Integrated psychological therapy for people with bipolar disorder and co-morbid alcohol use: A feasibility and acceptability randomised controlled trial

Steven Jones\textsuperscript{a,∗}, Heather Robinson\textsuperscript{a}, Lisa Riste\textsuperscript{b}, Chris Roberts\textsuperscript{c}, Sarah Peters\textsuperscript{b}, Lucy Bateman\textsuperscript{b}, Emma Weymouth\textsuperscript{b}, Christine Barrowclough\textsuperscript{b}

\textsuperscript{a}Spectrum Centre for Mental Health Research, Faculty of Health and Medicine, Lancaster University, United Kingdom
\textsuperscript{b}Centre for Biostatistics Research, University of Manchester, Manchester, United Kingdom
\textsuperscript{c}Division of Psychology and Mental Health, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, United Kingdom

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\textbf{ABSTRACT}

\textbf{Background:} Co-morbid substance misuse, particularly alcohol, is common in bipolar disorder (BD) and associated with worse treatment outcomes. Research into psychological interventions for substance misuse in BD is at an early stage and no studies have specifically targeted problematic alcohol use. This paper describes the context and protocol for a feasibility and acceptability randomised controlled trial (RCT) evaluating a novel intervention combining motivational interviewing and cognitive behavioural therapy (MI-CBT) for participants with BD and problematic alcohol use, developed in collaboration with people with lived experience of both issues.

\textbf{Methods and design:} An RCT will assess the feasibility and acceptability of MI-CBT in addition to treatment as usual (TAU) compared with TAU alone. Participants will be recruited from across the North West of England through NHS services and self-referral. The primary outcomes will be the feasibility and acceptability of the intervention assessed by recruitment to target, adherence to intervention, retention rate at follow-up, absence of adverse events and qualitative analysis of participants’ reported experiences of intervention. The effect size of the impact of the intervention on alcohol use and mood outcomes will also be estimated. In addition, we will explore a number of potential process variables in therapy.

\textbf{Discussion:} This is the first RCT evaluating MI-CBT for BD and problematic alcohol use. Given the prevalence and impact of alcohol problems in BD this novel integrated intervention may have potential to offer important improvements in clinical and functional outcomes.

1. Introduction

Bipolar disorder (BD) has a prevalence rate of 1–2\% [1] and is the sixth leading cause of disability [2], estimated cost to the English economy in excess of £5 billion per annum [3]. BD is likely be comorbid with alcohol or substance misuse [4], and even at more moderate levels, alcohol use is associated with poorer prognosis and more severe mood disturbance [5]. Whilst psychological treatments for relapse in BD are shown to be effective, cost effective and popular with services users [6], there is no established treatment to address alcohol use in BD.

Intervention research for substance use in BD is at an early stage and to our knowledge there are only three published RCTs (and a single open trial) evaluating approaches targeted at this client group [7–10]. Schmitz et al. [7] compared 16 sessions of CBT for BD and substance use with 4 medication monitoring assessments over 3 months. No differences were observed in substance use but participants in the CBT group experienced fewer days with depression or mania symptoms. Three other published studies from Weiss and colleagues [8–10], report the development and evaluation of an integrated group therapy (IGT) for people with BD and substance use. They found that 20 sessions of IGT led to better substance use outcomes but worse mood outcomes whereas a 12 session version of IGT led to both better substance use and mood outcomes (both compared with group drug counselling) [9] [10].

Although promising, Weiss’s [8–10] research only included individuals who were treatment seeking for both BD and substance use. As ambivalence is common in BD and linked to substance use, this approach risks excluding individuals most in need of help [11,12]. Motivational interviewing (MI) offers an established approach to engaging individuals with substance use issues [13,14] and reducing
treatment ambivalence [15]. This protocol paper describes an RCT to evaluate the feasibility and acceptability of delivering an integrated MI-CBT intervention to individuals with BD who use alcohol. The focus is on BD with comorbid alcohol misuse as it is the most common substance of abuse and research indicates more positive psychological treatment outcomes for alcohol than other substances [9]. The intervention, individually tailored to address idiosyncratic reasons for alcohol use and relationships to mood symptoms in BD [16,17], has been successfully employed in a previous case series study [18].

MI-CBT was developed with the help of individuals with lived experience of both BD and alcohol use issues consistent with the growing recognition of the importance of involving service users in treatment development [19]. As a feasibility and acceptability study the primary outcomes are recruitment to target, adherence to intervention, retention rate at follow-up, absence of adverse events and qualitative analysis of participant experiences of intervention. In addition, the study will provide preliminary evidence of the impact of the intervention with respect to alcohol use and bipolar mood symptoms and relapse as potential primary outcomes for a future definitive RCT.

2. Methods

This RCT is conducted by a multidisciplinary team of researchers, clinicians, statisticians and therapists from academic institutions and NHS trusts in the North West of England. The study was approved by the UK NHS Ethics Committee process (REC ref: 10/H1014/75).

2.1. Objective

To determine the feasibility and acceptability of an integrated motivational interviewing and cognitive behaviour therapy (MI-CBT) intervention for alcohol use in the context of bipolar disorder compared with treatment as usual.

Main research aims:

- To explore feasibility of recruitment and consenting procedures, adherence to treatment protocol and retention to both arms of the trial across assessment, intervention and follow-up periods. Specific targets are specified in the outcome section below.
- To provide initial parameter estimates of clinical outcomes including alcohol use (both frequency and severity of use), bipolar relapse, mood, social functioning, medication adherence and cost effectiveness.
- To systematically examine acceptability of the intervention from the perspective of service users.

2.2. Trial design

A rater-blind randomised controlled trial which compares up to 20 sessions of integrated MI-CBT for alcohol use in the context of bipolar disorder plus treatment as usual with TAU alone. The trial is based in...
the North West of England with recruitment across rural and urban areas and a wide range of sociodemographic and ethnic groups. Randomisation is carried out by the independent Clinical Trials Unit at The Christie NHS Foundation Trust, Manchester. Minimisation [19] is used with respect to gender, number of previous bipolar episodes (<12, 12 or more episodes) mania (including mixed episode), hypomania or depression) and level scored on the Alcohol Use Disorders Identification Test (AUDIT; [20]) by category (Medium alcohol problems 8–15, High to severe alcohol problems ≥16). These factors were selected as there is evidence that clinical outcomes from psychological therapy are typically better for females [20], preliminary evidence for better outcomes in bipolar disorder for individuals with fewer previous episodes [21], and evidence that baseline AUDIT score predicts alcohol relapse [22]. In small studies there can be imbalance. Minimisation is superior to other standard methods in reducing marginal imbalance and is generally considered to be a good method for small studies. The table of baseline characteristics of the randomised group will include the minimising variables. It should be noted that the purpose of using minimisation was also to check the feasibility of procedures associated with it use in this context. Fig. 1 gives an outline of the study design.

2.3. Sample size

A formal power calculation is not required for this study since its primary purpose is to evaluate the feasibility and acceptability of delivering and evaluating the proposed intervention. It has been estimated that primary feasibility outcomes can be reliably determined with a sample of 24 participants per group, consistent with previous recommendations for total sample sizes between 24 and 50 for feasibility studies [23,24]. Measures of clinical outcome will be recorded at baseline and follow-up assessments to provide a preliminary indication of the effect of the intervention in regulating mood, decreasing the frequency and severity of alcohol use, and its impact on other clinical outcomes. This number will also allow us to evaluate the secondary objective of the trial; to estimate the potential treatment effect sizes to inform a future more definitive trial.

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2.4. Recruitment

Participants are recruited through NHS services and self-referral in the North West UK. Community mental health teams, out-patient clinics, GP surgeries, primary care mental health teams and voluntary services are approached to identify potential participants. Potential participants receive a participant information sheet outlining the study and their role should they wish to take part.

The study is also advertised in local media, and posters and leaflets distributed to both NHS and non NHS sites to maximise participant access. Care co-ordinators and other relevant health professionals are informed of a participant’s involvement in the study with the participant’s consent. Participants are made aware on entry to the study that their care co-ordinator or relevant health professional will be contacted on their behalf if they wish to take part.

2.5. Inclusion/exclusion criteria

Potential participants must meet the inclusion criteria of:

- SCID DSM-IV diagnosis of bipolar disorder I or II.
- Alcohol use exceeding 21 units for males/14 units for females on at least half of the weeks of the previous 3 months; Or at least one alcohol ‘binge’ per fortnight in each of the previous 3 months (6 binges in 3 months): a binge is defined as a person exceeding the government recommended number of units of alcohol in a day; for males this is 6 units daily, and for females this is 4 units daily [23].
- A score of 8 or more on the Alcohol Use Disorders Identification Test (AUDIT; [20]).
- Aged 18 or over.
- An ability to provide informed consent.
- Having a fixed abode.

Exclusion criteria:

- Presence of current manic, hypomanic, mixed affective or major depressive episode currently or within the last 4 weeks.
- Current significant suicidal ideation or intent.
- An inability to communicate in written and verbal English to a sufficient level to allow participants to complete the measures and participate in therapy sessions.
- Individuals requiring/currently seeking referral for, or undergoing, specialist alcohol treatment requiring medical management such as detoxification.

2.6. Outcome measures

In order to evaluate the feasibility and acceptability of delivering the MI-CBT intervention to individuals with a diagnosis of bipolar disorder, the following data will be evaluated: recruitment to target into the trial, retention of participants in both arms of the study and adherence to the intervention. Qualitative interviews are also conducted to explore people’s experience of the trial including acceptability. At baseline the Structured Clinical Interview for DSM-IV [25] is completed to confirm bipolar diagnosis and to provide information on alcohol disorder diagnoses as well as information on sociodemographic variables. Measures of clinical outcome are recorded at baseline and follow-ups to provide a preliminary indication of the effect of the intervention in reducing frequency and severity of alcohol use, increasing time to bipolar relapse, and its impact on other clinical outcomes.

2.6.1. Clinical outcomes

Hypotheses for the primary clinical outcomes are that MI-CBT will: i) decrease the frequency and severity of alcohol use as measured by the Time Line Follow Back (TLFB) Interview [26]; and ii) increase time to bipolar relapse as measured by the Structured Clinical Interview for Diagnosis: Research Version (SCID DSM-IV; SCID Life; [27]).

Hypotheses for secondary outcomes are that MI-CBT will improve: i) mood symptoms as measured by Hamilton Depression Rating Scale (HAM-D; [28]) and Bech-Rafaelsen Mania Scale (MAS; [29]); ii) self-reported mood symptoms as measured by the Patient Health Questionnaire – 9 (PHQ-9; [30]) and Internal States Scale (ISS; [31]); iii) quality of life and social functioning as measured by the Personal and Social Performance Scale (PSP; [32,33]); (iv) medication adherence as measured by the Stephenson Medication Adherence Interview (MEDAD; [33]).

2.6.2. Process measures

The Barratt Impulsiveness Scale (BIS-11; [34]) is used to assess whether MI-CBT improved clinical outcomes through reducing impulsivity.

The Readiness for Change Questionnaire [35] is employed to evaluate the extent to which progression through stages of change [36] (pre-contemplation, contemplation, preparation and action) is associated with clinical outcomes.
2.6.3. Measures to assess therapeutic alliance and adherence to treatment protocol

Engagement in therapy will be assessed by means of the Work Alliance Inventory (short-form, therapist and client versions: WAI-S; [36]). Treatment fidelity will be assessed by the MI-CBT Fidelity Scale used in previous studies evaluating integrated MI-CBT therapy for substance use disorders in people with mental health problems [37].

2.7. Assessment schedule (see Table 1)

The follow-up period will be 12 months from initial randomisation. Participants are assessed on all measures at baseline, prior to randomisation, and at 6, and 12 month follow-up appointments. A sub-set of follow-up measures (SCID Life including the MAS and HAM-D, and the Time Line Follow Back) are also to be carried out at 3 and 9 months. All measures are administered by a trained research assistant (RA) blind to the participant’s condition. Any RA unbinderd are recorded and an alternative RA will conduct the next assessment where required.

2.8. The MI-CBT intervention

The intervention was developed from a treatment programme with benefits for people with alcohol use and psychosis [38]. The approach integrates motivational interviewing (MI) and CBT, through a case formulation approach which acknowledges the variation in the reasons and functions of use in each person, proposes a dynamic relationship between alcohol use and symptom exacerbation, matches therapy to take account of people’s motivation for change, and emphasises increasing motivation to reduce alcohol use in recognition of the frequency of low motivation or ambivalence in clients entering therapy. A case series applying key elements of this approach to BD patients [18] has demonstrated its transferability to BD and that the case formulation approach accommodates the more variable, relapsing course experienced by patients with BD. The intervention follows a detailed therapy manual based on that used in a therapy trial for substance use in people with psychosis [38] modified for people with BD [18] and further refined through structured consultations with service users and clinicians with experience of bipolar disorder. Initial sessions focus on engagement and use motivational interviewing to develop a shared understanding of the client’s key life goals and concerns. This phase aims to elicit and selectively reinforce the client’s own self-motivational statements and to monitor the client’s readiness to reduce their drinking. The therapist will help the client to understand how goals and concerns, particularly bipolar-relevant symptoms and relapses (depression, hypomania, anger, irritability, impulsiveness and disrupted social rhythms) might be related to drinking alcohol. The shared formulation developed from this phase of therapy will identify the individual determinants and consequences of the client’s key problems, especially with respect to alcohol use. In clients where motivation for change is achieved, the next stage will involve developing an alcohol reduction/abstinence plan. The specific plan in each case will be guided by the individual formulation and by the needs of the client in terms of severity of current alcohol problems. For all participants, the plan will likely incorporate appropriate evidence based cognitive behavioural strategies focussed on implementing changes in drinking behaviour. This phase may also include CBT to facilitate alternative approaches to dealing with symptoms which have been associated with alcohol use including depressed or elevated mood or interpersonal concerns. The intervention will also include the development of a relapse prevention plan which summarises what has been learnt from therapy and provides a reference for the client following completion of treatment. For those clients who are not ready to change alcohol use by this stage the therapist will aim to work on other client led problems to maintain engagement whilst continuing to link alcohol use to their concerns through MI techniques.

Participants will be offered up to 20 therapy sessions over 6 months. Sessions are typically 45–60 min long. Therapy will take place at participants’ homes or a location of their choice.

2.9. Analysis plans

2.9.1. Feasibility of intervention

We propose to recruit 48 subjects in total. With this sample size a recruitment rate of 50% can be estimated with precision ± 15% (95% confidence intervals). A 70% rate of treatment adherence can be estimated with precision ± 20% (95% confidence intervals).

2.9.2. Acceptability of intervention

Qualitative data will be obtained from in-depth interviews with a subgroup recipients of MI-CBT using a flexible topic guide to elicit information on participants’ expectations and experiences of therapy. Sampling for this nested study will seek to ensure maximum variance, e.g. different levels of baseline alcohol use, participants who have completed therapy as well as those who dropped out. An inductive analysis will be conducted consistent with the principles of Thematic Analysis [39]. Emergent themes will be reviewed by a group comprising academic researchers, clinicians and service users using a constant comparative technique in light of emerging data. The iterative process will be used to refine themes across the dataset. It is intended that engaging a wide range of individuals from different background in the analysis will enhance the trustworthiness of the final findings [40].

2.9.3. Clinical outcomes

Distributional properties of the Time-Line Follow Back outcome measures will be investigated as this measure is known to generate outcomes that may be highly skewed [38], with a view to determining an appropriate method of analysis. Each model will adjust for baseline values of the outcome measure and the following prognostic variables: gender, number of previous episodes, and AUDIT score. A Cox model will be used to analyse time to bipolar relapse adjusting for the

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Table 1

| Assessment | Baseline | 3 months | 6 months | 9 months | 12 months |
|------------|----------|----------|----------|----------|-----------|
| Primary Outcome Measures |          |          |          |          |           |
| Time Line Follow Back | ✓        |          |          |          |           |
| SCID Life | ✓        |          |          |          |           |
| Secondary Outcome Measures |          |          |          |          |           |
| Hamilton Depression Rating Scale | ✓        |          |          |          |           |
| Bech-Rafaelsen Mania Scale | ✓        |          |          |          |           |
| Internal State Scale | ✓        |          |          |          |           |
| Personal & Social Performance Scale | ✓        |          |          |          |           |
| Stephenson Medication Adherence Interview | ✓        |          |          |          |           |
| Patient Health Questionnaire, PHQ-9 | ✓        |          |          |          |           |
| Barratt Impulsiveness Scale | ✓        |          |          |          |           |
| Readiness to change questionnaire – Alcohol | ✓        |          |          |          |           |

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Abstinence plan. The specific plan in each case will be guided by the individual formulation and by the needs of the client in terms of severity of current alcohol problems. For all participants, the plan will likely incorporate appropriate evidence based cognitive behavioural strategies focussed on implementing changes in drinking behaviour. This phase may also include CBT to facilitate alternative approaches to dealing with symptoms which have been associated with alcohol use including depressed or elevated mood or interpersonal concerns. The intervention will also include the development of a relapse prevention plan which summarises what has been learnt from therapy and provides a reference for the client following completion of treatment. For those clients who are not ready to change alcohol use by this stage the therapist will aim to work on other client led problems to maintain engagement whilst continuing to link alcohol use to their concerns through MI techniques.

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prognostic variables given above.

The statistical analysis of (what are likely to be secondary) clinical and process outcome measures will be limited to summary statistics in line with status of this as a feasibility and acceptability study.

2.9.4. Multiple testing

This is a preliminary study with a relatively small sample size, therefore there will be no adjustment for multiple testing.

3. Discussion

There have been no RCT evaluations to date of MI-CBT for alcohol use in bipolar disorder, although a pilot case series employing this approach across individuals with either cannabis or alcohol use problems produced promising results [18]. This study will provide feasibility and acceptability information with respect to a novel MI-CBT intervention trial for bipolar disorder and alcohol use problems which will help to inform the development and evaluation of a future definitive trial. Data from clinical outcome measures will also provide preliminary indications of effect sizes for the intervention. The MI-CBT intervention was modified from that used in therapy for people with psychosis [38] in partnership with individuals with lived experience of bipolar disorder consistent with Mental Health Research Network Good Practice Guidelines [41] and research indicating the benefits of collaborative approaches to clinical interventions [42,43] including service user involvement in developing the content and format of delivery of the therapy.

3.1. Study strengths

Strengths of the study include targeting a clearly defined sample who have historically not been offered an integrated approach to care for their problems with alcohol use and mood. This group also expressed significant interest in such an integrated approach to their care in consultations leading to the development of this intervention. Participants will be recruited from a range of sources including NHS primary and secondary care services and through self-referral. This approach should lead to more representative findings than in a trial in which participants are only recruited from specialist mental health services, as many individuals with a diagnosis of bipolar disorder either do not access such services or do so only periodically [1].

3.2. Study weaknesses

There are some weaknesses to the study that it is important to acknowledge. Firstly, the study is designed to follow participants for up to 6 months following treatment. This should be adequate to indicate short term changes in alcohol use and mood but may be insufficient to more definitively evaluate long term changes. Secondly, the study compares an active intervention with treatment as usual. Exploring potential benefits of a novel therapy compared to routine care is appropriate at this level of therapy development, but a final definitive evaluation of the approach could also explore the specificity of any treatment benefits with respect to a different active intervention such as CBT or psychoeducation for bipolar disorder alone.

4. Conclusion

If the current study indicates that the proposed approach to integrated therapy for alcohol and bipolar disorder is feasible and acceptable, this will be important in informing thinking about developing better care for individuals living with these comorbid problems. By taking a mixed methods approach we aim to obtain comprehensive information on both trial design and intervention to inform the development of a future definitive trial.

Conflicts of interest

Members of the research team developed the MI-CBT intervention under evaluation in this protocol.

Authors contributions

SJ is Chief Investigator for the PARADES programme and worked closely with CB who was lead investigator for this study. SJ led the writing of this paper. HR, EW & LB contributed to assessment of participants and write up of the paper. LR coordinated the study as part of her role as PARADES trial manager. CR developed the statistical analysis plan for the paper. SP led the qualitative analysis plan. All authors contributed to the writing of the paper and approved the final version.

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