The clinical and cost-effectiveness of Stimulant compared with Non-stimulant medication for adults with Attention-deficit/hyperactivity disorder and a history of Psychosis or bipolar disordER: SNAPPER

BACKGROUND AND RATIONALE

Attention-Deficit/Hyperactivity Disorder (ADHD) is a common neurodevelopmental disorder involving inattention, hyperactivity and impulsivity, which starts in childhood and frequently persists into adulthood. Stimulant and non-stimulant medication are the mainstay of treatment in adults. ADHD in adults is commonly comorbid with psychosis and bipolar disorder. There is substantial uncertainty over the effectiveness of stimulant and non-stimulant medication in adult ADHD comorbid with psychosis or bipolar. There is also concern that these medications could trigger or worsen psychotic or manic symptoms. Whilst National Institute of Health and Care Evidence (NICE) ADHD guidelines indicate available evidence does not justify a deviation from their main recommendations of using stimulants, this is based on limited studies of individuals with ADHD and comorbid conditions. A randomised controlled trial is needed to address this evidence gap. To address this evidence gap, SNAPPER was funded in response to a commissioned call from the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Programme, 19/34 Medication for ADHD in adults with a history of psychosis or bipolar disorder.

OBJECTIVES

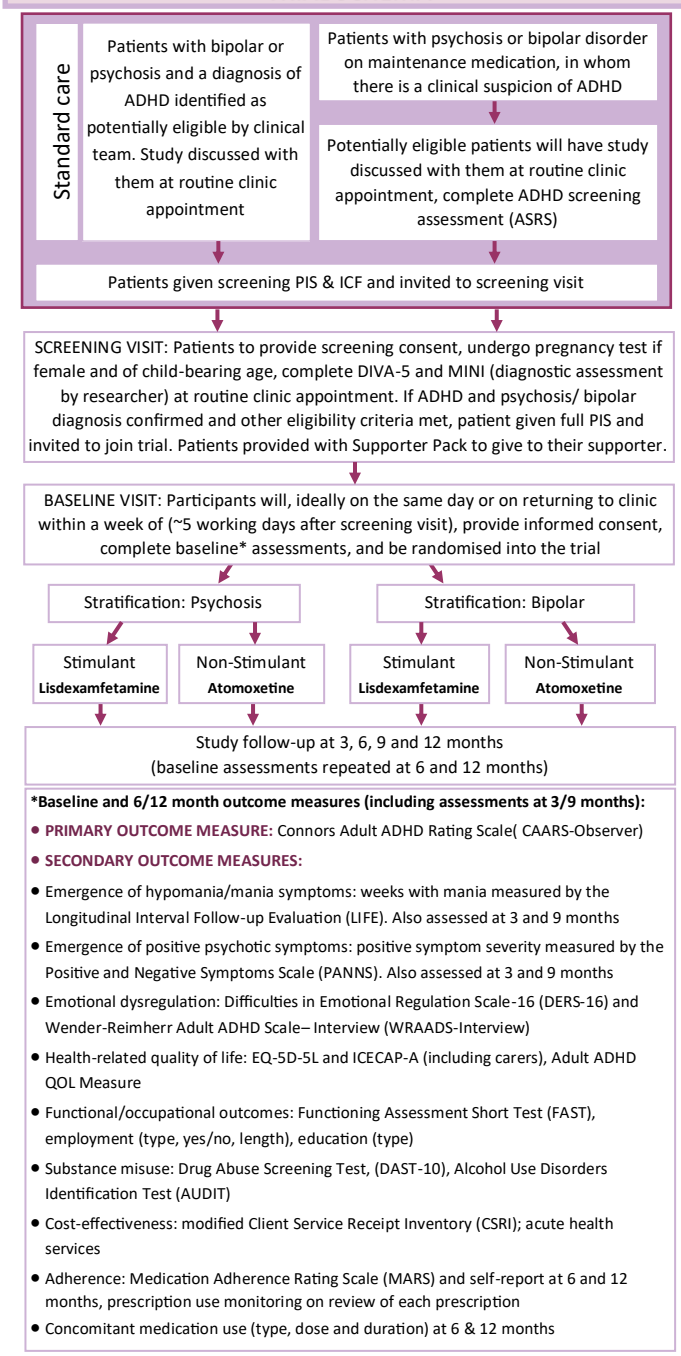
PRIMARY OBJECTIVE: To evaluate separately in adults with ADHD and a history of either psychosis or bipolar disorder whether stimulant (Lisdexamfetamine) vs. non-stimulant (Atomoxetine) medication reduces ADHD symptom severity at 12 months

SECONDARY OBJECTIVES:

To evaluate separately in adults with ADHD and a history of either psychosis or bipolar disorder the impact of stimulant vs. non-stimulant medication on:

- ADHD symptom severity at 6 months
- Emergence of symptoms of bipolar or psychosis over 12 months
- Health-related quality of life, occupational, functional, substance misuse and other outcomes at 6 and 12 months, and to examine the cost-effectiveness of stimulant vs. non-stimulant medication.

TRIAL SCHEMA



***Baseline and 6/12 month outcome measures (including assessments at 3/9 months):**

- **PRIMARY OUTCOME MEASURE:** Connors Adult ADHD Rating Scale(CAARS-Observer)
- **SECONDARY OUTCOME MEASURES:**
- Emergence of hypomania/mania symptoms: weeks with mania measured by the Longitudinal Interval Follow-up Evaluation (LIFE). Also assessed at 3 and 9 months
- Emergence of positive psychotic symptoms: positive symptom severity measured by the Positive and Negative Symptoms Scale (PANNS). Also assessed at 3 and 9 months
- Emotional dysregulation: Difficulties in Emotional Regulation Scale-16 (DERS-16) and Wender-Reimherr Adult ADHD Scale– Interview (WRAADS-Interview)
- Health-related quality of life: EQ-5D-5L and ICECAP-A (including carers), Adult ADHD QOL Measure
- Functional/occupational outcomes: Functioning Assessment Short Test (FAST), employment (type, yes/no, length), education (type)
- Substance misuse: Drug Abuse Screening Test, (DAST-10), Alcohol Use Disorders Identification Test (AUDIT)
- Cost-effectiveness: modified Client Service Receipt Inventory (CSRI); acute health services
- Adherence: Medication Adherence Rating Scale (MARS) and self-report at 6 and 12 months, prescription use monitoring on review of each prescription
- Concomitant medication use (type, dose and duration) at 6 & 12 months

TRIAL DESIGN

- **Design**

A pragmatic, observer-blind, multi-centre, stratified, 2-arm, parallel group randomised controlled trial with an internal pilot.

- **Participant Population and Sample Size**

648 participants, aged 18 years or above, will be recruited from secondary NHS mental health services across the UK.

- **Setting**

Secondary and tertiary community or inpatient mental health services. This is primarily where care is provided for the target population and where the clinical uncertainty is faced.

- **Randomisation**

Participants will be randomised in a 1:1 ratio to one of the two study arms and stratified by diagnosis of psychosis bipolar disorder. Within each stratum the minimisation variables will be recruiting centre, number of previous acute care episodes and previous treatment for ADHD. Study IMP interventions:

- **ADHD stimulant medication:** Lisdexamfetamine 30mg one daily increasing to maximum dose 70mg once daily (if on Fluoxetine halve starting dose) for 12 months
- **ADHD non-stimulant:** Atomoxetine initiated at 40mg daily, increasing to maximum dose 100mg for 12 months

ELIGIBILITY CRITERIA

Inclusion criteria

- Diagnosis of ADHD according to the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5) based on DIVA-5
- Bipolar disorder (Strata 1) OR Psychosis (schizophrenia spectrum disorders) (Strata 2) according to DSM-5 based on MINI 7.0
- Stable (based on clinical judgement) and on suitable mood stabilisers or anti-psychotics
- Males and females aged 18 years and over
- Not currently (or within the last month) on medication for ADHD
- Able to give written informed consent

Exclusion criteria

- ADHD medication contra-indicated
- Currently in an acute episode of bipolar disorder or psychosis
- Severe suicide risk or severe risk of violence to others
- Severe drug seeking behaviour or a current drug / alcohol withdrawal syndrome
- History of epilepsy or seizures
- Congenital or acquired long QT syndrome (LQTS); OR family history of QT prolongation; OR on medication associated with increased risk of QT interval prolongation such as class IA and III anti-arrhythmics, moxifloxacin, erythromycin, methadone, mefloquine, tricyclic antidepressants or cisapride.
- Currently taking CYP2D6 inhibitors e.g., quinidine, terbinafine
- Participating in another interventional or conflicting/incompatible clinical trial
- Females of child-bearing age only:
  - Pregnant. *Note: Spot urine test will be performed at screening and/or randomisation to rule out pregnancy in females of child-bearing age*
  - Not willing to take highly effective contraceptive measures to prevent pregnancy during the study participation period AND for 30 days following administration of the last trial medication dose.

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PATIENT IDENTIFICATION

(1) Pre-existing patients

Potential participants who are currently under the care of secondary mental health services with either a history of psychosis or bipolar disorder and a pre-existing diagnosis of ADHD who are not currently taking ADHD medication or who have not taken ADHD medication within the last month.

- Patients seen routinely under secondary care
- Discuss caseload with clinical research team to consider whether eligible for SNAPPER trial.

(2) New patients

Patients with a diagnosis of psychosis or bipolar disorder and are on maintenance medication that do not currently have a diagnosis of ADHD.

- Screen hospital waiting lists for patients with clinical suspicion of ADHD and complete **Adult ADHD Self-Report Scale (ASRS)** as per standard practice to consider whether full diagnosis is warranted.
- ASRS can be completed in 5 minutes at face-to-face appointment or by the patient at home and returned to the clinician.

Discuss study at routine clinic visit and provide potential participant PIS & ICF

If patient interested in participating, invite for screening visit to conduct diagnostic screening assessments and confirm full eligibility for randomisation

KEY POINTS

- Pragmatic study designed in line with current clinical practice and patient visits.
- Adopted by the CRN portfolio so access to the NIHR CRN Study Support Service and NHS support costs available.
- Patients provided payment in recognition of their time in trial participation (3 visits x £25 each) and costs towards per prescription payment.
- Mental health advisory consultants on board to provide participating Trusts bespoke trial support and advice (remotely).
- Remote patient consent and assessments conducted if preferred by Site/ as necessary (BP & pulse rate monitors provided for patient at-home use).
- No pharmacy involvement as IMP is an off-the-shelf product which can be dispensed from any community or hospital pharmacy.
- Training package on all diagnostic screenings assessments and measures available for all RAs/CSOs.
- Sites provided tablet/iPad for SNAPPER online data entry.

INTERNAL PILOT OBJECTIVES

Stop/Go Traffic light system criteria:

After 9 months of recruitment, the stop/go criteria will be assessed for each stratum independently. At this point, we anticipate that we will have recruited 17% of the total recruitment target. Therefore, the internal pilot recruitment target is 56 for each stratum (112 overall).

GREEN	≥7 centres open	≥99% of target participant recruitment met	Progress to full trial.
AMBER	5-6 centres open	60%-98% of target participant recruitment met	Discuss feasibility with Trial Steering Committee (TSC) and develop improvement plans. Aspects evaluated to guide enhancing recruitment will include: number of eligible patients identified, percentage of patients randomised and reasons for non-randomisation, recruitment site performance, and review of recruitment procedures.
RED	<5 centres open	<60% of the target participant recruitment	Discuss cessation of the strata with the TSC and NIHR.

CURRENT STATUS

Current trial status: Approvals in place; Site's open and Site set-up ongoing

Regulatory approvals: REC approval: 14th Jan 2022, HRA approval: 19th Jan 2022, Confirmation of CTA: 25th Jan 2022

First Site open: April 2022 (original Sept 2021)

Recruitment start: May 2022 (original Sept 2021)

End of target recruitment: October 2024 (original March 2024)

Number of participating sites in set-up for internal pilot: 6

Total number of participating sites required overall: 13+

We are welcoming on board new Sites. Please get in touch at the details below if you wish to participate.

STUDY REFERENCE INFORMATION

Sponsor: University of Birmingham

IRAS ID: 1003970

CPMS ID: 49907

Sponsor Ref No.: RG_19_246

REC Ref No.: 21/SW/0172

ISRCTN: 79796233

EUDRACT: 2021-000302-21

REC Name: Central Bristol

STUDY CONTACTS

The SNAPPER Trial Team

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