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Effects of adjunctive brexpiprazole on sleep-wake and circadian parameters in youth with depressive syndromes: Study protocol for a clinical trial

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ABSTRACT

Introduction

Sleep-wake and circadian disturbance is a key feature of mood disorders with a potential causal role and particular relevance to young people. Brexpiprazole is an atypical antipsychotic medication with demonstrated efficacy as an adjunct to antidepressant treatment for Major Depressive Disorder (MDD) in adults, with preliminary evidence suggesting greater effectiveness in subgroups of depressed patients with sleep disturbances. This clinical trial aims to evaluate the relationships between changes in sleep-wake and circadian parameters and changes in depressive symptoms following adjunctive brexpiprazole treatment in young adults with MDD and sleep-wake disturbance.

Methods and analysis

This study is designed as a 16 week (8 weeks active treatment, 8 weeks follow up) mechanistic, open-label, single-arm phase IV clinical trial and aims to recruit 50 young people aged 18 to 30 with MDD and sleep-wake cycle disturbance through an early intervention youth mental health clinic in Sydney, Australia.
At baseline, participants will undergo multidimensional outcome assessment and subsequently receive 8 weeks of open-label treatment with brexpiprazole as adjunctive to their stable psychotropic medication. Following 4 weeks of treatment, clinical and self-report measures will be repeated. Ambulatory sleep-wake monitoring will be conducted continuously for the duration of treatment. After 8 weeks of treatment, all multidimensional outcome assessments will be repeated. Follow-up visits will be conducted 4 and 8 weeks after trial completion (including sleep-wake, clinical, and self-report assessments).

Ethics and dissemination

This trial protocol has been approved by the Human Research Ethics Committee of the Sydney Local Health District (X19-0417 and 2019/ETH12986, Protocol Version v 1-3, dated 25.02.2021).
The results of this study, in de-identified form, will be disseminated through publication in peer-reviewed journals, scholarly book chapters, presentation at conferences and publication in conference proceedings.

Trial Registration

Australian New Zealand Clinical Trials Registry (ANZCTR) Number: ACTRN12619001456145p, Date 22 October, 2019.

KEYWORDS:

Mental health, adjunctive brexpiprazole, sleep-wake cycle, youth depression.

ARTICLE SUMMARY

Strengths and limitations of this study

- The use of comprehensive assessment battery, including actigraphy and circadian assessment, and collection of metabolic and inflammatory markers to help acquire a greater understanding of the mechanisms of antidepressant action of adjunctive brexpiprazole
- This trial will help to inform personalised treatment plans for specific clinical phenotypes, placing the participant at the centre of care
- As part of the study, all participants will receive a psychoeducational session about sleep and circadian rhythms with information on how to improve their sleep based on their actigraphy data

INTRODUCTION

In young adults, Major Depressive Disorder (MDD) is highly prevalent, recurrent, and comorbid with other mental and physical conditions, generating a substantial burden of disease and disability [1, 2]. While multiple psychological and pharmacological treatments are commonly provided, a large proportion of patients with MDD fail to respond to first-line psychotherapy or antidepressant treatments [3-5], and augmentation with atypical antipsychotics is often recommended in these treatment-resistant cases [6]. Common features of depressive disorders are sleep-wake cycle disturbances, including not only insomnia [7-9], hypersomnia [10, 11], and abnormal sleep duration [7, 8], but also abnormal timing of 24-hour patterns of rest and activity [12, 13]. In addition, abnormalities

in biological circadian rhythms have been reported in depressive disorders [14, 15], suggesting that in some cases sleep disturbances are accompanied or underpinned by disturbances of the underlying circadian timing system [16].

Adolescents and young adults are particularly vulnerable to circadian perturbations due to significant developmental changes in circadian rhythms across this age period [17], and sleep-wake phase delays are common in young people with depressive disorders [18]. Recently, we reported delayed and disrupted circadian rhythms in a subgroup of young people with depressive disorders, and this group also presented with greater symptom severity [19]. Furthermore, there is some evidence that correction of circadian abnormalities is associated with antidepressant effects in response to treatments targeting the circadian system such as Agomelatine [20] and bright light therapy [21].

Brexpiprazole is an atypical antipsychotic with demonstrated efficacy as an adjunct to antidepressant treatment in major depressive disorder in adults, as evidenced by multiple randomised controlled trials [22-25], however the exact mechanism of antidepressant action is unknown [26]. The pharmacodynamic properties of brexpiprazole, together with evidence from preclinical studies, suggest that there may be specific effects on anxiety, cognitive function, and sleep [26, 27]. Further, there is preliminary evidence to suggest that brexpiprazole may have greater effectiveness in subgroups of depressed patients with sleep disturbances, anxiety, or irritability [16, 28].

One previous study has investigated sleep disturbances in individuals with MDD treated with adjunctive brexpiprazole and reported both reduced insomnia symptoms and improved daytime alertness [29]. This is consistent with effects on circadian rhythms, with potential influences on the entire 24-hour pattern of rest and activity rather than simply on the sleep period in isolation. In order to improve the personalisation of treatment selection for mood disorders, it is necessary to acquire a greater understanding of the mechanisms of antidepressant action of specific compounds. As such, we aim to

investigate whether the impact of brexpiprazole on depressive symptoms is linked to changes in sleep-wake cycle or circadian parameters in young people with MDD.

METHODS AND ANALYSIS

Study Objectives

The primary objective of this study is to determine if changes in depressive symptoms following adjunctive brexpiprazole treatment are correlated with changes in sleep-wake cycle or circadian parameters in young people with depressive syndromes.

The secondary objective is to determine if changes in social and occupational functioning following adjunctive brexpiprazole are correlated with changes in sleep-wake cycle or circadian parameters in young people with depressive syndromes.

The tertiary objectives of this study are to determine if changes in depressive symptoms or changes in sleep-wake cycle or circadian parameters following adjunctive brexpiprazole treatment are associated with a range of multidimensional outcome measures in young people with depressive syndromes[30]. These include other mental illness symptoms, self-harm and suicidal thoughts and behaviours, physical health parameters, alcohol and substance use, and genomic markers.

Trial design

This investigator-initiated, mechanistic study involving 50 young people with depressive syndromes and sleep-wake cycle disturbances is designed as a 16-week (8 weeks active treatment, 8 weeks follow-up) open-label, single-arm, phase IV clinical trial.

Participants

Participants aged 18 to 30 with a diagnosis of MDD according to DSM-5 criteria on a current antidepressant treatment of either selective serotonin reuptake inhibitor (SSRI) or serotonin-

norepinephrine reuptake inhibitor (SNRI) with a disrupted sleep-wake cycle will be recruited through the youth mental health clinics associated with the Brain and Mind Centre (BMC), University of Sydney. All participants will provide written informed consent. The research team will make explicit to any potential participants both verbally and in writing (in the Participant Information Statement) that participation is voluntary and will not affect the patient's care received by the mental health service.

The inclusion criteria for this trial are: (i) aged 18 to 30, (ii) diagnosis of MDD as per DSM-5 (Structured Clinical Interview for DSM; SCID[31]) criteria, (iii) current major depressive episode of moderate severity as defined by a Quick Inventory of Depressive Symptomatology (QIDS)[32] rating ≥ 11 at two assessments two weeks apart, (iv) failure to respond to at least one adequate (minimum four weeks) trial of pharmacological treatment, (v) current antidepressant treatment with SSRI or SNRI for at least 6 weeks, at a stable dose for two weeks prior to study commencement, and (vi) a perturbed sleep-wake cycle as evidenced by: delayed sleep onset; delayed sleep offset; disrupted sleep; high day-to-day variability of sleep-wake cycle; non-restorative sleep; or daytime fatigue.

Exclusion criteria are: (i) any adjunctive antipsychotic treatment for current episode in the past month, (ii) use of medications which affect sleep, (iii) primary psychotic disorder diagnosis, (iv) acute suicidal behaviour (score of 6 on Comprehensive Assessment of At-Risk Mental States (CAARMS) item 7.3[33]), (v) medical condition contributing to sleep-wake dysfunction, (vi) significant alcohol or substance misuse or dependence (assessed via DSM-5 SCID[31] and World Health Organisation Alcohol, Smoking and Substance Involvement Screening Test (WHO-ASSIST[34, 35]), (vii) shift work or (viii) recent transmeridian travel, (ix) previous hypersensitivity to brexpiprazole, (x) taking CYP2D6 or CYP3A4 inhibitors, and (xi) pregnancy or lactation.

Study course and procedure

Patients presenting for mental health care who may be eligible for the study will be screened by phone before being invited to participate and attending an enrolment visit. The enrolment visit will formally assess

eligibility criteria and confirm the presence of MDD as per DSM-5 (SCID)[31]. Participants will be provided with an actigraphy device (non-invasive, wrist-worn device used to objectively measure activity and sleep patterns) and will be given instructions to wear the device for the following two week period.

Visit 1 (Baseline): Within two weeks of completing the diagnostic and screening assessments, data from the actigraphy device will be downloaded and reviewed. A further assessment of depressive symptom severity (QIDS Clinician-Rated; QIDS-CR)[32] will be conducted to ensure that participants meet all inclusion criteria. Bloods will be collected for the assessment of metabolic and inflammatory measures, and genomic analysis. Clinical and self-report assessments will be conducted, as well as circadian assessments in which the participant will remain in the sleep lab overnight. The following morning, participants will attend a 1-hour psychoeducation session about sleep and circadian rhythms covering the following topics: i) sleep and circadian education with tailored discussion based on their personal actigraphy data; ii) individualized plan for progressive sleep rescheduling; and iii) lifestyle factors and behaviours impacting on sleep (e.g. exercise, light, sleep environment, sleep regulation, foods, stress, anxiety, mood).

Once all baseline clinical and self-report assessments have been conducted, and the medical assessment completed by the study doctor to confirm the inclusion and exclusion criteria, participants will be issued with the study medication to receive 8 weeks of open-label pharmacotherapy with brexpiprazole (REXULTI®-Lundbeck) as adjunctive to their stable psychotropic medication (treatment as usual). Brexpiprazole will be provided to participants at Visit 1 (Baseline) and Visit 2 (Week 4) for the following four weeks and will be titrated from 1 mg once daily in week 1, to 2 mg once daily in weeks 2-8.

Monitoring visits: Participants will be contacted by telephone on a weekly basis for the duration of the 8 week treatment period to monitor adverse events and adherence. Any changes in concomitant medications will also be investigated and recorded. In addition, participants will be provided with a medication diary and asked to complete during the study to monitor adherence.

More detailed information about potential side-effects will be further assessed by the study doctor at visits 2, 3, 4 and 5 using the UKU Side Effect Rating Scale [36], Abnormal Involuntary Movement Scale (AIMS) [37] and the Simpson-Angus Scale (SAS) [38] for evaluation of extrapyramidal symptoms (EPS).

Visit 2 (Week 4): Following four weeks of the treatment phase, participants will return to BMC, where clinical and self-report assessments will be completed to assess changes in clinical and functional measures.

Visit 3 (Week 8): Following eight weeks of the treatment phase, participants will return again to complete clinical and self-report assessments, and will also complete a second circadian (overnight) in-lab assessments. Bloods will be collected at this visit for follow-up metabolic and inflammatory markers.

Visit 4 and 5 (Follow-up visits 1 and 2, 12 and 16 weeks respectively): Twelve and sixteen weeks after commencing treatment (i.e. four and eight weeks after completing the eight-week treatment period respectively), participants will return to BMC and complete clinical and self-report assessments. Participants will be provided with an actigraphy device to wear for two weeks prior to these assessments.

Participants will be reimbursed for their time and the cost of transportation to and from the BMC and/or sleep labs.

Outcomes

Primary Outcome Measures

The primary endpoint will be the correlation between change in sleep-wake and circadian parameters and change in depressive symptoms from baseline to week eight.

Notably, the primary depressive symptom measures (QIDS-CR total score, QIDS-Self Report (QIDS-SR) total score, The Montgomery–Åsberg Depression Rating Scale (MADRS) total score) contain sleep items. These will be removed from these scales for analyses to provide a measure of depressive symptoms that is not biased by changes in sleep-wake parameters.

Primary sleep-wake and circadian variables of interest include actigraphy parameters, as well as in-lab circadian and self-report measures.

Secondary Outcome Measures

The secondary endpoint will be correlation between change in sleep-wake and circadian parameters and change in functioning from baseline to week eight.

Tertiary Outcome Measures

Tertiary endpoints will be correlation between change in sleep-wake and circadian parameters and other multidimensional outcome measures based on assessments of symptoms, self-harm and suicidal thoughts and behaviours, physical health, and alcohol and substance use.

Further tertiary endpoints will be comparison of primary endpoints between Clinical Stages [39-42], illness trajectories [43], and genomic variants with potential relevance to mood disorders and/or circadian rhythms (e.g. CLOCK, BMAL1).

Detailed outcome measures are summarized in Table 1.

Table 1 – Primary, Secondary and Tertiary Outcome Measures

Primary Outcome Measures (Correlation between change in sleep-wake and circadian parameters and change in depressive symptoms from baseline to week eight)	**Secondary Outcome Measures** (Correlation between change in sleep-wake and circadian parameters and change in functioning from baseline to week eight)	**Tertiary Outcome measures** (Ccorrelation between change in sleep-wake and circadian parameters and other multidimensional outcome measures)
Primary depressive symptom measures: • QIDS-CR total score (minus sleep items) • QIDS-Self Report (QIDS-SR) total score (minus sleep items) • The Montgomery–Åsberg Depression Rating Scale (MADRS) total score (minus sleep items) **Primary sleep-wake and circadian variables of interest:** Actigraphy parameters (in the two-week period prior to baseline and prior to week eight): • Sleep onset time • Sleep offset (wake) time • Total sleep time (duration) • Wake after sleep onset (estimation of number of minutes awake during the sleep period) • Sleep efficiency (% of sleep period estimated as sleep) • Inter-daily stability • Intra-daily variability **In-lab circadian measures:** • Dim Light Melatonin Onset (DLMO) timing • Phase angle (time lapse) between DLMO and habitual sleep • Core body temperature nadir	**Functioning measures:** • Social and Occupational Functioning Assessment Scale (SOFAS) rating • The Work and Social Adjustment Scale (WSAS) total score • Adapted Schuster Social Support Scale (SSSS) total score • Not in Education, Employment, or Training (NEET) status • Number of days 'out of role' (unable to perform usual activities) in the past 30 days	**Symptom Measures:** • Young Mania Rating Scale (YMRS) total score • Brief Psychiatric Rating Scale (BPRS) total score and subscale scores • Overall Anxiety Severity Impairment Scale (OASIS) total score • Altman Self-Rating Mania scale (ASRM) total score • Prodromal Questionnaire (brief version) (PQ-16) total score • DSM-5 Primary Care Post-Traumatic Stress Disorder screen (PC-PTSD-5) total score • Adapted Eating Disorder Examination (EDE) total score • Clinical Global Impressions scale (CGI) severity and improvement scores **Self-harm and suicidal thoughts and behaviours:** • Suicidal risk (score from Suicidal Ideation Attributes Scale (SIDAS) and Columbia-Suicide Severity Rating Scale (C-SSRS) items) • Adapted Brief Non-Suicidal Self-Injury Assessment Tool (B-NSSI-AT) total score **Physical Health:** • Body Mass Index (BMI) calculated from height and weight • Waist circumference

• Evening cortisol area under the curve **Self-report measures:** • Non-restorative sleep score (based on the Pittsburgh Sleep Quality Index (PSQI), and Munich Chronotype Questionnaire (MCTQ) • *Pittsburgh Sleep Quality Index* (PSQI) total score • Epworth Sleepiness *Score* (ESS) total score • Insomnia Severity Index (ISI) total score • Morningness -Eveningness Questionnaire (MEQ) total score* • Seasonal Pattern Assessment Questionnaire (SPAQ) total score* *baseline scores will be used rather than change scores as these are trait measures		• International Physical Activity Questionnaire (IPAQ) total score • Metabolic blood markers including triglycerides, cholesterol (total, Low Density Lipoprotein (LDL), High Density Lipoprotein (HDL)), and Homeostasis Model of Insulin Resistance (HOMA2-IR) calculated from fasting glucose and insulin measures • Inflammatory blood markers including Interleukin-1β (IL-1β), Interleukin-6 (IL-6), Tissue Necrosis Factor (TNF-α), C-Reactive Protein (CRP) **Alcohol and Substance Use:** • World Health Organisation Alcohol, Smoking, and Substance Involvement Screening Test (WHO ASSIST) score for tobacco, and cannabis • Alcohol Use Disorders Identification Test-Consumption (AUDIT C) total score • WHO ASSIST alcohol-related impairment • Age of onset of alcohol use **Comparison of primary endpoints between:** • Clinical Stages • Illness Trajectories • Genomic variants with potential relevance to mood disorders and/or circadian rhythms (e.g. CLOCK, BMAL1).

Assessments

Assessments used in this trial are based on the multidimensional assessment and outcomes framework [30] and include clinical ratings of mental health symptoms, social and occupational functioning, self-

harm, suicidal thoughts and behaviours, self-report questionnaires, physical health parameters, alcohol and substance use, illness type, stage and trajectory, as well as circadian parameters and metabolic, inflammatory and genomic markers.

Our recent research[30, 44-46] indicates the capacity of the multidimensional outcomes framework to further deepen our understanding of the pathophysiological mechanisms and illness progression in this cohort, as well as to inform more personalized and measurement-based models of care.

Diagnostic assessments

The presence of MDD and any comorbidity will be evaluated using the Structured Clinical Interview for DSM-5 Axis I Disorders (SCID) [31]. The diagnostic assessment is expected to take 30-75 minutes to complete.

Mental Risk Assessment

Acute suicidal behaviour will be assessed by relevant subscale of the Comprehensive Assessment of At-Risk Mental States (CAARMS) [33]. The mental risk assessment is expected to take 5 minutes to complete.

Clinical Assessments

1. *Clinical-rated Quick Inventory of Depressive Symptomatology (QIDS-CR)* [32], a rating scale that assesses the nine criterion symptom domains designated by the DSM to diagnose a major depressive episode.
2. *Montgomery-Åsberg Depression Rating Scale (MADRS)* [47] will also be used to assess depressive symptoms, to allow for direct comparisons with previous studies of brexpiprazole in MDD.
3. *Young Mania Rating Scale (YMRS)* [48], an eleven-item, multiple-choice diagnostic questionnaire which psychiatrists use to measure the severity of manic episodes in patients.

4. *Brief Psychiatric Rating Scale (BPRS)* [49], a rating scale used to measure psychiatric symptoms such as depression, anxiety, hallucinations and unusual behaviour.

5. *Social and Occupational Functioning Assessment Scale (SOFAS)* [50] a clinician-rated measure will assess functioning on a 0 to 100 scale, with lower scores suggesting more severe impairment.

6. *Clinical Global Impressions scale (CGI)* [51] will be used as a measure of clinical improvement.

7. Participants will also be rated on previously established *clinical stage* [39-42] and *illness trajectory* [43] models on the basis of information collected throughout the clinical interview.

8. *World Health Organisation (WHO) Alcohol, Smoking and Substance Involvement Screening Test (WHO-ASSIST) [34, 35]* : a reliable, culturally adaptable, valid screening test for problematic or risky substance use.

The clinical interview is expected to take around 35 minutes to complete.

Self-report Assessments

1. *Demographics and Mental Health History:* including details of work and education, physical health (height, weight, and waist circumferences), history of mental health as well as family history
2. *International Physical Activity Questionnaire (IPAQ) - short version [52, 53] a* 7-item questionnaire providing internationally comparable data on health–related physical activity.
3. *Alcohol Use Disorders Identification Test – Consumption (AUDIT-C) [54]:* the questionnaire has three short questions that estimate alcohol consumption in a standard, meaningful and non-judgmental manner. Additional questions assessing age of onset of alcohol consumption will also be used.
4. *Suicidal Ideation Attributes Scale (SIDAS) [55]:* a five-item self-report questionnaire assessing the frequency, controllability, closeness to attempt, distress, and interference with daily activities on a 10-point Likert scale over the past month.

5. *Columbia-Suicide Severity Rating Scale (C-SSRS) [56]:* The scale comprises 3 sections: suicidal ideation, intensity of ideation, and suicidal behaviour. In this study, a self-rating adaptation of this questionnaire will be used in combination with the SIDAS.
6. *Brief Non-Suicidal Self-Injury Assessment Tool (B-NSSI-AT)* [57]: a measure of NSSI designed to assess primary (such as form, frequency, and function) and secondary (including but not limited to NSSI habituation; contexts in which NSSI is practiced; and NSSI perceived life interference, treatment, and impacts) NSSI characteristics.
7. *Quick Inventory of Depressive Symptomatology – self-report (QIDS-SR) [58]: a* self-rating (SR) version includes 16 questions with equivalent weightings (0-3) for each symptom item that assesses the nine criterion symptom domains designated by the DSM-IV to diagnose a major depressive episode.
8. *Overall Anxiety Severity Impairment Scale (OASIS) [59]:* a 5-item self-report measure that can be used to assess severity and impairment associated with any anxiety disorder or multiple anxiety disorders.
9. *Altman Self-Rating Mania Scale (ASRM) [60]*: a five-item self-rating scale, designed to assess the presence and/or severity of manic symptoms.
10. *Primary Care Post-Traumatic Stress Disorder Screen for DSM-5 (PC-PTSD-5) [61]:* a 5-item screen that was designed for use in primary care settings, designed to identify respondents with probable PTSD.
11. *Prodromal Questionnaire (PQ-16) [62]:* a self-report screen for use in secondary mental health care services to select subjects for psychosis risk.
12. *Eating Disorder Examination (EDE) [63, 64]*: comprises a range of health-related and demographic questions, including present height and weight, and a detailed and comprehensive assessment of symptoms, particularly binge eating. In this study, three eating disorder behaviours are assessed, namely binge eating, purging and strict dieting or fasting.
13. *Sleep questions*: 7 questions regarding time falling asleep, waking up during weekdays and weekends, hours of sleep, feelings when waking up. Sleep timing items are based on the

Pittsburgh Sleep Quality Index (PSQI), and Munich Chrono Type Questionnaire (MCTQ), while sleep quality items are based on expert consensus in the literature.

14. *Work and Social Adjustment Scale (WSAS) [65]:* a five-item scale of functional impairment attributable to an identified problem.
15. *Schuster Social Support Scale (SSSS) [66]:* a 15-item measure of social support used to examine an individual's social relationships with others (relatives, friends, spouse) and the associated impact on their emotional functioning
16. *Additional sleep questionnaires:* participants will complete the BMC sleep-wake self-report questionnaire battery including questions regarding ethnicity, caffeine consumption, menstrual cycle, visual impairments, and non-restorative sleep, as well as the *Pittsburgh Sleep Quality Inventory (PSQI)* [67], *Epworth Sleepiness Scale (ESS)* [68], *Insomnia Severity Index (ISI)* [69], *Horne-Ostberg Morningness-Eveningness Questionnaire (MEQ*) [70], and the *Seasonal Patterns Assessment Questionnaire (SPAQ)* [71].

The questionnaires are tailored (using skip logic) to the individual so the amount of time taken to complete the questionnaire varies, but we estimate that on average the self-report assessment will take around 45 minutes to complete.

Sleep wake assessments

24-hour sleep-wake and circadian rest-activity parameters will be measured by actigraphy recordings (ambulatory measurement of motor activity using a wrist-worn device). Actigraphy is a non-invasive tool to objectively measure activity profiles used to estimate sleep and circadian patterns based on validated algorithms. Participants will be asked to complete a sleep diary and to wear an actigraph (GENEActiv device; Activinsights, Kimbolton, UK) on the non-dominant wrist for at least 10 days prior to commencing the study, and continuously for the 8-week treatment phase. Two-week actigraphy recordings will also be completed at the 12- and 16-week follow up assessments. The GENEActiv devices have been validated against several types of accelerometry-based activity monitors [72-75] as well as for sleep-wake scoring [76, 77]. For over three decades, actigraphy monitors like the GENEActiv devices

have been considered as non-invasive instruments to measure sleep and activity patterns and have been used extensively for research purposes in diverse clinical settings including sleep disorders, various medical illnesses (e.g. cancer, HIV, traumatic brain injuries, neurodegenerative diseases) and mental disorders (e.g. anxiety, depression, bipolar and psychotic disorders)[13, 78, 79].

For details on the parameters measured, please refer to the actigraphy parameters under the 'Primary sleep-wake and circadian variables of interest' in Table 1.

In-Lab Circadian Assessment

Biological circadian rhythms will be measured in an evening/overnight recording period, including collection of salivary melatonin, salivary cortisol, and core body temperature to characterise 24-hour rhythms. All circadian assessments will be performed in accordance with established Dim Light Melatonin Onset (DLMO) protocols [80-83].

For details on the parameters measured, please refer to the in-lab circadian measures in the 'Primary Outcome Measures column' in Table 1.

Metabolic and inflammatory markers

The following markers will be collected at Baseline and 8-weeks follow up visits: (i) Triglycerides, (ii) Cholesterol (including total, High Density Lipoprotein (HDL), and Low Density Lipoprotein (LDL)), (iii) Fasting glucose, (iv) Fasting insulin, (v) Interleukin (IL)-1β, (vi) IL-6, (vii) Tissue Necrosis Factor (TNF)-α, (viii) C-Reactive Protein (CRP). Height, weight, and waist circumference will also be recorded. Furthermore, insulin resistance will be estimated based on paired fasting plasma glucose and insulin levels [84] by the updated homeostatic model assessment (HOMA2-IR) using iHOMA2 software V.8.8 [85].

Genomics

Additional blood will be collected at baseline for the assessment of genomic risk markers as per established procedures from the University of Queensland Human Studies Unit.

The schedule of trial assessments is summarized in Table 2.

Table 2. Schedule of assessments

	Enrolment Visit	Visit 1 (Baseline)	Visit 2 (Week 4)	Visit 3 (Week 8)	Visit 4 (Follow-up 1)	Visit 5 (Follow-up 2)
Study week		***0***	***4***	***8***	***12***	***16***
Informed Consent	✓					
Inclusion/Exclusion Criteria	✓	✓				
Diagnostic Assessment (SCID)	✓					
Mental Risk Assessment (CAARMS)	✓	✓	✓	✓	✓	✓
Demographics and Mental Illness History		✓				
Clinical Assessment (QIDS-CR, MADRS, YMRS, BPRS, SOFAS)		✓	✓	✓	✓	✓
Self-report Assessment		✓	✓	✓	✓	✓
Sleep-wake Assessment (actigraphy monitoring)		✓	✓	✓	✓	✓
In-lab Circadian Assessment		✓		✓		
Blood Sample Collection (Metabolic and Inflammatory Markers)		✓		✓		
Safety, side-effects, and adherence assessment			✓	✓	✓	✓
IP dispensing		✓	✓	✓*	✓*	✓*
IP return			✓	✓		

*if clinically indicated, at the discretion of the treating clinician

In addition to the visits listed above, safety, side-effects, and adherence assessment will be conducted weekly between weeks 0 and 8 via phone calls.

The Participant timeline is presented in Figure 1 – Study flow chart.

Sample Size

Sample size was determined based on a previous study of circadian changes in response to Agomelatine [20] where a correlation coefficient of 0.54 was found for the key outcome of interest, namely correlation between change in DLMO and change in depressive symptoms. We conservatively estimated that the correlation coefficient for Brexpiprazole would be smaller, around 0.35 (i.e. a medium effect size), as the effects on the circadian system may be less direct. Assuming an alpha of 0.05 and 80% power for a one-tailed correlation analysis, a sample size of 49 would be required to detect this effect.

Data Analysis/Statistical methods

Correlations will be performed between change scores (i.e., Visit 2 score minus Visit 1 score) for sleep and circadian measures, and change scores for depressive symptoms. The intention-to-treat principle will be used for missing data, with last observations carried forward. Prior to analysis, scatter plots and box plots with outlier and normality statistics will be generated for all variables to identify outliers and issues with variable distribution. Extreme outliers (beyond three z scores in either direction) will be checked against source data and testing notes to verify whether they are the result of an error in data entry or a specific issue during testing (e.g., equipment failure), and any errors rectified. If they are not the result of an error in data entry, outliers will be curtailed. Pearson's or Spearman's correlations will be selected to perform analyses based on normative or non-normative data distribution; a significance level will be set at α=0.05. Correlations will be performed between other change scores to assess secondary and tertiary endpoints using the same methodology. Further tertiary endpoints will be assessed by partial correlations comparing categorical variables.

Patient and public involvement

Clinical professionals working with young people with mental health issues were invited to comment on the study design and procedures. Research findings will be disseminated into the scientific, clinical and wider community.

Ethics and dissemination

This trial has been approved by the Human Research Ethics Committee of the Sydney Local Health District (X19-0417 and 2019/ETH12986, Protocol Version v 1-3, dated 25.02.2021). The study will be conducted in compliance with all stipulations of the protocol, the conditions of ethics committee approval, the NHMRC National Statement on Ethical Conduct in Human Research and the Good Clinical Practice guidelines.

The results of this study will be disseminated as widely as possible into the scientific and broader community. This will include publication in peer-reviewed journals, scholarly book chapters, presentation at conferences and publication in conference proceedings. Publications arising from this project will be deposited into an open access institutional repository, where possible. Results will also be disseminated into the wider community in a format appropriate for a lay audience, through links including the BMC website and social media, as well as newsletters.

CONCLUSION

This clinical trial investigates the effects of the adjunctive brexpiprazole treatment and the associated changes in sleep-wake cycle or circadian parameters in young people with depressive syndromes.

This protocol is one of a series of clinical trials that have been established to support a broader Youth Mental Health Clinical Trial Program at the BMC[86]. A series of clinical trials underpin the broader need to improve diagnosis and treatment outcomes for the youth mental health population. These trials aim to inform personalised treatment plans for specific clinical phenotypes, assisting to provide more effective and targeted interventions, thus necessitating the breadth of assessments used in this clinical trial, to reflect a wider range of questions than just the research questions asked in the current study.

Specifically, this trial will help to understand brexpiprazole's antidepressant mechanism of action in depressed youth with disturbed sleep patterns, and to determine the effectiveness of this treatment in this vulnerable population.

Figure 1. Study flow chart

Legend: This figure illustrates the study design and participant timeline from referral to the last follow up visit, including withdrawal and safety procedures.

TRIAL STATUS

Protocol ID: BMC-YMH-005-2018, Version: v 1-3, dated 25/02/2021.

The trial has not commenced recruitment.

LIST OF ABBREVIATIONS

ABBREVIATION	TERM
AE	Adverse Event
AIMS	Abnormal Involuntary Movement Scale
ANZCTR	Australian New Zealand Clinical Trials Registry
ASRM	Altman Self-Rating Mania scale
AUDIT-C	Alcohol Use Disorders Identification Test- Consumption
BMC	Brain and Mind Centre
BMI	Body Mass Index
B-NSSI-AT	Brief Non-Suicidal Self-Injury Assessment Tool
BPRS	Brief Psychiatric Rating Scale
CAARMS	Comprehensive Assessment of At-Risk Mental States
CGI	Clinical Global Impressions scale
CRP	C-Reactive Protein
C-SSRS	Columbia- Suicide Severity Rating Scale
DLMO	Dim Light Melatonin Onset
DSM-5	Diagnostic and Statistical Manual for Mental Disorders, 5th Edition
EDE	Eating Disorder Examination
EPS	Extrapyramidal Symptoms
ESS	Epworth Sleepiness Scale
HDL	High Density Lipoprotein
HOMA2-IR	Homeostasis Model of Insulin Resistance
HREC	Human Research Ethics Committee
IL	Interleukin
IP	Investigational Product
IPAQ	International Physical Activity Questionnaire
ISI	Insomnia Severity Index
LDL	Low Density Lipoprotein
MADRS	Montgomery-Åsberg Depression Rating Scale
MCTQ	Munich Chronotype Questionnaire
MDD	Major Depressive Disorder
MEQ	Morningness-Eveningness Questionnaire
NEET	Not in Education, Employment or Training
OASIS	Overall Anxiety Severity Impairment Scale

PC-PTSD-5	Primary Care Post-Traumatic Stress Disorder screen
PIS	Participant Information Statement
PQ-16	Prodromal Questionnaire (brief version)
PSQI	Pittsburgh Sleep Quality Index
QIDS-CR	Quick Inventory of Depressive Symptomatology (clinician-rated)
QIDS-SR	Quick Inventory of Depressive Symptomatology (self-report)
SAS	Simpson-Angus Scale
SCID	Structured Clinical Interview for DSM 5
SIDAS	Suicidal Ideation Attributes Scale
SNRI	Selective Serotonin and Norepinephrine Reuptake Inhibitor
SOFAS	Social and Occupational Functioning Assessment Scale
SPAQ	Seasonal Patterns Assessment Questionnaire
SSRI	Selective Serotonin Reuptake Inhibitor
SSSS	Schuster Social Support Scale
TAU	Treatment As Usual
TNF	Tissue Necrosis Factor
WHO-ASSIST	World Health Organisation Alcohol, Smoking, and Substance Involvement Screening Test
WSAS	Work and Social Adjustment Scale
YMRS	Young Mania Rating Scale

AUTHOR CONTRIBUTIONS

JSC and IBH conceived the study, led the proposal and protocol development. JSC wrote the trial protocol. AG drafted the first version of the manuscript. NZ drafted the final version of the manuscript with input from other authors. JSC, AG, AN, NZ, YJSS, CW, CR, JJC, CMM, FML, DK and EMS were all involved with modifications to the design of the study and with drafting of this paper. All authors have read and approved the final manuscript.

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COMPETING INTERESTS

Professor Ian Hickie is the Co-Director, Health and Policy at the Brain and Mind Centre (BMC) University of Sydney, Australia. The BMC operates an early-intervention youth services at Camperdown under contract to headspace. Professor Hickie has previously led community-based and pharmaceutical industry-

supported (Wyeth, Eli Lily, Servier, Pfizer, AstraZeneca) projects focused on the identification and better management of anxiety and depression. He is the Chief Scientific Advisor to, and a 5% equity shareholder in, InnoWell Pty Ltd. InnoWell was formed by the University of Sydney (45% equity) and PwC (Australia; 45% equity) to deliver the $30 M Australian Government-funded Project Synergy (2017-20) and to lead transformation of mental health services internationally through the use of innovative technologies.

Associate Professor Elizabeth M Scott is the Medical Director, Young Adult Mental Health Unit, St Vincent's Hospital Darlinghurst, Discipline Leader of Adult Mental Health, School of Medicine, University of Notre Dame, Research Affiliate, The University of Sydney and Consultant Psychiatrist. She has received honoraria for educational seminars related to the clinical management of depressive disorders supported by Servier and Eli-Lilly pharmaceuticals. She has participated in a national advisory board for the antidepressant compound Pristiq, manufactured by Pfizer. She was the National Coordinator of an antidepressant trial sponsored by Servier.

Other authors declare no competing interests.

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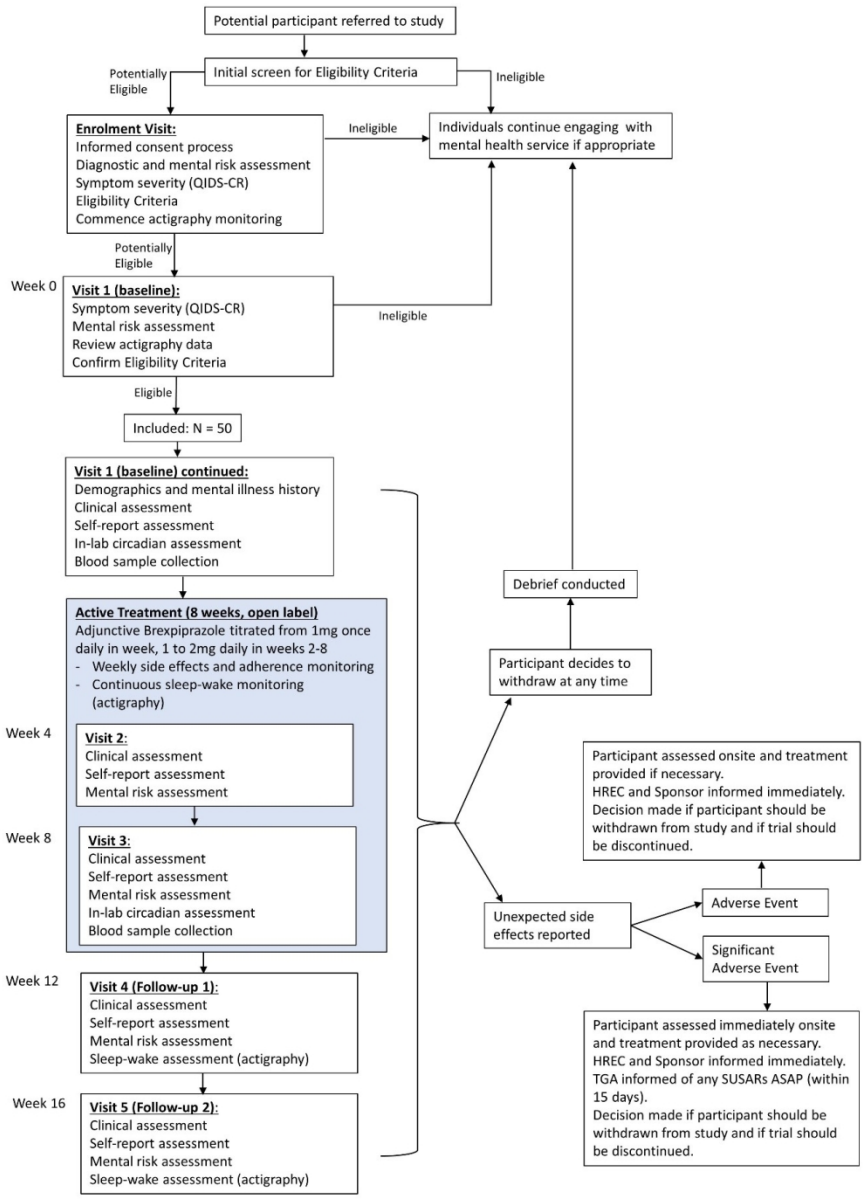

This figure illustrates the study design and participant timeline from referral to the last follow up visit, including withdrawal and safety procedures.

155x209mm (220 x 220 DPI)

BMJ Open

Effects of adjunctive brexpiprazole on sleep-wake and circadian parameters in youth with depressive syndromes: Study protocol for a clinical trial

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Effects of adjunctive brexpiprazole on sleep-wake and circadian parameters in youth with depressive syndromes: Study protocol for a clinical trial

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ABSTRACT

Introduction

Sleep-wake and circadian disturbance is a key feature of mood disorders with a potential causal role and particular relevance to young people. Brexpiprazole is a second generation antipsychotic medication with demonstrated efficacy as an adjunct to antidepressant treatment for Major Depressive Disorder (MDD) in adults, with preliminary evidence suggesting greater effectiveness in subgroups of depressed patients with sleep disturbances. This clinical trial aims to evaluate the relationships between changes in sleep-wake and circadian parameters and changes in depressive symptoms following adjunctive brexpiprazole treatment in young adults with MDD and sleep-wake disturbance.

Methods and analysis

This study is designed as a 16 week (8 weeks active treatment, 8 weeks follow up) mechanistic, open-label, single-arm phase IV clinical trial and aims to recruit 50 young people aged 18 to 30 with MDD and sleep-wake cycle disturbance through an early intervention youth mental health clinic in Sydney, Australia. At baseline, participants will undergo multidimensional outcome assessment and subsequently receive 8 weeks of open-label treatment with brexpiprazole as adjunctive to their stable psychotropic medication. Following 4 weeks of treatment, clinical and self-report measures will be repeated. Ambulatory sleep-wake monitoring will be conducted continuously for the duration of treatment. After 8 weeks of treatment, all multidimensional outcome assessments will be repeated. Follow-up visits will be conducted 4 and 8 weeks after trial completion (including sleep-wake, clinical, and self-report assessments). Circadian rhythm biomarkers including salivary melatonin, cortisol, and core body temperature will be collected during an in-lab assessment. Additionally, metabolic, inflammatory, and genetic risk markers will be collected at baseline and after 8 weeks of treatment.

Ethics and dissemination

This trial protocol has been approved by the Human Research Ethics Committee of the Sydney Local Health District (X19-0417 and 2019/ETH12986, Protocol Version v 1-3, dated 25.02.2021). The results of this study,

in de-identified form, will be disseminated through publication in peer-reviewed journals, scholarly book chapters, presentation at conferences and publication in conference proceedings.

Trial Registration

Australian New Zealand Clinical Trials Registry (ANZCTR) Number: ACTRN12619001456145p, Date 22 October, 2019.

KEYWORDS:

Mental health, adjunctive brexpiprazole, sleep-wake cycle, youth depression.

ARTICLE SUMMARY

Strengths and limitations of this study

- The use of comprehensive assessment battery, including actigraphy and circadian assessment, and collection of metabolic and inflammatory markers to help acquire a greater understanding of the mechanisms of antidepressant action of adjunctive brexpiprazole.
- This trial will help to inform personalised treatment plans for specific clinical phenotypes, placing the participant at the centre of care.
- As part of the study, all participants will receive a psychoeducational session about sleep and circadian rhythms with information on how to improve their sleep based on their actigraphy data
- This trial focuses on the measurement of the 24-hour sleep-wake cycle and will not examine the sleep quality or the parameters of any sleep disorder.
- Circadian assessment used in the study will provide important information about the participants current sleep wake cycle patterns but will not include the assessment of the possible factors that may be contributing to circadian rhythms disruption in the long term.

INTRODUCTION

In young adults, Major Depressive Disorder (MDD) is highly prevalent, recurrent, and comorbid with other mental and physical conditions, generating a substantial burden of disease and disability [1, 2]. While multiple psychological and pharmacological treatments are commonly provided, a large proportion of patients fail to respond to first-line psychotherapy or antidepressant treatments [3-10], and augmentation with a second generation antipsychotic is often recommended in these treatment-resistant cases [11, 12]. Sleep-wake cycle disturbances are common features of depressive disorders, including insomnia [13-15], hypersomnia [16, 17], abnormal sleep duration [13, 14], and abnormal timing of 24-hour patterns of rest/activity [18, 19]. Moreover, abnormalities in biological circadian rhythms (e.g., melatonin) have been reported [20, 21], suggesting that in some cases sleep disturbances are accompanied or underpinned by disturbances of the underlying circadian system [22].

The human circadian system is controlled by a master oscillator in the brain's hypothalamus (suprachiasmatic nucleus) which projects to circuits that govern bio-behavioural processes altered in depression (e.g., mood, vigilance, 24-hour sleep-wake cycle). The circadian system is primarily entrained by bright light, and its functioning can be disrupted by factors including aberrant light exposure and irregular sleep-wake behaviours [23, 24]. Adolescents and young adults are particularly vulnerable to circadian perturbations due to significant developmental changes in circadian rhythms across this age period [25], and sleep-wake phase delays are common in young people with depressive disorders [26]. Recently, we reported delayed and disrupted circadian rhythms in a subgroup of young people with depressive disorders (who also presented with greater symptom severity) [27]. During adolescence there is a phase shift in the circadian rhythm of the sleep-wake cycle, such that adolescents typically develop a bio-behavioural preference for going to sleep later and waking later (a manifestation of changes in the biology of the circadian system) [28, 29]. Furthermore, there is some evidence that correction of circadian abnormalities is associated with antidepressant effects of treatments targeting the circadian system such as Agomelatine [30] and light therapy [31].

Brexpiprazole is a second generation antipsychotic with demonstrated efficacy by multiple randomised controlled trials as an adjunct to antidepressant treatment in MDD in adults [32-35]; however the mechanism of antidepressant action is unknown [36]. The pharmacodynamic properties of brexpiprazole, together with evidence from preclinical studies, suggest that there may be specific effects on anxiety, cognitive function, and sleep [36, 37]. Further, there is preliminary evidence to suggest that brexpiprazole may have greater effectiveness in subgroups of depressed patients with sleep disturbances, anxiety, or irritability [22, 38]. As an adjunctive treatment in MDD patients with inadequate response to antidepressant treatment, brexpiprazole has been reported to lead to clinical improvement of sleep disturbances (e.g., insomnia) and depressive symptoms, as well as improvement of daytime alertness and functioning [39]. This pattern of changes is consistent with effects on circadian rhythms, with potential influences on the entire 24-hour pattern of rest/activity, rather than simply on sleep period in isolation. To improve the personalisation of treatment selection for mood disorders, a greater understanding of the mechanisms of antidepressant action of specific compounds is needed.

Accordingly, in this clinical trial we aim to investigate whether the effect of brexpiprazole on depressive symptoms is associated with changes in 24-hour sleep-wake cycle or circadian parameters in young people with MDD. While disturbances in electrophysiological measures of sleep (e.g., REM sleep) have been considered by some to represent biomarkers for depression [40-43], this trial focuses instead on the investigation and measurement of bio-behavioural changes associated with the circadian system (e.g., rest/activity, melatonin, cortisol, and core body temperature rhythms), rather than changes in electrophysiological sleep architecture (which is beyond the scope of this study).

METHODS AND ANALYSIS

Study Objectives

The primary objective of this study is to determine if changes in depressive symptoms following adjunctive brexpiprazole treatment are correlated with changes in sleep-wake cycle or circadian parameters in young people with depressive syndromes.

The secondary objective is to determine if changes in social and occupational functioning following adjunctive brexpiprazole are correlated with changes in sleep-wake cycle or circadian parameters in young people with depressive syndromes.

The tertiary objectives of this study are to determine if changes in depressive symptoms or changes in sleep-wake cycle or circadian parameters following adjunctive brexpiprazole treatment are associated with a range of multidimensional outcome measures in young people with depressive syndromes[44]. These include other mental illness symptoms, self-harm and suicidal thoughts and behaviours, physical health parameters, alcohol and substance use, and genomic markers.

Trial design

This investigator-initiated, mechanistic study involving 50 young people with depressive syndromes and sleep-wake cycle disturbances is designed as a 16-week (8 weeks active treatment, 8 weeks follow-up) open-label, single-arm, phase IV clinical trial.

Participants

Participants aged 18-30 years with a diagnosis of MDD according to DSM-5 criteria on a current antidepressant treatment of either selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI) with a disrupted sleep-wake cycle will be recruited through the youth mental health clinics associated with the Brain and Mind Centre (BMC), University of Sydney. All participants will provide written informed consent. The research team will make explicit to any potential participants both verbally and in writing (in the Participant Information Statement) that participation is voluntary and will not affect the patient's care received by the mental health service.

The inclusion criteria for this trial are: (i) aged 18-30, (ii) diagnosis of MDD as per DSM-5 (Structured Clinical Interview for DSM; SCID[45]) criteria, (iii) current major depressive episode (MDE) of moderate severity as defined by a Quick Inventory of Depressive Symptomatology (QIDS)[46] rating ≥ 11 at two assessments two weeks apart, (iv) failure to respond to at least one adequate (minimum four weeks) trial of pharmacological treatment, (v) current antidepressant treatment with SSRI or SNRI for at least 6 weeks, at a stable dose for two weeks prior to study commencement, and (vi) a perturbed sleep-wake cycle as evidenced by: delayed sleep onset; delayed sleep offset; disrupted sleep; high day-to-day variability of sleep-wake cycle; non-restorative sleep; or daytime fatigue.

Exclusion criteria are: (i) any adjunctive antipsychotic treatment for current episode in the past month, (ii) use of medications which affect sleep, (iii) primary psychotic disorder diagnosis, (iv) acute suicidal behaviour (score of 6 on Comprehensive Assessment of At-Risk Mental States (CAARMS) item 7.3[47]), (v) medical condition contributing to sleep-wake dysfunction, (vi) significant alcohol or substance misuse or dependence (assessed via DSM-5 SCID[45] and World Health Organisation Alcohol, Smoking and Substance Involvement Screening Test (WHO-ASSIST[48, 49]), (vii) shift work or (viii) recent transmeridian travel (i.e., participants will be required to wait three days for each jet lag hour before entering the study), (ix) previous hypersensitivity to brexpiprazole, (x) taking CYP2D6 or CYP3A4 inhibitors (or other contraindicated medications listed in the Rexulti product information), and (xi) pregnancy or lactation.

Study course and procedure

Patients presenting for mental health care who may be eligible for the study will be screened by phone before being invited to participate and attending an enrolment visit. The enrolment visit will formally assess eligibility criteria and confirm the presence of MDD as per DSM-5 (SCID)[45]. Participants will be provided with an actigraphy device (non-invasive wrist-worn device used to objectively measure rest/activity patterns) and will be given instructions to wear the device for the following two-week period.

Visit 1 (Baseline): Within two weeks of completing the diagnostic and screening assessments, data from the actigraphy device will be downloaded and reviewed. A further assessment of depressive symptom severity (QIDS Clinician-Rated; QIDS-CR)[46] will be conducted to ensure participants meet all inclusion criteria. Bloods will be collected for assessment of metabolic and inflammatory measures and genomic analysis. Clinical and self-report assessments will be conducted, as well as circadian assessments in which participants will remain in the sleep lab overnight. The following morning, participants will attend a 1-hour psychoeducation session about sleep and circadian rhythms covering the following topics: i) sleep and circadian education with tailored discussion based on their personal actigraphy data; ii) individualized plan for progressive sleep rescheduling; and iii) lifestyle factors and behaviours impacting on sleep (e.g., exercise, light, sleep environment, sleep regulation, foods, stress, anxiety, mood).

Once all baseline clinical and self-report assessments have been conducted, and the medical assessment completed by the study doctor to confirm inclusion and exclusion criteria, participants will be issued with the study medication to receive 8 weeks of open-label pharmacotherapy with brexpiprazole (REXULTI®-Lundbeck) as adjunctive to their stable psychotropic medication (treatment as usual). Brexpiprazole will be provided to participants at Visit 1 (Baseline) and Visit 2 (Week 4) for the following four weeks and will be titrated from 1 mg once daily in week 1, to 2 mg once daily in weeks 2-8.

Patients will receive 2mg/day, once daily as tablets, for oral use. The brexpiprazole dosage will be steadily increased from 1mg/day during week 1, to 2mg/day during weeks 2-8 (up-titration). This is the dosage and titration regime recommended for adjunctive use in major depression by the Federal Drug Administration (USA). Several previous clinical trials have used this titration regime from 1mg to 2mg [33, 39, 50], and a dose of 2mg has been shown to be effective in reducing depressive symptoms [32]. As doses higher than 2mg have been shown to increase incidence of akathisia [36], a maximum dose of 2mg will be used in the present study to minimise side effects.

Monitoring visits: Participants will be contacted by telephone on a weekly basis for the duration of the 8-week treatment period to monitor adverse events and adherence. Any changes in concomitant medications will also be investigated and recorded. In addition, participants will be provided with a medication diary and asked to complete during the study to monitor adherence. More detailed information about potential side-effects will be further assessed by the study doctor at visits 2, 3, 4 and 5 using the UKU Side Effect Rating Scale [51], Abnormal Involuntary Movement Scale (AIMS) [52] and the Simpson-Angus Scale (SAS) [53] for evaluation of extrapyramidal symptoms (EPS).

Visit 2 (Week 4): Following four weeks of the treatment phase, participants will return for clinical and self-report assessments to assess changes in clinical and functional measures.

Visit 3 (Week 8): Following eight weeks of the treatment phase, participants will return to complete clinical and self-report assessments and will also complete a second circadian (overnight) in-lab assessment. Bloods will be collected at this visit for follow-up metabolic and inflammatory markers.

Visit 4 and 5 (Follow-up visits 1 and 2, 12 and 16 weeks respectively): Twelve and sixteen weeks after commencing treatment (i.e., four and eight weeks after completing the eight-week treatment period respectively), participants will return to complete clinical and self-report assessments. Participants will be provided with an actigraphy device to wear for two weeks prior to these assessments.

Participants will be reimbursed for their time and the cost of transportation to and from the research sites.

Outcomes

Primary Outcome Measures

The primary endpoint will be the correlation between change in sleep-wake and circadian parameters and change in depressive symptoms from baseline to week eight. Notably, the primary depressive symptom

measures (QIDS-CR total score, QIDS-Self Report (QIDS-SR) total score, The Montgomery–Åsberg Depression Rating Scale (MADRS) total score) contain sleep items. These will be removed from these scales for analyses to provide a measure of depressive symptoms not biased by changes in sleep-wake parameters.

Primary sleep-wake and circadian variables of interest include actigraphy parameters, as well as in-lab circadian and self-report measures.

Secondary Outcome Measures

The secondary endpoint will be correlation between change in sleep-wake and circadian parameters and change in functioning from baseline to week eight.

Tertiary Outcome Measures

Tertiary endpoints will be correlation between change in sleep-wake and circadian parameters and other multidimensional outcome measures based on assessments of symptoms, self-harm and suicidal thoughts and behaviours, physical health, and alcohol and substance use.

Further tertiary endpoints will be comparison of primary endpoints between Clinical Stages [54-57], illness trajectories [58], and genomic variants with potential relevance to mood disorders and/or circadian rhythms (e.g. CLOCK, BMAL1).

Detailed outcome measures are summarized in Table 1.**Table 1 – Primary, Secondary and Tertiary Outcome Measures**

Primary Outcome Measures (Correlation between change in sleep-wake and circadian parameters and change in depressive symptoms from baseline to week eight)	**Secondary Outcome Measures** (Correlation between change in sleep-wake and circadian parameters and change in functioning from baseline to week eight)	**Tertiary Outcome measures** (Correlation between change in sleep-wake and circadian parameters and other multidimensional outcome measures)
Primary depressive symptom measures:	**Functioning measures:**	**Symptom Measures:**

- QIDS-CR total score (minus sleep items)
- QIDS-Self Report (QIDS-SR) total score (minus sleep items)
- The Montgomery–Åsberg Depression Rating Scale (MADRS) total score (minus sleep items)

Primary sleep-wake and circadian variables of interest:

Actigraphy parameters (in the two-week period prior to baseline and prior to week eight):

- Sleep onset time
- Sleep offset (wake) time
- Total sleep time (duration)
- Wake after sleep onset (estimation of number of minutes awake during the sleep period)
- Sleep efficiency (% of sleep period estimated as sleep)
- Inter-daily stability
- Intra-daily variability

In-lab circadian measures:

- Dim Light Melatonin Onset (DLMO) timing
- Phase angle (time lapse) between DLMO and habitual sleep
- Core body temperature nadir
- Evening cortisol area under the curve

Self-report measures:

- Non-restorative sleep score (based on the Pittsburgh Sleep Quality Index
- Social and Occupational Functioning Assessment Scale (SOFAS) rating
- The Work and Social Adjustment Scale (WSAS) total score
- Adapted Schuster Social Support Scale (SSSS) total score
- Not in Education, Employment, or Training (NEET) status
- Number of days 'out of role' (unable to perform usual activities) in the past 30 days
- Young Mania Rating Scale (YMRS) total score
- Brief Psychiatric Rating Scale (BPRS) total score and subscale scores
- Overall Anxiety Severity Impairment Scale (OASIS) total score
- Altman Self-Rating Mania scale (ASRM) total score
- Prodromal Questionnaire (brief version) (PQ-16) total score
- DSM-5 Primary Care Post-Traumatic Stress Disorder screen (PC-PTSD-5) total score
- Adapted Eating Disorder Examination (EDE) total score
- Clinical Global Impressions scale (CGI) severity and improvement scores

Self-harm and suicidal thoughts and behaviours:

- Suicidal risk (score from Suicidal Ideation Attributes Scale (SIDAS) and Columbia-Suicide Severity Rating Scale (C-SSRS) items)
- Adapted Brief Non-Suicidal Self-Injury Assessment Tool (B-NSSI-AT) total score

Physical Health:

- Body Mass Index (BMI) calculated from height and weight
- Waist circumference
- International Physical Activity Questionnaire (IPAQ) total score
- Metabolic blood markers including triglycerides, cholesterol (total, Low Density Lipoprotein (LDL), High Density Lipoprotein (HDL)), and Homeostasis

(PSQI), and Munich Chronotype Questionnaire (MCTQ) • *Pittsburgh Sleep Quality Index* (PSQI) total score • Epworth Sleepiness *Score* (ESS) total score • Insomnia Severity Index (ISI) total score • Morningness -Eveningness Questionnaire (MEQ) total score* • Seasonal Pattern Assessment Questionnaire (SPAQ) total score* *Baseline scores will be used rather than change scores as these are trait measures		Model of Insulin Resistance (HOMA2-IR) calculated from fasting glucose and insulin measures • Inflammatory blood markers including Interleukin-1β (IL-1β), Interleukin-6 (IL-6), Tissue Necrosis Factor (TNF-α), C-Reactive Protein (CRP) **Alcohol and Substance Use:** • World Health Organisation Alcohol, Smoking, and Substance Involvement Screening Test (WHO ASSIST) score for tobacco, and cannabis • Alcohol Use Disorders Identification Test-Consumption (AUDIT C) total score • WHO ASSIST alcohol-related impairment • Age of onset of alcohol use **Comparison of primary endpoints between:** • Clinical Stages • Illness Trajectories • Genomic variants with potential relevance to mood disorders and/or circadian rhythms (e.g., CLOCK, BMAL1).

Assessments

Assessments used here are based on the multidimensional assessment and outcomes framework [44] and include clinical and self-report ratings of mental health symptoms, social and occupational functioning, self-harm, suicidal thoughts and behaviours, physical health, alcohol and substance use, illness type, stage and trajectory, as well as circadian parameters and metabolic, inflammatory and genomic markers.

Our recent research [44, 59-61] indicates the capacity of the multidimensional outcomes framework to further our understanding of the pathophysiological mechanisms and illness progression in this cohort, as well as to inform more personalized and measurement-based models of care.

Diagnostic assessments

The presence of MDD and any comorbidity will be evaluated using the Structured Clinical Interview for DSM-5 Axis I Disorders (SCID) [45]. This assessment is expected to take 30-75 minutes to complete.

Mental Risk Assessment

Acute suicidal behaviour will be assessed by relevant subscale of the Comprehensive Assessment of At-Risk Mental States (CAARMS) [47]. This assessment is expected to take 5 minutes to complete.

Clinical Assessments

1. *Clinical-rated Quick Inventory of Depressive Symptomatology (QIDS-CR)* [46]: assesses the nine criterion symptom domains designated by the DSM to diagnose a MDE.

2. *Montgomery-Åsberg Depression Rating Scale (MADRS)* [62]: will also be used to assess depressive symptoms, to allow for direct comparisons with previous studies of brexpiprazole in MDD.

3. *Young Mania Rating Scale (YMRS)* [63]: an 11-item, multiple-choice diagnostic questionnaire which psychiatrists use to measure the severity of manic episodes.

4. *Brief Psychiatric Rating Scale (BPRS)* [64]: used to measure psychiatric symptoms (e.g., depression, anxiety, hallucinations, unusual behaviour).

5. *Social and Occupational Functioning Assessment Scale (SOFAS)* [65]: clinician-rated measure used to assess functioning on a 0-100 scale (lower scores suggesting greater impairment).

6. *Clinical Global Impressions scale (CGI)* [66]: will be used as a measure of clinical improvement.

7. Participants will also be rated on previously established *clinical stage* [54-57] and *illness trajectory* [58] models on the basis of information collected throughout the clinical interview. The clinical staging

framework differentiates those in the earliest phases of mental health problems with non-specific clinical presentations (stage 1a; 'help-seeking') from those at greater-risk with more specific, sub-threshold presentations (stage 1b; 'attenuated syndromes') and those who have already reached a threshold for a progressive or recurrent disorder meeting diagnostic criteria (stage 2, 3, or 4). The illness trajectory model is a novel tripartite framework based on three proposed pathophysiological pathways leading to youth-onset mental disorders: (i) "neurodevelopmental-psychosis", (ii) "circadian-bipolar spectrum", and (iii) "hyperarousal-anxious depression"[67-69].

8. *World Health Organisation (WHO) Alcohol, Smoking and Substance Involvement Screening Test (WHO-ASSIST) [48, 49]* : a reliable, culturally adaptable, valid screening test for problematic or risky substance use.

The clinical interview is expected to take around 35 minutes to complete.

Self-report Assessments

1. *Demographics and Mental Health History:* including details of work and education, physical health (height, weight, waist circumference), history of mental health, and family history
2. *International Physical Activity Questionnaire (IPAQ) - short version [70, 71]:* 7-item questionnaire providing internationally comparable data on health–related physical activity.
3. *Alcohol Use Disorders Identification Test – Consumption (AUDIT-C) [72]:* includes three short questions that estimate alcohol consumption in a standard, meaningful, non-judgmental manner. Additional questions assessing age of onset of alcohol consumption will also be used.
4. *Suicidal Ideation Attributes Scale (SIDAS) [73]:* 5-item self-report questionnaire assessing the frequency, controllability, closeness to attempt, distress, and interference with daily activities on a 10-point Likert scale over the past month.
5. *Columbia-Suicide Severity Rating Scale (C-SSRS) [74]:* The scale comprises 3 sections: suicidal ideation, intensity of ideation, and suicidal behaviour. A self-rating adaptation will be used in combination with the SIDAS.

6. *Brief Non-Suicidal Self-Injury Assessment Tool (B-NSSI-AT)* [75]: designed to assess primary (such as form, frequency, and function) and secondary (including but not limited to NSSI habituation; contexts in which NSSI is practiced; and NSSI perceived life interference, treatment, and impacts) NSSI characteristics.
7. *Quick Inventory of Depressive Symptomatology – self-report (QIDS-SR) [76]: a* self-rating (SR) version includes 16 questions with equivalent weightings (0-3) for each symptom item that assesses the nine criterion symptom domains designated by the DSM-IV to diagnose a MDE.
8. *Overall Anxiety Severity Impairment Scale (OASIS) [77]:* 5-item self-report measure used to assess severity and impairment associated with any anxiety disorder or multiple anxiety disorders.
9. *Altman Self-Rating Mania Scale (ASRM) [78]*: 5-item self-rating scale designed to assess the presence and/or severity of manic symptoms.
10. *Primary Care Post-Traumatic Stress Disorder Screen for DSM-5 (PC-PTSD-5) [79]:* 5-item screen designed for use in primary care settings to identify respondents with probable PTSD.
11. *Prodromal Questionnaire (PQ-16) [80]:* self-report screen for use in secondary mental health care services to select subjects for psychosis risk.
12. *Eating Disorder Examination (EDE) [81, 82]*: comprises a range of health-related and demographic questions, including present height and weight, and a detailed and comprehensive assessment of symptoms, particularly binge eating. In this study, three eating disorder behaviours are assessed: binge eating, purging, and strict dieting or fasting.
13. *Sleep questions*: 7 questions regarding time falling asleep, waking up during weekdays and weekends, hours of sleep, feelings when waking up. Sleep timing items are based on the Pittsburgh Sleep Quality Index (PSQI) and Munich Chrono Type Questionnaire (MCTQ), while sleep quality items are based on expert consensus in the literature.
14. *Work and Social Adjustment Scale (WSAS) [83]:* 5-item scale of functional impairment attributable to an identified problem.

15. *Schuster Social Support Scale (SSSS) [84]:* 15-item measure of social support used to examine an individual's social relationships with others (relatives, friends, spouse) and the associated impact on their emotional functioning
16. *Additional sleep questionnaires:* participants will complete the BMC sleep-wake self-report questionnaire battery including questions regarding ethnicity, caffeine consumption, menstrual cycle, visual impairments, and non-restorative sleep, as well as the *Pittsburgh Sleep Quality Inventory (PSQI)* [85], *Epworth Sleepiness Scale (ESS)* [86], *Insomnia Severity Index (ISI)* [87], *Horne-Ostberg Morningness-Eveningness Questionnaire (MEQ*) [88], and the *Seasonal Patterns Assessment Questionnaire (SPAQ)* [89].

The questionnaires are tailored (using skip logic) to the individual so the amount of time taken to complete the questionnaire varies, but we estimate that on average the self-report assessment will take 45 minutes to complete.

Sleep wake assessments

24-hour sleep-wake and circadian rest-activity parameters will be measured by actigraphy recordings. Actigraphy is a non-invasive tool to objectively measure activity profiles used to estimate sleep and circadian patterns based on validated algorithms. Participants will be asked to complete a sleep diary and to wear an actigraph (GENEActiv device; Activinsights, Kimbolton, UK) on the non-dominant wrist for at least 10 days prior to commencing the study, and continuously for the 8-week treatment phase. The device is comfortable and easy to use, battery operated wrist-worn device, similar in appearance to Fitbit, designed to record and provide data on movement, light, temperature and sleep patterns. The device will provide objective monitoring of participants' 24-hour circadian rhythm, including their sleep onset and duration, rise time, any night-time sleep interruptions, and activity patterns (for details, see Table 1). The device allows for the outputting of real time raw measurement data for up to a month without charging. Instructions will be provided to participants on how to use the device upon their recruitment into the study. Two-week actigraphy

recordings will also be completed at the 12- and 16-week follow up assessments. The GENEActiv devices have been validated against several types of accelerometry-based activity monitors [90-93] as well as for sleep-wake scoring [94, 95]. For decades, actigraphy monitors like the GENEActiv devices have been used extensively in research to measure sleep and activity patterns in diverse clinical settings including sleep disorders, medical illnesses (e.g. cancer, neurodegenerative diseases) and mental disorders (e.g. anxiety, depression, bipolar, and psychotic disorders) [19, 96, 97].

In-Lab Circadian Assessment

Biological circadian rhythms will be measured in an evening/overnight recording period, including collection of salivary melatonin, salivary cortisol, and core body temperature to characterise 24-hour rhythms. All circadian assessments will be performed in accordance with established Dim Light Melatonin Onset (DLMO) protocols [98-101]. For details on the parameters measured, please refer to the in-lab circadian measures in Table 1.

Metabolic and inflammatory markers

The following markers will be collected at Baseline and 8-weeks follow up visits: (i) Triglycerides, (ii) Cholesterol (including total, High Density Lipoprotein (HDL), and Low-Density Lipoprotein (LDL)), (iii) Fasting glucose, (iv) Fasting insulin, (v) Interleukin (IL)-1β, (vi) IL-6, (vii) Tissue Necrosis Factor (TNF)-α, (viii) C-Reactive Protein (CRP). Height, weight, and waist circumference will also be recorded. Furthermore, insulin resistance will be estimated based on paired fasting plasma glucose and insulin levels [102] by the updated homeostatic model assessment (HOMA2-IR) using iHOMA2 software V.8.8 [103].

Genomics

Additional blood will be collected at baseline for the assessment of genomic risk markers as per established procedures from the University of Queensland Human Studies Unit.

The schedule of trial assessments is summarized in Table 2.

Table 2. Schedule of assessments

	Enrolment Visit	Visit 1 (Baseline)	Visit 2 (Week 4)	Visit 3 (Week 8)	Visit 4 (Follow-up 1)	Visit 5 (Follow-up 2)
Study week		***0***	***4***	***8***	***12***	***16***
Informed Consent	✓					
Inclusion/Exclusion Criteria	✓	✓				
Diagnostic Assessment (SCID)	✓					
Mental Risk Assessment (CAARMS)	✓	✓	✓	✓	✓	✓
Demographics and Mental Illness History		✓				
Clinical Assessment (QIDS-CR, MADRS, YMRS, BPRS, SOFAS)		✓	✓	✓	✓	✓
Self-report Assessment		✓	✓	✓	✓	✓
Sleep-wake Assessment (actigraphy monitoring)		✓	✓	✓	✓	✓
In-lab Circadian Assessment		✓		✓		
Blood Sample Collection (Metabolic and Inflammatory Markers)		✓		✓		
Safety, side-effects, and adherence assessment			✓	✓	✓	✓
IP dispensing		✓	✓	✓*	✓*	✓*
IP return			✓	✓		

*if clinically indicated, at the discretion of the treating clinician

In addition to the visits listed above, safety, side-effects, and adherence assessment will be conducted weekly between weeks 0 and 8 via phone calls.

The Participant timeline is presented in Figure 1 – Study flow chart.

Safety and Side-Effects Monitoring

Previous studies have shown that brexpiprazole is generally well tolerated, with no unexpected or severe side effects [32, 35, 104, 105].

Safety and tolerability of the investigational product will be closely monitored throughout the trial. For the duration of the 8-week treatment period, weekly phone calls will be conducted to participants to monitor safety and elicit information regarding side effects and potential adverse events. Any changes in concomitant

medications will also be investigated and recorded. In addition, participants will be provided with a medication diary and asked to complete during the study to monitor tolerability and adherence.

Further formal assessment of side effects and potential adverse events following the end of the treatment phase will be conducted at the two follow-up visits (visit 4 and 5). At the baseline visit, participants will be informed that any serious negative side effects should be reported to the study doctor immediately and will be provided with the relevant contact details to do so.

All Adverse Events will be assessed for causality and symptom severity according to the study protocol and followed up by the study doctor if required. In the occurrence of a Serious Adverse Event, appropriate diagnostic and therapeutic measures will be taken and the participant will be kept under observation for as long as is medically indicated. The Principal Investigator will then determine if the seriousness of the event warrants the removal of the participant from the study or abandonment of the study. For serious side effects or medical problems, the patient may be taken immediately to Royal Prince Alfred Hospital for further treatment. The Principal Investigator will ensure that follow-up of the participant is appropriate to the nature of any event, and that it continues until resolution.

Throughout the trial the study doctor will monitor participants for pregnancy. It is not currently included in the protocol, but the trial Standard Operating Procedures manual explains that the study doctor will be giving relevant contraception advice to the participants based on the current investigational product information.

According to the investigational product information, participants will be advised to not drive a car, operate machinery, or do other dangerous activities until they know how the investigational product affects them, as it may induce drowsiness in some subjects.

Sample Size

Sample size was determined based on a previous study of circadian changes in response to Agomelatine [30] where a correlation coefficient of 0.54 was found for the key outcome of interest, namely correlation between change in DLMO and change in depressive symptoms. We conservatively estimated that the correlation coefficient for Brexpiprazole would be smaller, around 0.35 (i.e., a medium effect size), as the effects on the circadian system may be less direct. Assuming an alpha of 0.05 and 80% power for a one-tailed correlation analysis, a sample size of 49 would be required to detect this effect.

Data Analysis/Statistical methods

Correlations will be performed between change scores (i.e., Visit 2 score minus Visit 1 score) for sleep and circadian measures, and change scores for depressive symptoms. The intention-to-treat principle will be used for missing data, with last observations carried forward. Prior to analysis, scatter plots and box plots with outlier and normality statistics will be generated for all variables to identify outliers and issues with variable distribution. Extreme outliers (beyond three z scores in either direction) will be checked against source data and testing notes to verify whether they are the result of an error in data entry or a specific issue during testing (e.g., equipment failure), and any errors rectified. If they are not the result of an error in data entry, outliers will be curtailed. Pearson's or Spearman's correlations will be selected to perform analyses based on normative or non-normative data distribution; a significance level will be set at α=0.05. Correlations will be performed between other change scores to assess secondary and tertiary endpoints using the same methodology. Further tertiary endpoints will be assessed by partial correlations comparing categorical variables.

Patient and public involvement

Clinical professionals working with young people with mental health issues were invited to comment on the study design and procedures. Research findings will be disseminated into the scientific, clinical, and wider community.

Ethics and dissemination

This trial has been approved by the Human Research Ethics Committee of the Sydney Local Health District (X19-0417 and 2019/ETH12986, Protocol Version v 1-3, dated 25.02.2021). The study will be conducted in compliance with all stipulations of the protocol, the conditions of ethics committee approval, the NHMRC National Statement on Ethical Conduct in Human Research and the Good Clinical Practice guidelines.

The results of this study will be disseminated as widely as possible into the scientific and broader community. This will include publication in peer-reviewed journals, scholarly book chapters, presentation at conferences and publication in conference proceedings. Publications arising from this project will be deposited into an open access institutional repository, where possible. Results will also be disseminated into the wider community in a format appropriate for a lay audience, through links including the BMC website and social media, as well as newsletters.

Figure 1. Study flow chart

Legend: This figure illustrates the study design and participant timeline from referral to the last follow up visit, including withdrawal and safety procedures.

TRIAL STATUS

Protocol ID: BMC-YMH-005-2018, Version: v 1-3, dated 25/02/2021.

The trial has not commenced recruitment.

LIST OF ABBREVIATIONS

ABBREVIATION	TERM
AE	Adverse Event
AIMS	Abnormal Involuntary Movement Scale
ANZCTR	Australian New Zealand Clinical Trials Registry
ASRM	Altman Self-Rating Mania scale
AUDIT-C	Alcohol Use Disorders Identification Test- Consumption
BMC	Brain and Mind Centre

BMI	Body Mass Index
B-NSSI-AT	Brief Non-Suicidal Self-Injury Assessment Tool
BPRS	Brief Psychiatric Rating Scale
CAARMS	Comprehensive Assessment of At-Risk Mental States
CGI	Clinical Global Impressions scale
CRP	C-Reactive Protein
C-SSRS	Columbia- Suicide Severity Rating Scale
DLMO	Dim Light Melatonin Onset
DSM-5	Diagnostic and Statistical Manual for Mental Disorders, 5th Edition
EDE	Eating Disorder Examination
EPS	Extrapyramidal Symptoms
ESS	Epworth Sleepiness Scale
HDL	High Density Lipoprotein
HOMA2-IR	Homeostasis Model of Insulin Resistance
HREC	Human Research Ethics Committee
IL	Interleukin
IP	Investigational Product
IPAQ	International Physical Activity Questionnaire
ISI	Insomnia Severity Index
LDL	Low Density Lipoprotein
MADRS	Montgomery-Åsberg Depression Rating Scale
MCTQ	Munich Chronotype Questionnaire
MDD	Major Depressive Disorder
MEQ	Morningness-Eveningness Questionnaire
NEET	Not in Education, Employment or Training
OASIS	Overall Anxiety Severity Impairment Scale
PC-PTSD-5	Primary Care Post-Traumatic Stress Disorder screen
PIS	Participant Information Statement
PQ-16	Prodromal Questionnaire (brief version)
PSQI	Pittsburgh Sleep Quality Index
QIDS-CR	Quick Inventory of Depressive Symptomatology (clinician-rated)
QIDS-SR	Quick Inventory of Depressive Symptomatology (self-report)
SAS	Simpson-Angus Scale
SCID	Structured Clinical Interview for DSM 5
SIDAS	Suicidal Ideation Attributes Scale
SNRI	Selective Serotonin and Norepinephrine Reuptake Inhibitor
SOFAS	Social and Occupational Functioning Assessment Scale
SPAQ	Seasonal Patterns Assessment Questionnaire
SSRI	Selective Serotonin Reuptake Inhibitor
SSSS	Schuster Social Support Scale
TAU	Treatment As Usual
TNF	Tissue Necrosis Factor
WHO-ASSIST	World Health Organisation Alcohol, Smoking, and Substance Involvement Screening Test
WSAS	Work and Social Adjustment Scale
YMRS	Young Mania Rating Scale

493

494 **AUTHOR CONTRIBUTIONS**

JSC and IBH conceived the study, led the proposal and protocol development. JSC wrote the trial protocol. AG drafted the first version of the manuscript. NZ drafted the final version of the manuscript with input from other authors. JSC, AG, AN, NZ, YJSS, CW, CR, JJC, CMM, FML, DK and EMS were all involved with modifications to the design of the study and with drafting of this paper. All authors have read and approved the final manuscript.

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COMPETING INTERESTS

Professor Ian Hickie is the Co-Director, Health and Policy at the Brain and Mind Centre (BMC) University of Sydney, Australia. The BMC operates an early-intervention youth services at Camperdown under contract to headspace. Professor Hickie has previously led community-based and pharmaceutical industry-supported (Wyeth, Eli Lily, Servier, Pfizer, AstraZeneca) projects focused on the identification and better management of anxiety and depression. He is the Chief Scientific Advisor to, and a 5% equity shareholder in, InnoWell Pty Ltd. InnoWell was formed by the University of Sydney (45% equity) and PwC (Australia; 45% equity) to deliver the $30 M Australian Government-funded Project Synergy (2017-20) and to lead transformation of mental health services internationally through the use of innovative technologies.

Associate Professor Elizabeth M Scott is the Medical Director, Young Adult Mental Health Unit, St Vincent's Hospital Darlinghurst, Discipline Leader of Adult Mental Health, School of Medicine, University of Notre Dame, Research Affiliate, The University of Sydney and Consultant Psychiatrist. She has received honoraria

for educational seminars related to the clinical management of depressive disorders supported by Servier and Eli-Lilly pharmaceuticals. She has participated in a national advisory board for the antidepressant compound Pristiq, manufactured by Pfizer. She was the National Coordinator of an antidepressant trial sponsored by Servier.

Other authors declare no competing interests.

DATA AVAILABILITY STATEMENT

As this trial has not commenced recruitment, no data is available at present. Once the dataset is generated, de-identified data may be made available from the corresponding author upon reasonable request.

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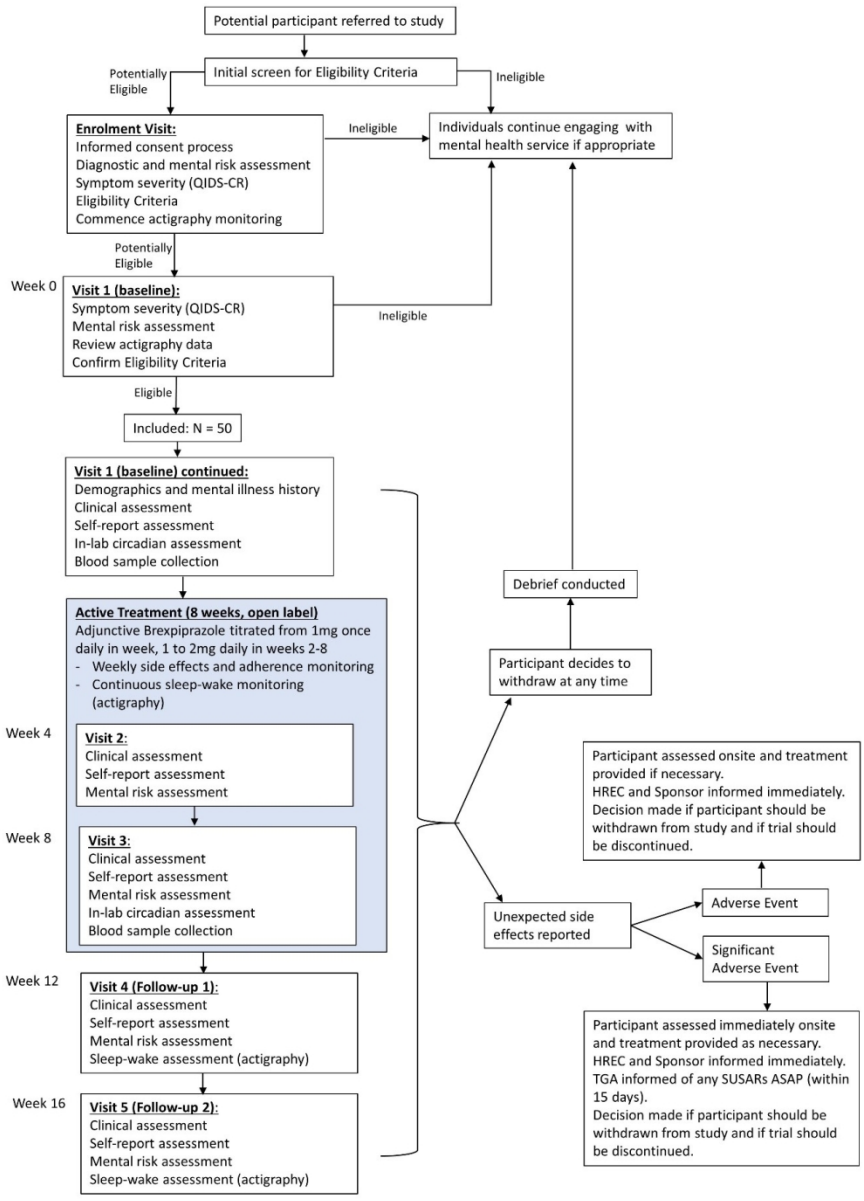

This figure illustrates the study design and participant timeline from referral to the last follow up visit, including withdrawal and safety procedures.

155x209mm (220 x 220 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	3
Protocol version	3	Date and version identifier	2; 21
Funding	4	Sources and types of financial, material, and other support	23
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1; 22-23
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Please refer to the Protocol (page 37)
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	___4-5_____
	6b	Explanation for choice of comparators	N/A as one arm study
Objectives	7	Specific objectives or hypotheses	____5-6_____
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	_____6_____
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	____6____
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	____7____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	____7-9____
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	____19____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	__9; 18-19__
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	_____7_____
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	____9-12____

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	____18_____ Please also refer to Figure 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	_____19-20____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	_____6_____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	N/A as not a controlled trial
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	N/A as not a controlled trial
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	N/A as not a controlled trial
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A as not a controlled trial
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A as not a controlled trial
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	____12-17_____

	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Please refer to Figure 1
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	____20_____ Please also refer to the Protocol (page 35)
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	____20_____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	_____N/A_____
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	_____20_____
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Please refer to the Protocol (page 11)
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Please refer to the Protocol (page 28)
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	____19_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Please refer to the Protocol (page 34)
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	_____21_____

Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	_____21_____ Please also refer to the Protoocl (page 36)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	_____6_____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Please refer to the Supplementary materials (page 2)
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Please refer to the Protocol (page 36)
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	____23-24_____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Please refer to the Protocol (page 35)
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Please refer to the Protocol (page 28)
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	_____20-21____
	31b	Authorship eligibility guidelines and any intended use of professional writers	_____N/A_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____N/A_____

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Please refer to the Consent form in the Supplementary files
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Please refer to the Supplementary materials (page 2)

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Effects of adjunctive brexpiprazole on sleep-wake and circadian parameters in youth with depressive disorders: Study protocol for a clinical trial

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Effects of adjunctive brexpiprazole on sleep-wake and circadian parameters in youth with depressive disorders: Study protocol for a clinical trial

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ABSTRACT

Introduction

Sleep-wake and circadian disturbance is a key feature of mood disorders with a potential causal role and particular relevance to young people. Brexpiprazole is a second-generation antipsychotic medication with demonstrated efficacy as an adjunct to antidepressant treatment for Major Depressive Disorder (MDD) in adults, with preliminary evidence suggesting greater effectiveness in subgroups of depressed patients with sleep disturbances. This clinical trial aims to evaluate the relationships between changes in sleep-wake and circadian parameters and changes in depressive symptoms following adjunctive brexpiprazole treatment in young adults with MDD and sleep-wake disturbance.

Methods and analysis

This study is designed as a 16 week (8 weeks active treatment, 8 weeks follow up) mechanistic, open-label, single-arm phase IV clinical trial and aims to recruit 50 young people aged 18 to 30 with MDD and sleep-wake cycle disturbance through an early intervention youth mental health clinic in Sydney, Australia. At baseline, participants will undergo multidimensional outcome assessment and subsequently receive 8 weeks of open-label treatment with brexpiprazole as adjunctive to their stable psychotropic medication. Following 4 weeks of treatment, clinical and self-report measures will be repeated. Ambulatory sleep-wake monitoring will be conducted continuously for the duration of treatment. After 8 weeks of treatment, all multidimensional outcome assessments will be repeated. Follow-up visits will be conducted 4 and 8 weeks after trial completion (including sleep-wake, clinical, and self-report assessments). Circadian rhythm biomarkers including salivary melatonin, cortisol, and core body temperature will be collected during an in-lab assessment. Additionally, metabolic, inflammatory, and genetic risk markers will be collected at baseline and after 8 weeks of treatment.

Ethics and dissemination

This trial protocol has been approved by the Human Research Ethics Committee of the Sydney Local Health District (X19-0417 and 2019/ETH12986, Protocol Version v 1-3, dated 25.02.2021). The results of this study,

in de-identified form, will be disseminated through publication in peer-reviewed journals, scholarly book chapters, presentation at conferences and publication in conference proceedings.

Trial Registration

Australian New Zealand Clinical Trials Registry (ANZCTR) Number: ACTRN12619001456145p, Date 22 October, 2019.

KEYWORDS:

Mental health, adjunctive brexpiprazole, sleep-wake cycle, youth depression, body clock

ARTICLE SUMMARY

Strengths and limitations of this study

- Use of a comprehensive battery that includes ecologically valid and laboratory based circadian assessments (alongside genetic, metabolic, and inflammatory markers) may provide greater insights into the antidepressant mechanisms of adjunctive brexpiprazole.
- Participants will receive a psychoeducational session about sleep and circadian rhythms, including information on how to improve their sleep-wake cycle based on their individual actigraphy data.
- This trial focuses on ascertainment of the current 24-hour sleep-wake cycle and will not examine possible factors that may contribute to sleep/circadian disruption in the long term (e.g., stressors) or the physiologic properties of sleep.
- Some extraneous factors that influence the sleep-wake cycle and/or circadian rhythms (e.g., ambient temperature, natural light exposure) are not measured in this study.

INTRODUCTION

In young adults, major depressive disorder (MDD) is highly prevalent, recurrent, and comorbid with other mental and physical conditions, generating a substantial burden of disease and disability [1, 2]. While multiple psychological and pharmacological treatments are commonly provided, a large proportion of patients fail to respond to first-line psychotherapy or antidepressant treatments [3-10], and augmentation with a second generation antipsychotic is often recommended in these treatment-resistant cases [11, 12]. Sleep-wake cycle disturbances are common features of depressive disorders, including insomnia [13-15], hypersomnia [16, 17], abnormal sleep duration [13, 14], and abnormal timing of 24-hour patterns of rest/activity [18, 19]. Moreover, abnormalities in biological circadian rhythms (e.g., melatonin) have been reported [20, 21], suggesting that in some cases sleep disturbances are accompanied or underpinned by disturbances of the underlying circadian system [22, 23].

The human circadian system is controlled by a master oscillator in the brain's hypothalamus (suprachiasmatic nucleus) which projects to circuits that govern bio-behavioural processes altered in depression (e.g., mood, vigilance, 24-hour sleep-wake cycle). The circadian system is primarily entrained by bright light, and its functioning can be disrupted by factors including aberrant light exposure and irregular sleep-wake behaviours [24, 25]. Adolescents and young adults are particularly vulnerable to circadian perturbations due to significant developmental changes in circadian rhythms across this age period [26], and sleep-wake phase delays are common in young people with depressive disorders [27]. Recently, we reported delayed and disrupted circadian rhythms in a subgroup of young people with depressive disorders (who also presented with greater symptom severity) [28]. During adolescence there is a phase shift in the circadian rhythm of the sleep-wake cycle, such that adolescents typically develop a bio-behavioural preference for going to sleep later and waking later (a manifestation of changes in the biology of the circadian system) [29, 30]. Furthermore, there is some evidence that correction of circadian abnormalities is associated with antidepressant effects of treatments targeting the circadian system such as Agomelatine [31] and light therapy [32].

Brexpiprazole is a second-generation antipsychotic with demonstrated efficacy by multiple randomised controlled trials as an adjunct to antidepressant treatment in MDD in adults [33-36]; however the mechanism of antidepressant action is unknown [37]. The pharmacodynamic properties of brexpiprazole, together with evidence from preclinical studies, suggest that there may be specific effects on anxiety, cognition, and sleep [37, 38]. Further, there is preliminary evidence to suggest that brexpiprazole may have greater effectiveness in subgroups of depressed patients with sleep disturbances, anxiety, or irritability [22, 39]. As an adjunctive treatment in MDD patients with inadequate response to antidepressant treatment, brexpiprazole has been reported to lead to clinical improvement of sleep disturbances (e.g., insomnia) and depressive symptoms, as well as improvement of daytime alertness and functioning [40]. This pattern of changes is consistent with effects on circadian rhythms, with potential influences on the entire 24-hour pattern of rest/activity, rather than simply on sleep period (in isolation). To improve the personalisation of treatment selection for mood disorders, a greater understanding of the mechanisms of antidepressant action of specific compounds is needed.

The goal of this clinical trial is to investigate whether the effect of brexpiprazole on depressive symptoms is associated with changes in 24-hour sleep-wake or circadian parameters in young people with MDD. While disturbances in electrophysiological measures of sleep (e.g., REM sleep) have been considered to represent biomarkers for depression [41-44], this trial focuses instead on the investigation and measurement of bio-behavioural changes associated with the circadian system (e.g., rest/activity, melatonin, cortisol, and core body temperature rhythms), rather than changes in electrophysiological sleep architecture (beyond the scope of this study).

METHODS AND ANALYSIS

Study objectives

The primary objective of this study is to determine if changes in depressive symptoms following adjunctive brexpiprazole treatment are correlated with changes in sleep-wake or circadian parameters in youth with depressive disorders.

The secondary objective is to determine if changes in social and occupational functioning following adjunctive brexpiprazole are correlated with changes in sleep-wake or circadian parameters in youth with depressive disorders.

The tertiary objectives of this study are to determine if changes in depressive symptoms or changes in sleep-wake or circadian parameters following adjunctive brexpiprazole treatment are associated with a range of multidimensional outcome measures in youth with depressive syndromes [45] (e.g., other mental illness symptoms, self-harm and suicidal thoughts and behaviours, physical health, alcohol/substance use, and genetic markers).

Trial design

This investigator-initiated, mechanistic study involving 50 young people with depressive disorders and sleep-wake cycle disturbances is designed as a 16-week (8 weeks active treatment, 8 weeks follow-up) open-label, single-arm, phase IV clinical trial.

Participants

Participants aged 18-30 years with a diagnosis of MDD according to DSM-5 criteria on a current antidepressant treatment of either selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI) with a disrupted sleep-wake cycle will be recruited through the youth mental health clinics associated with the Brain and Mind Centre (BMC), University of Sydney. All participants will provide written informed consent. The research team will make explicit to any potential participants both verbally and in writing (in the Participant Information Statement) that participation is voluntary and will not affect the patient's care.

The inclusion criteria for this trial are: (i) aged 18-30, (ii) diagnosis of MDD as per DSM-5 (Structured Clinical Interview for DSM; SCID[46]) criteria, (iii) current major depressive episode of moderate severity as defined by a Quick Inventory of Depressive Symptomatology [47] rating ≥11 at two assessments two weeks apart, (iv) failure to respond to at least one adequate (minimum four weeks) trial of pharmacological treatment, (v) current antidepressant treatment with an SSRI or SNRI (including citalopram, fluoxetine, paroxetine, sertraline, escitalopram, venlafaxine, desvenlafaxine, or duloxetine) for at least 6 weeks, at a stable dose for two weeks prior to study commencement, and (vi) a perturbed sleep-wake cycle as evidenced by: delayed sleep onset; delayed sleep offset; disrupted sleep; high day-to-day variability of sleep-wake cycle; non-restorative sleep; or daytime fatigue.

Exclusion criteria are: (i) any adjunctive antipsychotic treatment for current episode in the past month, (ii) use of medications which affect sleep, melatonin, circadian rhythms, or alertness (e.g., agomelatine, modafinil), (iii) primary psychotic disorder, (iv) acute suicidal behaviour (score of 6 on Comprehensive Assessment of At-Risk Mental States item 7.3 [48], (v) evidence of a medical condition (primary, respiratory, neurological) that could contribute to sleep-wake dysfunction, (vi) significant alcohol or substance misuse or dependence (assessed via DSM-5 SCID[46] and World Health Organisation Alcohol, Smoking and Substance Involvement Screening Test [49, 50], (vii) shift work or (viii) recent transmeridian travel (i.e., participants will be required to wait three days for each jet lag hour before entering the study), (ix) previous hypersensitivity to brexpiprazole, (x) taking CYP2D6 or CYP3A4 inhibitors (or other contraindicated medications listed in the Rexulti product information), and (xi) pregnancy or lactation.

Study course and procedure

Patients presenting for mental health care who may be eligible for the study will be screened by phone before being invited to participate and attending an enrolment visit. The enrolment visit will formally assess eligibility criteria and confirm the presence of MDD as per DSM-5 (SCID)[46]. Participants will be provided

with an actigraphy device (non-invasive wrist-worn device used to objectively measure rest/activity patterns) and will be given instructions to wear the device for the following two-week period.

Visit 1 (Baseline): Within two weeks of completing the diagnostic and screening assessments, data from the actigraphy device will be downloaded and reviewed. A further assessment of depressive symptom severity (QIDS Clinician-Rated; QIDS-CR)[47] will be conducted to ensure participants meet all inclusion criteria. Bloods will be collected for assessment of metabolic and inflammatory measures and genomic analysis. Clinical and self-report assessments will be conducted, as well as circadian assessments in which participants will remain in the sleep lab overnight. The following morning, participants will attend a 1-hour psychoeducation session about sleep and circadian rhythms covering the following topics: i) sleep and circadian education with tailored discussion based on their personal actigraphy data; ii) individualized plan for progressive sleep rescheduling; and iii) lifestyle factors and behaviours impacting on sleep (e.g., exercise, light, sleep environment, sleep regulation, foods, stress, anxiety, mood).

Once all baseline clinical and self-report assessments have been conducted, and the medical assessment completed by the study doctor to confirm inclusion and exclusion criteria, participants will be issued with the study medication to receive 8 weeks of open-label pharmacotherapy with brexpiprazole (REXULTI®-Lundbeck) as adjunctive to their stable psychotropic medication (treatment as usual). Brexpiprazole will be provided to participants at Visit 1 (Baseline) and Visit 2 (Week 4) for the following four weeks and will be titrated from 1 mg once daily in week 1, to 2 mg once daily in weeks 2-8.

Patients will receive 2mg/day, once daily as tablets, for oral use. The brexpiprazole dosage will be steadily increased from 1mg/day during week 1, to 2mg/day during weeks 2-8 (up-titration). This is the dosage and titration regime recommended for adjunctive use in major depression by the Federal Drug Administration (USA). Several previous clinical trials have used this titration regime from 1mg to 2mg [34, 40, 51], and a dose of 2mg has been shown to be effective in reducing depressive symptoms [33]. As doses higher than

2mg have been shown to increase incidence of akathisia [37], a maximum dose of 2mg will be used in the present study to minimise side effects.

Monitoring visits: Participants will be contacted by telephone on a weekly basis for the duration of the 8-week treatment period to monitor adverse events and adherence. Any changes in concomitant medications will also be investigated and recorded. In addition, participants will be provided with a medication diary and asked to complete during the study to monitor adherence. More detailed information about potential side-effects will be further assessed by the study doctor at visits 2, 3, 4 and 5 using the UKU Side Effect Rating Scale [52], Abnormal Involuntary Movement Scale (AIMS) [53] and the Simpson-Angus Scale (SAS) [54] for evaluation of extrapyramidal symptoms (EPS).

Visit 2 (Week 4): Following four weeks of the treatment phase, participants will return for clinical and self-report assessments to assess changes in clinical and functional measures.

Visit 3 (Week 8): Following eight weeks of the treatment phase, participants will return to complete clinical and self-report assessments and will also complete a second circadian (overnight) in-lab assessment. Bloods will be collected at this visit for follow-up metabolic and inflammatory markers. Participants will continue to be provided the brexpiprazole for up to 12 months following completion of the treatment phase as clinically indicated, at the discretion of their treating clinician. Analyses will account for whether participants have continued or discontinued the medication during the follow-up period.

Visit 4 and 5 (Follow-up visits 1 and 2, 12 and 16 weeks respectively): Twelve and sixteen weeks after commencing treatment (i.e., four and eight weeks after completing the eight-week treatment period respectively), participants will return to complete clinical and self-report assessments. Participants will be provided with an actigraphy device to wear for two weeks prior to these assessments.

Participants will be reimbursed for their time and the cost of transportation to and from the research sites.

Outcomes

Outcome measures are summarized in Table 1.

Primary outcomes

The primary endpoint will be the correlation between change in sleep-wake and circadian parameters and change in depressive symptoms from baseline to week eight. Sleep items in the primary depressive symptom measures (QIDS-CR total score, QIDS-Self Report (QIDS-SR) total score, The Montgomery–Åsberg Depression Rating Scale (MADRS) total score) will be removed in analyses to provide a measure of depressive symptoms not biased by changes in sleep-wake parameters.

Secondary outcomes

The secondary endpoint will be correlation between change in sleep-wake and circadian parameters and change in functioning from baseline to week eight.

Tertiary outcomes

Tertiary endpoints will be correlation between change in sleep-wake and circadian parameters and other multidimensional outcome measures based on assessments of symptoms, self-harm and suicidal thoughts and behaviours, physical health, and alcohol/substance use. Further tertiary endpoints will be comparison of primary endpoints between Clinical Stages [55-58], illness trajectories [59], and genetic variants with potential relevance to mood disorders and/or circadian rhythms (e.g. CLOCK, BMAL1).

Table 1. Primary, secondary, and tertiary outcome measures.

Primary Outcome Measures (Correlation between change in sleep-wake and circadian parameters and change in	**Secondary Outcome Measures**	**Tertiary Outcome measures**

depressive symptoms from baseline to week eight)	(Correlation between change in sleep-wake and circadian parameters and change in functioning from baseline to week eight)	(Correlation between change in sleep-wake and circadian parameters and other multidimensional outcome measures)
Primary depressive symptom measures: • QIDS-CR total score (minus sleep items) • QIDS-Self Report (QIDS-SR) total score (minus sleep items) • The Montgomery–Åsberg Depression Rating Scale (MADRS) total score (minus sleep items) **Sleep-wake and circadian variables:** Actigraphy parameters (in the two-week period prior to baseline and prior to week eight): • Sleep onset time • Sleep offset (wake) time • Total sleep time (duration) • Wake after sleep onset (estimation of number of minutes awake during the sleep period) • Sleep efficiency (% of sleep period estimated as sleep) • Inter-daily stability • Intra-daily variability **In-lab circadian measures:** • Dim Light Melatonin Onset (DLMO) timing • Phase angle (time lapse) between DLMO and habitual sleep • Core body temperature nadir • Evening cortisol area under the curve **Self-report measures:** • Non-restorative sleep score (based on the Pittsburgh Sleep Quality Index (PSQI), and Munich Chronotype Questionnaire (MCTQ) • *Pittsburgh Sleep Quality Index* (PSQI) total score • Epworth Sleepiness *Score* (ESS) total score • Insomnia Severity Index (ISI) total score • Morningness -Eveningness Questionnaire (MEQ) total sore* • Seasonal Pattern Assessment Questionnaire (SPAQ) total score*	**Functioning measures:** • Social and Occupational Functioning Assessment Scale (SOFAS) rating • The Work and Social Adjustment Scale (WSAS) total score • Adapted Schuster Social Support Scale (SSSS) total score • Not in Education, Employment, or Training (NEET) status • Number of days 'out of role' (unable to perform usual activities) in the past 30 days	**Symptom measures:** • Young Mania Rating Scale (YMRS) total score • Brief Psychiatric Rating Scale (BPRS) total score and subscale scores • Overall Anxiety Severity Impairment Scale (OASIS) total score • Altman Self-Rating Mania scale (ASRM) total score • Prodromal Questionnaire (brief version) (PQ-16) total score • DSM-5 Primary Care Post-Traumatic Stress Disorder screen (PC-PTSD-5) total score • Adapted Eating Disorder Examination (EDE) total score • Clinical Global Impressions scale (CGI) severity and improvement scores **Self-harm and suicidal thoughts and behaviours:** • Suicidal risk (score from Suicidal Ideation Attributes Scale (SIDAS) and Columbia- Suicide Severity Rating Scale (C-SSRS) items) • Adapted Brief Non-Suicidal Self-Injury Assessment Tool (B-NSSI-AT) total score **Physical Health:** • Body Mass Index (BMI) calculated from height and weight • Waist circumference • International Physical Activity Questionnaire (IPAQ) total score • Metabolic blood markers including triglycerides, cholesterol (total, Low Density Lipoprotein (LDL), High Density Lipoprotein (HDL)), and Homeostasis Model of Insulin Resistance (HOMA2-IR) calculated from fasting glucose and insulin measures • Inflammatory blood markers including Interleukin-1β (IL-1β), Interleukin-6 (IL-6), Tissue Necrosis Factor (TNF-α), C-Reactive Protein (CRP) **Alcohol and substance Use:**

*Baseline scores will be used rather than change scores as these are trait measures		• World Health Organisation Alcohol, Smoking, and Substance Involvement Screening Test (WHO ASSIST) score for tobacco, and cannabis • Alcohol Use Disorders Identification Test-Consumption (AUDIT C) total score • WHO ASSIST alcohol-related impairment • Age of onset of alcohol use **Comparison of primary endpoints between:** • Clinical Stages • Illness Trajectories • Genetic variants with potential relevance to mood disorders and/or circadian rhythms (e.g., CLOCK, BMAL1).

Assessments

Assessments used here are based on the multidimensional assessment and outcomes framework [45] and include clinical and self-report ratings of mental health symptoms, social and occupational functioning, self-harm, suicidal thoughts and behaviours, physical health, alcohol and substance use, illness type, stage and trajectory, as well as circadian parameters and metabolic, inflammatory and genetic markers. Our recent research [45, 60-62] indicates the capacity of the multidimensional outcomes framework to further our understanding of the pathophysiological mechanisms and illness progression in this cohort, as well as to inform more personalized and measurement-based models of care.

Diagnostic assessments

The presence of MDD and any comorbidity will be evaluated using the Structured Clinical Interview for DSM-5 Axis I Disorders (SCID) [46] (30-75 minutes to complete).

Mental risk assessment

Acute suicidal behaviour will be assessed by relevant subscale of the Comprehensive Assessment of At-Risk Mental States (CAARMS) [48] (5 minutes to complete).

Clinical assessments

The clinical interview is expected to take around 35 minutes to complete.

1. *Clinical-rated Quick Inventory of Depressive Symptomatology (QIDS-CR)* [47]: assesses the nine criterion symptom domains designated by the DSM to diagnose a MDE.
2. *Montgomery-Åsberg Depression Rating Scale (MADRS)* [63]: will also be used to assess depressive symptoms, to allow for direct comparisons with previous studies of brexpiprazole in MDD.
3. *Young Mania Rating Scale (YMRS)* [64]: an 11-item, multiple-choice diagnostic questionnaire used to measure severity of manic episodes.
4. *Brief Psychiatric Rating Scale (BPRS)* [65]: used to measure psychiatric symptoms (e.g., depression, anxiety, hallucinations).
5. *Social and Occupational Functioning Assessment Scale (SOFAS)* [66]: used to assess functioning on a 0-100 scale (lower scores suggesting greater impairment).
6. *Clinical Global Impressions scale (CGI)* [67]: used to measure of clinical improvement.
7. Participants will also be rated on previously established *clinical stage* [55-58] and *illness trajectory* [59] models on the basis of information collected throughout the clinical interview. The clinical staging framework differentiates those in the earliest phases of mental health problems with non-specific clinical presentations (stage 1a; 'help-seeking') from those at greater-risk with more specific, sub-threshold presentations (stage 1b; 'attenuated syndromes') and those who have already reached a threshold for a progressive or recurrent disorder meeting diagnostic criteria (stage 2, 3, or 4). The illness trajectory model is a novel tripartite framework based on three proposed pathophysiological pathways leading to youth-onset mental disorders: (i) neurodevelopmental-psychosis, (ii) circadian-bipolar spectrum, and (iii) hyperarousal-anxious depression[68-70].
8. *World Health Organisation (WHO) Alcohol, Smoking and Substance Involvement Screening Test (WHO-ASSIST) [49, 50]* : a reliable, culturally adaptable, valid screener for problematic or risky substance use.

Self-report assessments

The self-report questionnaires are tailored to the individual (using skip logic) so the amount of time taken to complete the questionnaire varies, but we estimate the assessment will take 45 minutes to complete.

1. *Demographics and Mental Health History:* including details of work and education, physical health (height, weight, waist circumference), history of mental health, and family history
2. *International Physical Activity Questionnaire (IPAQ) - short version [71, 72]:* 7-item questionnaire providing internationally comparable data on health–related physical activity.
3. *Alcohol Use Disorders Identification Test – Consumption (AUDIT-C) [73]:* includes three short questions that estimate alcohol consumption in a standard, meaningful, non-judgmental manner. Additional questions assessing age of onset of alcohol consumption will also be used.
4. *Suicidal Ideation Attributes Scale (SIDAS) [74]:* 5-item self-report questionnaire assessing the frequency, controllability, closeness to attempt, distress, and interference with daily activities on a 10-point Likert scale over the past month.
5. *Columbia-Suicide Severity Rating Scale (C-SSRS) [75]:* The scale comprises 3 sections: suicidal ideation, intensity of ideation, and suicidal behaviour. A self-rating adaptation will be used in combination with the SIDAS.
6. *Brief Non-Suicidal Self-Injury Assessment Tool (B-NSSI-AT)* [76]: designed to assess primary (such as form, frequency, and function) and secondary (including but not limited to NSSI habituation; contexts in which NSSI is practiced; and NSSI perceived life interference, treatment, and impacts) NSSI characteristics.
7. *Quick Inventory of Depressive Symptomatology – self-report (QIDS-SR) [77]: a* self-rating (SR) version includes 16 questions with equivalent weightings (0-3) for each symptom item that assesses the nine criterion symptom domains designated by the DSM-IV to diagnose a MDE.
8. *Overall Anxiety Severity Impairment Scale (OASIS) [78]:* 5-item self-report measure used to assess severity and impairment associated with any anxiety disorder or multiple anxiety disorders.
9. *Altman Self-Rating Mania Scale (ASRM) [79]*: 5-item self-rating scale designed to assess the presence and/or severity of manic symptoms.

10. *Primary Care Post-Traumatic Stress Disorder Screen for DSM-5 (PC-PTSD-5) [80]:* 5-item screen designed for use in primary care settings to identify respondents with probable PTSD.
11. *Prodromal Questionnaire (PQ-16) [81]:* self-report screen for use in secondary mental health care services to select subjects for psychosis risk.
12. *Eating Disorder Examination (EDE) [82, 83]*: comprises a range of health-related and demographic questions, including present height and weight, and a detailed and comprehensive assessment of symptoms, particularly binge eating. In this study, three eating disorder behaviours are assessed: binge eating, purging, and strict dieting or fasting.
13. *Sleep questions*: 7 questions regarding time falling asleep, waking up during weekdays and weekends, hours of sleep, feelings when waking up. Sleep timing items are based on the Pittsburgh Sleep Quality Index (PSQI) and Munich Chrono Type Questionnaire (MCTQ), while sleep quality items are based on expert consensus in the literature.
14. *Work and Social Adjustment Scale (WSAS) [84]:* 5-item scale of functional impairment attributable to an identified problem.
15. *Schuster Social Support Scale (SSSS) [85]:* 15-item measure of social support used to examine an individual's social relationships with others (relatives, friends, spouse) and the associated impact on their emotional functioning
16. *Additional sleep questionnaires:* participants will complete the BMC sleep-wake self-report questionnaire battery including questions regarding ethnicity, caffeine consumption, menstrual cycle, visual impairments, and non-restorative sleep, as well as the *Pittsburgh Sleep Quality Inventory (PSQI)* [86], *Epworth Sleepiness Scale (ESS)* [87], *Insomnia Severity Index (ISI)* [88], *Horne-Ostberg Morningness-Eveningness Questionnaire (MEQ*) [89], and the *Seasonal Patterns Assessment Questionnaire (SPAQ)* [90].

Sleep wake assessments

24-hour sleep-wake and circadian rest-activity parameters will be measured by actigraphy recordings. Actigraphy is a non-invasive tool to objectively measure activity profiles used to estimate sleep and circadian

patterns based on validated algorithms. Participants will be asked to complete a sleep diary and to wear an actigraph (GENEActiv device; Activinsights, Kimbolton, UK) on the non-dominant wrist for at least 10 days prior to commencing the study, and continuously for the 8-week treatment phase. The device is comfortable and easy to use, battery operated wrist-worn device, similar in appearance to Fitbit, designed to record and provide data on movement, light, temperature and sleep patterns. The device will provide objective monitoring of participants' 24-hour circadian rhythm, including their sleep onset and duration, rise time, any night-time sleep interruptions, and activity patterns (see Table 1). The device allows for the outputting of real-time raw measurement data for up to a month without charging. Instructions will be provided to participants on how to use the device upon their recruitment into the study. Two-week actigraphy recordings will also be completed at the 12- and 16-week follow up assessments. GENEActiv devices have been validated against several types of accelerometry-based activity monitors [91-94] as well as for sleep-wake scoring [95, 96]. For decades, actigraphy monitors like the GENEActiv devices have been used extensively in research to measure sleep and activity patterns in diverse clinical settings including sleep disorders, medical illnesses (e.g., neurodegenerative diseases) and various major mental disorders [19, 97, 98].

In-lab circadian assessment

Circadian rhythms will be measured in an evening/overnight recording period, including 24-hour rhythms of salivary melatonin, salivary cortisol, and core body temperature (Table 1). Circadian assessments will be performed in accordance with established dim light melatonin onset protocols [99-102].

Metabolic and inflammatory markers

The following markers will be collected at baseline and 8-weeks follow up visits: (i) Triglycerides, (ii) Cholesterol (including total, High Density Lipoprotein (HDL), and Low-Density Lipoprotein (LDL)), (iii) Fasting glucose, (iv) Fasting insulin, (v) Interleukin (IL)-1β, (vi) IL-6, (vii) Tissue Necrosis Factor (TNF)-α, (viii) C-Reactive Protein (CRP). Height, weight, and waist circumference will be recorded. Insulin resistance will be estimated based on paired fasting plasma glucose and insulin levels [103] by the updated homeostatic model assessment (HOMA2-IR) using iHOMA2 software V.8.8 [104].

Genetics

Additional blood (30mL) will be collected at baseline for assessment of genetic markers as per procedures from the University of Queensland Human Studies Unit.

The schedule of trial assessments is summarized in Table 2 and the participant timeline is presented in Figure 1.

Table 2. Schedule of assessments

	Enrolment Visit	Visit 1 (Baseline)	Visit 2 (Week 4)	Visit 3 (Week 8)	Visit 4 (Follow-up 1)	Visit 5 (Follow-up 2)
Study week		***0***	***4***	***8***	***12***	***16***
Informed Consent	✓					
Inclusion/Exclusion Criteria	✓	✓				
Diagnostic Assessment (SCID)	✓					
Mental Risk Assessment (CAARMS)	✓	✓	✓	✓	✓	✓
Demographics and Mental Illness History		✓				
Clinical Assessment (QIDS-CR, MADRS, YMRS, BPRS, SOFAS)		✓	✓	✓	✓	✓
Self-report Assessment		✓	✓	✓	✓	✓
Sleep-wake Assessment (actigraphy monitoring)		✓	✓	✓	✓	✓
In-lab Circadian Assessment		✓		✓		
Blood Sample Collection (Metabolic and Inflammatory Markers)		✓		✓		
Safety, side-effects, and adherence assessment			✓	✓	✓	✓
IP dispensing		✓	✓	✓*	✓*	✓*
IP return			✓	✓		

* If clinically indicated, at the discretion of the treating clinician

Safety and side-effects monitoring

Studies have shown that brexpiprazole is generally well tolerated, with no unexpected or severe side effects [33, 36, 105, 106]. Safety and tolerability of the investigational product (IP) will be closely monitored throughout the trial. For the duration of the 8-week treatment period, weekly phone calls will be conducted to monitor safety and elicit information regarding side effects and potential adverse events. Any changes in concomitant medications will also be investigated and recorded. In addition, participants

will be provided with a medication diary and asked to complete during the study to monitor tolerability and adherence. According to the IP information, participants will be advised to not drive a car, operate machinery, or do other dangerous activities until they know how the IP affects them, as it may induce drowsiness in some subjects.

Further formal assessment of side effects and potential adverse events following the end of the treatment phase will be conducted at the two follow-up visits (visit 4 and 5). At the baseline visit, participants will be informed that any serious negative side effects should be reported to the study doctor immediately and will be provided with the relevant contact details to do so. All Adverse Events will be assessed for causality and symptom severity according to the study protocol and followed up by the study doctor if required. In the occurrence of a Serious Adverse Event, appropriate diagnostic and therapeutic measures will be taken and the participant will be kept under observation for as long as is medically indicated. The Principal Investigator will then determine if the seriousness of the event warrants the removal of the participant from the study or abandonment of the study. For serious side effects or medical problems, the patient may be taken immediately to Royal Prince Alfred Hospital for treatment. The Principal Investigator will ensure that follow-up of the participant is appropriate to the nature of any event, and that it continues until resolution.

Throughout the trial the study doctor will monitor participants for pregnancy. It is not currently included in the protocol, but the trial Standard Operating Procedures manual explains that the study doctor will give relevant contraception advice to participants based on the current IP information.

Sample size calculation

Sample size was determined based on a study of circadian changes in response to agomelatine [31] where a coefficient of 0.54 was found for the correlation between change in DLMO and change in depressive symptoms. We conservatively estimated that the coefficient for brexpiprazole would be smaller (~0.35; i.e., medium effect size), as effects on the circadian system may be less direct. Assuming α=0.05 and 80% power for a one-tailed correlation analysis, a sample size of n=49 is required to detect this effect.

Data analysis plan

Correlations will be performed between change scores (i.e., Visit 2 score minus Visit 1 score) for sleep and circadian measures, and change scores for depressive symptoms. The intention-to-treat principle will be used for missing data (last observations carried forward). Before analysis, plots with outlier and normality statistics will be generated for all variables to identify outliers and issues with variable distribution. Extreme outliers (±3 z-scores) will be checked against source data and testing notes to verify whether they are the result of an error in data entry or a specific issue during testing (e.g., equipment failure), with errors rectified. If not the result of data entry error, outliers will be curtailed. Pearson's or Spearman's correlations will be selected to perform analyses based on normative or non-normative data distribution (significance level α=0.05). Correlations will also be examined between other change scores to assess secondary and tertiary endpoints. Further tertiary endpoints will be assessed by partial correlations comparing categorical variables.

Patient and public involvement

Clinical professionals working with young people with mental health problems were invited to comment on the study design and procedures. Findings will be disseminated to scientific, clinical, and wider communities.

Ethics and dissemination

This trial has been approved by the Human Research Ethics Committee of the Sydney Local Health District (X19-0417 and 2019/ETH12986, Protocol Version v 1-3, dated 25.02.2021). The study will be conducted in compliance with all stipulations of the protocol, the conditions of ethics committee approval, the NHMRC National Statement on Ethical Conduct in Human Research and the Good Clinical Practice guidelines. The results of this study will be disseminated as widely as possible into the scientific and broader community. This will include publication in peer-reviewed journals, scholarly book chapters, presentation at conferences and publication in conference proceedings. Publications arising from this project will be deposited into an open access institutional repository, where possible. Results will also be disseminated into the wider community in

a format appropriate for a lay audience, through links including the BMC website and social media, as well as newsletters.

Figure 1. Study flow chart

Legend: This figure illustrates the study design and participant timeline from referral to the last follow up visit, including withdrawal and safety procedures.

TRIAL STATUS

Protocol ID: BMC-YMH-005-2018, Version: v 1-3, dated 25/02/2021.

The trial has not commenced recruitment.

AUTHOR CONTRIBUTIONS

JSC and IBH conceived the study, led the proposal and protocol development. JSC wrote the trial protocol. AG drafted the first version of the manuscript. NZ drafted the final version of the manuscript with input from other authors. JSC, AG, AN, NZ, YJSS, CW, CR, JJC, CMM, FML, DK and EMS were all involved with modifications to the design of the study and with drafting of this paper. All authors have read and approved the final manuscript.

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COMPETING INTERESTS

Professor Ian Hickie is the Co-Director, Health and Policy at the Brain and Mind Centre (BMC) University of Sydney, Australia. The BMC operates an early-intervention youth services at Camperdown under contract to headspace. Professor Hickie has previously led community-based and pharmaceutical industry-supported (Wyeth, Eli Lily, Servier, Pfizer, AstraZeneca) projects focused on the identification and better management of anxiety and depression. He is the Chief Scientific Advisor to, and a 5% equity shareholder in, InnoWell Pty Ltd. InnoWell was formed by the University of Sydney (45% equity) and PwC (Australia; 45% equity) to deliver the $30 M Australian Government-funded Project Synergy (2017-20) and to lead transformation of mental health services internationally through the use of innovative technologies.

Associate Professor Elizabeth M Scott is the Medical Director, Young Adult Mental Health Unit, St Vincent's Hospital Darlinghurst, Discipline Leader of Adult Mental Health, School of Medicine, University of Notre Dame, Research Affiliate, The University of Sydney and Consultant Psychiatrist. She has received honoraria for educational seminars related to the clinical management of depressive disorders supported by Servier and Eli-Lilly pharmaceuticals. She has participated in a national advisory board for the antidepressant compound Pristiq, manufactured by Pfizer. She was the National Coordinator of an antidepressant trial sponsored by Servier.

Other authors declare no competing interests.

DATA AVAILABILITY STATEMENT

As this trial has not commenced recruitment, no data is available at present. Once the dataset is generated, de-identified data may be made available from the corresponding author upon reasonable request.

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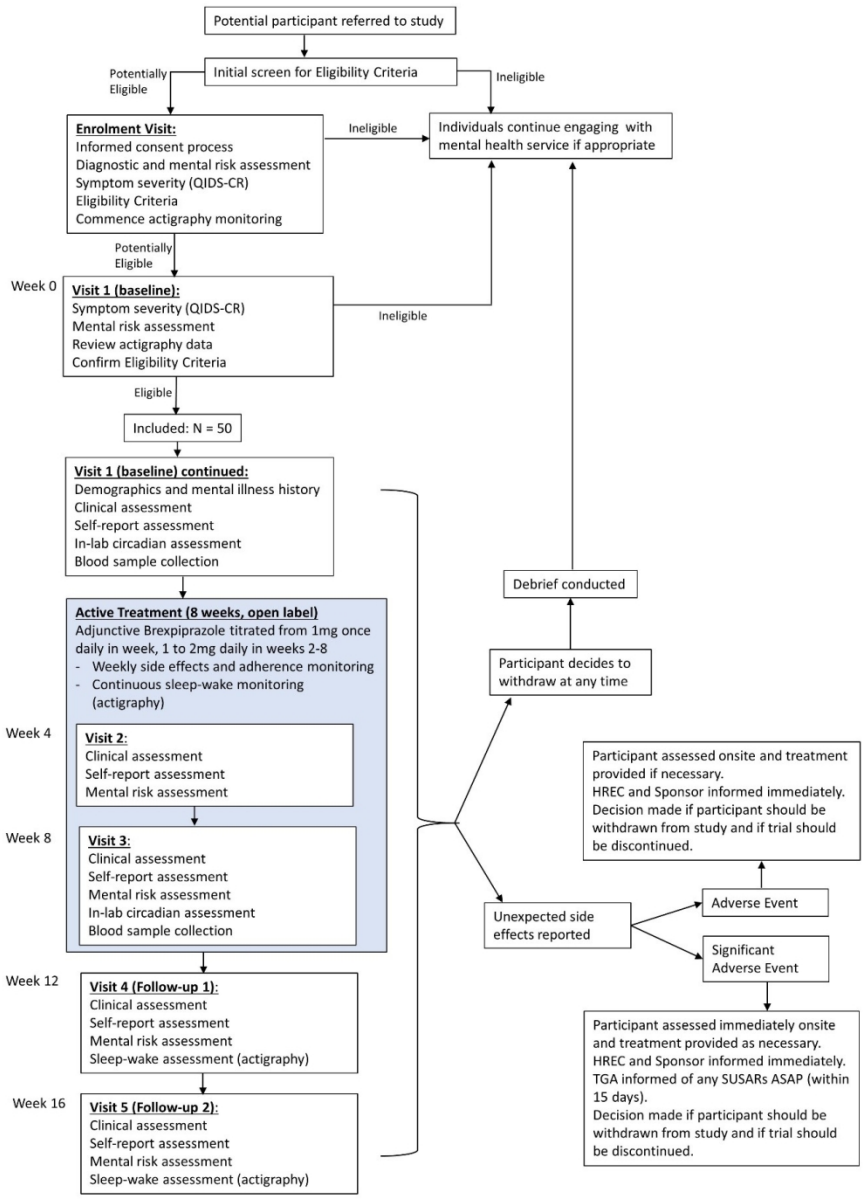

This figure illustrates the study design and participant timeline from referral to the last follow up visit, including withdrawal and safety procedures.

155x209mm (220 x 220 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	3
Protocol version	3	Date and version identifier	2; 21
Funding	4	Sources and types of financial, material, and other support	23
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1; 22-23
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Please refer to the Protocol (page 37)
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	___4-5_____
	6b	Explanation for choice of comparators	N/A as one arm study
Objectives	7	Specific objectives or hypotheses	____5-6_____
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	_____6_____
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	____6____
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	____7____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	____7-9____
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	____19____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	__9; 18-19__
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	_____7_____
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	____9-12____

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	____18_____ Please also refer to Figure 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	_____19-20____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	_____6_____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	N/A as not a controlled trial
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	N/A as not a controlled trial
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	N/A as not a controlled trial
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A as not a controlled trial
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A as not a controlled trial
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	____12-17_____

	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Please refer to Figure 1
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	____20_____ Please also refer to the Protocol (page 35)
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	____20_____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	_____N/A_____
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	_____20_____
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Please refer to the Protocol (page 11)
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Please refer to the Protocol (page 28)
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	____19_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Please refer to the Protocol (page 34)
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	_____21_____

Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	_____21_____ Please also refer to the Protoocl (page 36)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	_____6_____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Please refer to the Supplementary materials (page 2)
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Please refer to the Protocol (page 36)
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	____23-24_____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Please refer to the Protocol (page 35)
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Please refer to the Protocol (page 28)
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	_____20-21____
	31b	Authorship eligibility guidelines and any intended use of professional writers	_____N/A_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____N/A_____

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Please refer to the Consent form in the Supplementary files
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Please refer to the Supplementary materials (page 2)

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.