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Olanzapine for young people with anorexia nervosa

Submission date
06/04/2022

Recruitment status
No longer recruiting

Registration date
27/04/2022

Overall study status
Completed

Last Edited
15/11/2024

Condition category
Mental and Behavioural Disorders

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Anorexia is a life-threatening eating disorder that is characterized by self-starvation and excessive weight loss. The present treatments for anorexia are not really helping severely ill people with anorexia. Many doctors prescribe medications that are not approved for treating anorexia; however, it is unclear whether these drugs are safe or help at all. Researchers talked to patients, their families and leading experts about their views on drugs that could help with anorexia and have evaluated what has been written on the subject by experts. Olanzapine appears to be a helpful and safe medication; it may help with anorexic thoughts, low mood, sleep and anxieties, which are considered important factors for patients. Olanzapine has also been shown to help increase weight gain; however, further evidence is required. It is not currently approved for anorexia. The researchers have gathered a team with strong expertise in anorexia and mental health medicines. The team includes patients with lived experience of anorexia. A twin study will be conducted by the University of Sydney (Australia). The data from both studies will be input into a shared database.

Who can participate?
Patients with anorexia in the UK who are aged 12–24 years, can safely take olanzapine and have not gained sufficient weight under specialist treatment.

What does the study involve?
Participants are recommended to take olanzapine for a 12-month period. The researchers will determine how many patients need to be asked to recruit, who will agree to take part, receive olanzapine as a normal prescription alongside their usual treatment, and assess whether olanzapine has helped them. In addition to questionnaires, physical examinations and laboratory investigations are planned. A researcher will have in-depth talks with the study participants to find out about their experience, why they agreed/did not agree to olanzapine, and why they took it for 12 months or stopped. Participants will be examined after 8 and 16 weeks, after 6 months and after 12 months. At each timepoint, doctors will review the treatment together with the patients and make a decision on whether to continue with olanzapine. After this preliminary study, they will be able to determine whether the methods they intend to use to measure outcomes work. Once the researchers have the above information, they can prepare a larger study with over 300 participants. This number will be necessary to draw firm conclusions. The

findings will be published in journals in cooperation with patients with anorexia, and presented at patients' and carers' meetings, and scientific conferences. Interested participants will be kept up to date with the study progress. Before applying for this larger study, the researchers will discuss the full research plan with patients, carers and experts.

What are the possible benefits and risks of participating?
There may or may not be direct benefits from taking part in this study. However, the researchers have reviewed the literature, and olanzapine is the medication with the highest chance to help with anorexia nervosa.
It is hoped that the information learned from this study will increase general knowledge about anorexia nervosa and its treatment with olanzapine and assist others with the condition, as well as help in determining better treatment options for patients with anorexia nervosa.
Olanzapine is usually well tolerated. As with any medication, there is the possibility that participants may experience some side effects. Here are the side effects which are expected to appear in at least 1% of study participants.
Sleepiness/Sedation: There is a risk that of feeling sleepy when taking this medication, or a risk of fatigue which is like tiredness. Olanzapine is usually prescribed as an evening or night medication in order to help improve sleep.
Low blood pressure: There is a risk of a drop in blood pressure when standing from a seated or lying position.
Weight gain and increased appetite: There is a risk of experiencing increased appetite and gaining weight when taking the study medication. Some weight gain is, however, intended as part of the treatment of anorexia nervosa. The olanzapine tablets themselves do not include calories. The weight gain is a consequence of increased food intake.
Blood count changes: Olanzapine can cause changes in blood cells. For example, eosinophilia may appear, which is a higher-than-normal level of eosinophils, a type of disease-fighting white blood cell. Other potential blood count changes include leukopenia and neutropenia, which means lower-than-normal levels of white blood cells or neutrophils, which is another subgroup of disease-fighting white blood cells. For this reason, the researchers will obtain laboratory parameters for the study assessments.
Other changes in laboratory parameters: Other potential changes of laboratory parameters include transient elevated liver function tests (high aminotransferases or high gamma glutamyltransferase), increases in cholesterol, blood sugar or triglycerides in blood, or increases in alkaline phosphatase, uric acid or creatine phosphatase. These laboratory parameters will be checked during study visits.
Movement problems: There is a very low risk that participants may develop Parkinsonism. The signs of this are tremor, muscle stiffness, slow movement, and abnormal balance. Other potential movement problem is the feeling of inner restlessness or an inability to sit still (akathisia) or the feeling of physical weakness (asthenia).
Because the effects of olanzapine on an unborn child are not fully known, participants should not become pregnant while on this study. Effective methods of contraception (barrier methods such as male condom, female condom, cervical cap, diaphragm, contraceptive sponge) should be used to avoid pregnancy from the day participants sign consent up to the last dose of study drug, and for 7 days after dosing stops. Use of these methods of contraception may cause discomfort or side effects. It is not known whether olanzapine or its metabolites are excreted in human milk therefore participants should not breastfeed while taking this medication.
Whereas many participants find answering the questionnaires for this study interesting or challenging, some individuals may experience minor anxiety. It is possible that interview questions or questionnaires relating to your psychiatric history may also elicit minor distress. To minimise this, the researchers are providing information about the content and type of the questions participants will be asked in the information sheets. There will always be a clinician available to the participants during the interview and completion of the questionnaires if they

need support or to talk to them. Members of the research team will remain sensitive to signs of distress and will check the participants' mental state and safety upon completion of the processes at each encounter.

Where is the study run from?
King's College London (UK)

When is the study starting and how long is it expected to run for?
January 2021 to November 2023

Who is funding the study?
National Institute for Health Research (NIHR) (UK)

Who is the main contact?
Dr Olena Said
olena.said@kcl.ac.uk

Contact information

Type(s)
Scientific

Contact name
Dr Hubertus Himmerich

ORCID ID
http://orcid.org/0000-0003-1209-6073

Contact details
Institute of Psychiatry, Psychology & Neuroscience (IoPPN)
King's College London
London
United Kingdom
SE5 8AF
+44 (0)20 7848 0187
hubertus.himmerich@kcl.ac.uk

Type(s)
Scientific

Contact name
Ms Olena Said

ORCID ID
http://orcid.org/0000-0003-1090-839X

Contact details
King's College London
103 Denmark Hill
London
United Kingdom

SE5 8AF
+44 (0)20 7836 5454
olena.said@kcl.ac.uk

Additional identifiers

EudraCT/CTIS number
2021-004598-30

IRAS number
295297

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
CPMS 51657, IRAS 295297

Study information

Scientific Title
Olanzapine for young PEople with aNorexia nervosa (OPEN): an open-label feasibility study to test recruitment, treatment acceptance, adherence, safety, and outcome measures assessment and patients' experience to prepare for a definitive randomised placebo-controlled trial

Acronym
OPEN

Study objectives
The hypothesis of this feasibility study: a randomized controlled trial to test treatment with olanzapine in young people with anorexia nervosa is feasible.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 10/03/2022, Health and Social Care Research Ethics Committee B (HSC REC B, Office for Research Ethics Committees Northern Ireland (ORECNI), Customer Care & Performance Directorate, Unit 4, Lissue Industrial Estate West, Rathdown Walk, Moira Road, Lisburn, BT28 2RF, UK; +44 (0)28 95361400; email: not provided), ref: 22/NI/0010

Study design
Non-randomized; Interventional; Design type: Treatment, Drug

Primary study design
Interventional

Secondary study design
Non randomised study

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
See trial outputs table

Health condition(s) or problem(s) studied
Anorexia nervosa (AN)

Interventions
This is a one-arm open treatment design, there is no placebo and no comparator. The initial olanzapine dosage will start at 1.25 mg/day or 2.5 mg/day in adolescent patients and continue this dose or increase the dose slowly to up to 10 mg/day (in 1.25 or 2.5 mg/day increments each week for adolescents and 2.5 mg/day for adults). In adults, the start dose will be 2.5 mg/day. Olanzapine will be taken orally in the form of tablets. The treatment duration is 12 months. Participants will be examined at baseline, and at 8 weeks, 16 weeks, 6 months and 12 months after the start of treatment. Beyond the trial assessment 12 months after baseline, no long-term follow-up assessments are planned.

Recruitment will take place at specialist CAMHs and adult eating disorder units in inpatient, outpatient, and daycare settings.

Qualitative interviews will examine the decision-making process among an estimated 30 participants who either agree or decline to participate in the trial. After consent to participate in OPEN has been obtained or declined, participants will be given a participant information sheet for the qualitative interview and asked for verbal consent to be contacted by the qualitative research assistant who will follow up with a phone call to answer questions and schedule one-off appointments.

The aim of the screening process is to ascertain whether inclusion and exclusion criteria are met. The clinical research team will update the eCRF with the following information about the potential participant after informed consent is obtained:
1. Age
2. Gender
3. Diagnosis of AN
4. Level of nonresponse to TAU
5. Potential serious self-harm, suicidality, psychotic disorder
6. Serious medical comorbidities which are contraindications for olanzapine
7. Current alcohol or illicit drug use disorder
8. Use of major tranquilliser or opioids
9. QTc time
10. Liver function tests or white cell count
11. Use of other medication at a stable dose for <4 weeks
12. Use of medication potentially interacting with olanzapine
13. Pregnancy test, willingness to take further pregnancy tests after 8 weeks, 16 weeks, 6 months, and 12 months and to take contraceptive measures as specified in section 8.10. on trial restrictions (females of childbearing potential only)
14. Breastfeeding

15. Capacity of the adult participant or the adolescent participant and their legal representatives to agree to the study

To obtain this information and thus determine inclusion and exclusion criteria, a full psychiatric and medical history taking, physical examination and assessment will take place.

Trial assessments will take place 8 weeks, 16 weeks, 6 months, and 12 months after baseline with an appointment of approximately 3 hours and will take place in person at trial sites. They include:

Clinical examinations
1. Psychiatric and physical examination
2. Weight, height, blood pressure (BP), body temperature
3. Laboratory parameters
4. Body temperature
5. Electrocardiogram (ECG)

Treatment as Usual check
1. Treatment elements checklist
2. Concomitant medications

Adherence measures
1. Olanzapine plasma level
2. Pill count

Psychopathology measures
1. Eating Disorder Examination-Questionnaire (EDE-Q)
2. Depression Anxiety Stress Scales (DASS); adolescents: Revised Children's Anxiety and Depression Scale (RCADS)
3. Revised Beliefs about Voices Questionnaire (BAVQ-R; A/a>15 years)
4. Self-Regulation of Eating Behaviour Questionnaire (SREBQ)
5. Yale-Brown Obsessive-Compulsive Scale (Y-BOCS/CY-BOCS)
6. Columbia Suicide Severity Rating Scale (C-SSRS)

Rating and documentation of side effects
1. UKU-Side Effect Rating Scale (UKU-SERS)
2. Epworth Sleepiness Scale (ESS/ESS-CHAD)

Health economy and quality of life
1. EQ-5D™
2. Child, Adolescent and Adult Service Use Schedule (CAA-SUS)
3. Eating Disorders Symptom Impact Scale (EDSIS)

Qualitative research
1. Experience of treatment and the trial, including motivation for adherence/nonadherence (after 16 weeks only)

Questions on RCT
1. Willingness to take part in an RCT (double-blind; after 6 and after 12 months only)

Beyond the trial assessment 12 months after baseline which is described above, no long-term follow-up assessments are planned.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Olanzapine

Primary outcome measure
The feasibility of carrying out such a trial to inform a future definitive RCT, assessed using:
1. The proportion of patients in different settings (adolescent/adult, inpatient/daycare/ outpatient) who
1.1. Agree to take olanzapine (un-blinded, real-life conditions) at baseline
1.2. Adhere to olanzapine at week 8, week 16, 6 months, 12 months
1.3. Complete all study assessments and questionnaires at baseline, week 8, week 16, 6 months, 12 months
2. The quality of reporting of adverse events at baseline, week 8, week 16, 6 months, 12 months

Secondary outcome measures
The feasibility of data collection procedures for the following measures:
1. Demographics, smoking, alcohol, and substance abuse measured using interviews and ASSIST questionnaires at baseline
2. Body weight and BMI measured using the formula BMI = kg/m² at baseline, week 8, week 16, 6 months, 12 months
3. Eating disorder psychopathology measured using EDE-Q, BAVQ-R, SREBQ questionnaires at baseline, week 8, week 16, 6 months, 12 months
4. General psychopathology measured using DASS/RCADS, Y-BOCS/CY-BOCS, C-SSRS questionnaires at baseline, week 8, week 16, 6 months, 12 months
5. Health economic and quality of life measured using ESS/ESS-CHAD questionnaire at baseline, week 8, week 16, 6 months, 12 months, and EQ-5D, CAA-SUS, EDSIS questionnaires at baseline, 6 months and 12 months
6. Drug adherence measured using questionnaire, pill count at 6 weeks, 16 weeks, 6 months, 12 months, olanzapine plasma level at 8 weeks
7. Drug safety measured using adverse events at baseline, week 8, week 16, 6 months, 12 months
8. Qualitative methods will be used to explore attitudes around willingness or refusal to participate in this feasibility and a potential blinded, placebo-controlled RCT through qualitative interviews at baseline and 16 weeks for those who agree to take part in the trial and at baseline for those who decline

Overall study start date
01/01/2021

Completion date
30/11/2023

Eligibility

Key inclusion criteria

1. Adolescent or young adults (12-24 years old)
2. Receiving inpatient, day care or outpatient treatment
3. Diagnosed with AN, or atypical AN, according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5)
4. Patients have gained <2 kg within at least 1 month of TAU. Outpatients should have attended ≥4 therapeutic sessions. 2 kg within the time frame of at least 1 month appears most appropriate to predict further therapy response or non-response to the current treatment according to our systematic review and meta-analysis on early response and treatment outcome prediction
5. The patient can read and write in English
6. Written informed consent to participate

Participant type(s)
Patient

Age group
Mixed

Sex
Both

Target number of participants
Planned Sample Size: 55; UK Sample Size: 55

Key exclusion criteria
1. Serious self-harm, suicidality, psychotic disorder, serious medical comorbidities (as detailed below) which are contraindications for olanzapine
2. Current alcohol or illicit drug use disorder
3. On major tranquilliser or opioids
4. QTc interval >450 ms (two separate ECG measurements)
5. A QTc interval >500 ms in the ECG or rises by more than 60 msec from baseline or other severe cardiac side effects will stop study participation of this patient
6. A QTc interval >500 ms in the ECG or rises by more than 60 msec from baseline or other severe cardiac side effects in more than one patient in the feasibility study will lead to a stop of the study
7. Alerting liver function tests or white cell count
7.1. Bilirubin >40
7.2. Alkpase >200
7.3. AsT >80
7.4. ALT >90
7.5. GGT >90
8. On other medication at stable dose for <4 weeks
9. On medication interacting with olanzapine
10. Pregnancy
11. No willingness to pregnancy test (females of childbearing potential)
12. No willingness to take effective contraceptive measures as specified under section 8.10. on trial restrictions. The participant information and consent sheet include a section on pregnancy and appropriate birth control measures (females of childbearing potential).
13. Breastfeeding
14. Insufficient understanding of the trial/lack of capacity to agree to the trial procedures as

assessed by the responsible clinician
15. Hypersensitivity to olanzapine or to any of its excipients
16. Taking part in another pharmacological trial for AN
17. Involvement in research that includes contraindications for treatment with olanzapine

Serious self-harm means one of the following:
1. Recent (within the last 12 months) self-harm with suicidal intent
2. Recent self-harm with the risk to a person's own life (e.g., drug intake, deep cutting, burning, swallowing sharp items)
3. Recent self-harm which could lead, or has led, to long-lasting impairment of one's health and functioning

Serious medical comorbidities which are contraindications for olanzapine mean one of the following:
1. Coronary heart disease
2. Cerebrovascular disease
3. Parkinson's disease, parkinsonism or dementia
4. Hepatic or renal impairment

The researchers will examine and document all physical and mental comorbidities that are not exclusion criteria. For example, mood disorders, obsessive-compulsive disorder, anxiety disorders and personality disorders are common co-morbidities which are not exclusion criteria.

Date of first enrolment
30/04/2022

Date of final enrolment
31/05/2023

Locations

Countries of recruitment
Australia

England

United Kingdom

Study participating centre
Maudsley Hospital
Denmark Hill
London
United Kingdom
SE5 8AZ

Study participating centre

Bethlem Royal Hospital
Monks Orchard Road
Beckenham
United Kingdom
BR3 3BX

Study participating centre
Warwick Hospital
Lakin Road
Warwick
United Kingdom
CV34 5BW

Study participating centre
Vincent Square Eating Disorder Service
1 Nightingale Pl
London
United Kingdom
SW10 9NG

Study participating centre
Farnham Road Hospital - Day Care Programme
Albert Suite
Farnham Road Hospital
Farnham Road
Guildford
United Kingdom
GU2 7LX

Study participating centre
Eating Disorders Service for Adults – West Surrey
Albert Suite
Farnham Road Hospital
Farnham Road
Guildford
United Kingdom
GU2 7LX

Study participating centre
Eating Disorders Service for Adults – East Surrey
Loughta House

West Park Road
Epsom
United Kingdom
KT19 8NX

Study participating centre
Springfield University Hospital
61 Glenburnie Road
London
United Kingdom
SW17 7DJ

Study participating centre
The Children and Young People's Emotional Wellbeing and Mental Health Service – Community Eating Disorder Service
Willow
St Ebba's
Hook Road
Epsom
United Kingdom
KT19 8QJ

Sponsor information

Organisation
King's College London

Sponsor details
c/o Reza Razavi
Room 5.31
James Clerk Maxwell Building
57 Waterloo Road
London
England
United Kingdom
SE1 8WA
+44 (0)207 8483224
reza.razavi@kcl.ac.uk

Sponsor type
University/education

Website

http://www.kcl.ac.uk/index.aspx

ROR
https://ror.org/0220mzb33

Funder(s)

Funder type
Government

Funder Name
NIHR Evaluation, Trials and Studies Co-ordinating Centre (NETSCC); Grant Codes: NIHR130780

Results and Publications

Publication and dissemination plan
It is intended that the results of the study will be presented at national/international conferences, charities, as well as service user & carers meetings. Trial design and results will be published in open-access peer-reviewed journals at around 30/10/2024, as well as KCL/NHS press offices, scientific journals, and the NIHR HTA Journal. The trial results will be shared with and published in collaboration with the research team at the University of Sydney. Interested participants will be routinely informed about the study and updates related.

Intention to publish date
31/12/2025

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be stored in a non-publicly available repository. During the trial, the anonymized data will be put into a shared database (managed by King's Clinical Trials Unit (KCTU) and shared with the University of Sydney). Upon request, KCTU will provide a copy of the final exported dataset to the CI in .csv format and the CI will onward distribute as appropriate for archiving, etc. Following publication, the participant-level data will be available upon reasonable request from the CI.

IPD sharing plan summary
Stored in non-publicly available repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	version 1.1	04/03/2022	19/04/2022	No	Yes
Protocol file	version 1.1	24/02/2022	19/04/2022	No	No
HRA research summary			28/06/2023	No	No
Protocol file	version 1.3	02/12/2022	01/11/2023	No	No

Results article	07/11/2024	15/11/2024	Yes	No