	150.5	36.7	34
	16	147.0	31.8	30	143.7	30.6	31
	48	157.1	31.2	21	153.1	32.3	23
	80	151.5	32.3	23	160.1	38	24

Table 7. Repeated measures analyses of anxiety, mood and functional outcomes

Outcome measure	Week	Treatment Effect[a]	95% CI- Lower	95% CI- Upper	*Standarised Effect Size*	*P*-value
STAI-State						
M1	16	-2.39	-7.45	2.67	-0.188	0.355
	48	-2.50	-8.11	3.11	-0.189	0.382
	80	8.49	1.58	15.41	0.564	0.016
Time by treatment interaction						0.001*
STAI-Trait						
M1	16	-0.98	-5.16	3.20	-0.092	0.645
	48	-1.37	-6.64	3.90	-0.116	0.611
	80	3.70	-1.75	9.15	0.304	0.184
Time by treatment interaction						0.072*
M2 No interaction term		-0.403	(-4.38,	3.57)	-0.035	0.842
HAM-A						
M1	16	-0.09	-3.33	3.16	-0.012	0.959
	32	-0.30	-4.00	3.39	-0.040	0.872
	48	0.71	-3.38	4.80	0.100	0.734
	64	1.43	-3.06	5.92	0.184	0.533
	80	1.88	-2.59	6.35	0.250	0.409
Time by treatment interaction					0.027	0.798*
M2 No interaction term		0.246	(-2.44,	2.93)		0.858
HAM-D						
M1	16	-0.22	-3.74	3.30	-0.026	0.901
	32	1.28	-2.45	5.00	0.141	0.501
	48	1.68	-2.17	5.53	0.188	0.393
	64	2.53	-1.55	6.61	0.259	0.225

	80	0.91	-2.68	4.49	0.092	0.620
Time by treatment interaction						0.861*
M2 No interaction term		0.980	(-1.46,	3.42)	0.131	0.431
MAS						
M1	16	0.05	-1.04	1.14	0.022	0.928
	32	-0.63	-2.25	1.00	-0.176	0.450
	48	1.84	-0.26	3.94	0.449	0.086
	64	-0.89	-3.20	1.42	-0.216	0.449
	80	-2.14	-4.64	0.36	-0.442	0.094
Time by treatment interaction						0.032*
BRQ						
M1	16	138.40	-33.06	309.80	0.341	0.114
	48	-22.90	-199.90	154.10	-0.053	0.800
	80	-86.80	-269.10	95.80	-0.195	0.352
Time by treatment interaction						0.063*
M2 No interaction term		47.4	(-93.1	187.9)	0.111	0.508
PSP						
M1	16	1.00	-4.35	6.35	0.089	0.715
	48	0.27	-7.07	7.60	0.022	0.943
	80	-8.16	-15.48	-0.83	-0.541	0.029
Time by treatment interaction						0.072*
M2 No interaction term		1.22	-5.51	3.05	-0.088	0.574
QoLBD						
M1	16	4.92	-8.69	18.53	0.158	0.479
	48	2.81	-12.20	17.81	0.088	0.714
	80	-4.62	-21.19	11.95	-0.131	0.585
Time by treatment interaction						0.327*

M2	No interaction term	3.55	-8.95	16.04	0.578	0.108

a Based on a model with a treatment by discrete time interaction differences are between AIBD and TAU adjusting for sex, number of previous bipolar episodes, baseline HAM-AD Anxiety subscale, the baseline score, and the interaction between the baseline score and discrete time. * The p-value for the overall treatment by time interaction. M1 includes a time by treatment interaction; M2 omits the interaction.

FIGURE LEGENDS

Figure 1. Recruitment and retention

Figure 2. Kaplan-Meier estimates of time to first depression or mania-type bipolar episode

Figure 3. Kaplan-Meier estimates of time to first depression-type bipolar episode

Figure 4. Kaplan-Meier estimates of time to first mania-type bipolar episode