Received: 12 May 2023 | Revised: 13 December 2023 | Accepted: 30 December 2023

DOI: 10.1002/erv.3060

WILEY

RESEARCH ARTICLE

Olanzapine for young PEople with aNorexia nervosa (OPEN): A protocol for an open-label feasibility study

Olena Said[1] | **Ece Sengun Filiz**[2] | **Dominic Stringer**[3] | **Briana Applewhite**[1] | **Vanessa Kellermann**[4] | **Hiba Mutwalli**[1,5] | **Sevgi Bektas**[1] | **Melahat Nur Akkese**[1] | **Ashish Kumar**[1,6] | **Ben Carter**[3] | **Mima Simic**[7] | **Dilveer Sually**[1] | **Jessica Bentley**[1] | **Allan H. Young**[1,7] | **Sloane Madden**[8] | **Sarah Byford**[4] | **Sabine Landau**[3] | **Vanessa Lawrence**[4] | **Janet Treasure**[1,7] | **Ulrike Schmidt**[1,7] | **Dasha Nicholls**[2] | **Hubertus Himmerich**[1,7]

[1]Department of Psychological Medicine, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK

[2]Division of Psychiatry, Department of Brain Sciences, Imperial College London, London, UK

[3]Department of Biostatistics and Health Informatics, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK

[4]Department of Health Service and Population Research, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK

[5]Department of Clinical Nutrition, College of Applied Medical Sciences, Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia

[6]Mersey Care NHS Foundation Trust, Merseyside, UK

[7]South London and Maudsley NHS Foundation Trust, London, UK

[8]University of Sydney, Sydney, New South Wales, Australia

Correspondence
Olena Said, PO59 Section of Eating Disorders, Institute of Psychiatry, Psychology & Neuroscience, King's College London, De Crespigny Park, London SE5 8AD, UK.
Email: olena.said@kcl.ac.uk

Handling Editor: Andreas F. K. Karwautz

Funding information
National Institute for Health Research Evaluation, Trials and Studies Coordinating Centre Health Technology Assessment Programme, Grant/Award Number: NIHR130780

Abstract

Introduction: Antipsychotics are routinely prescribed off-label for anorexia nervosa (AN) despite limited evidence. This article presents a protocol of a study aiming to assess the feasibility of a future definitive trial on olanzapine in young people with AN.

Methods and analysis: In an open-label, one-armed feasibility study, 55 patients with AN or atypical AN, aged 12–24, receiving outpatient, inpatient or day-care treatment who are considered for olanzapine treatment will be recruited from NHS sites based in England. Assessments will be conducted at screening, baseline and at 8-, 16 weeks, 6- and 12 months. Primary feasibility parameters will be proportions of patients who agree to take olanzapine and who adhere to treatment and complete study assessments. Qualitative methods will be used to explore acceptability of the intervention and study design. Secondary feasibility parameters will be changes in body mass index, psychopathology, side effects, health-related quality of life, carer burden and proportion of participants who would enrol in a future randomised controlled

trial. The study is funded by the National Institute for Health Research via Health Technology Assessment programme.

Discussion: Olanzapine for young PEople with aNorexia nervosa will inform a future randomised controlled trial on the efficacy and safety of prescribing olanzapine in young people with AN.

KEYWORDS
anorexia nervosa, feasibility, olanzapine, weight restoration

Highlights

- There is a lack of evidence for the use of pharmacological treatment in anorexia nervosa (AN).
- The Olanzapine for young PEople with aNorexia nervosa study will assess the feasibility of exploring the safety and efficacy of olanzapine in adolescents and young adults with AN.
- The study will inform a future randomised controlled trial on the efficacy and safety of prescribing olanzapine for AN.

1 | INTRODUCTION

Anorexia nervosa (AN) is a serious mental disorder with high mortality, morbidity and treatment costs, specifically in young women. Prevalence is 1%–4% among women (Keski-Rahkonen & Mustelin, 2016), and peak incidence is between 14 and 17 years (Solmi et al., 2022). AN frequently coexists with depressive disorder, anxiety disorders and obsessive-compulsive disorder (OCD; Tan et al., 2023). Such comorbidities increase the burden of disease, and the impact on families and carers is devastating. The course is often chronic, leading to persistent disability (Schmidt et al., 2016). A recent longitudinal cohort study showed that only ~30% of patients with AN recovered after 9 years, although prognosis may be better in early onset AN (Eddy et al., 2017). The dietary deficit is accompanied by significant physical health issues, such as growth retardation, osteopenia, amenorrhoea and renal insufficiency, changes in laboratory parameters, cardiac and thyroid dysfunction (Treasure, 2004). The most common causes of death are sudden cardiac death associated with ventricular arrhythmias and suicide (Birmingham & Treasure, 2019). Mortality rates are nearly six times that of the general population (Schmidt et al., 2016).

While olanzapine is recommended by guidelines published in Australia (Hay et al., 2014), Germany (Association of the Scientific Medical Societies in Germany, 2010) and the Netherlands (Dutch Foundation for Quality Development in Mental Healthcare, 2017) for the short-term treatment of obsessional thinking in AN, none of the current guidelines, including the National Institute for Health and Care Excellence (NICE) for England and Wales recommend the use of psychotropic drugs for the promotion of weight gain due to limited evidence (National Institute for Health and Care Excellence, 2017).

Treatment for AN needs improvement, and antipsychotics may offer an additional avenue for this, although further research is required (Attia et al., 2019). In the UK and globally, practitioners routinely prescribe antipsychotics off-label for AN despite uncertainty regarding the efficacy and safety of antipsychotics in this patient group (Mutwalli et al., 2023). Moreover, published studies regarding antipsychotics for AN do not cover changes in general psychopathology, cost-effectiveness or quality-of-life-related aspects of treatment (Han et al., 2022).

A recent metanalysis concluded that olanzapine showed efficacy in AN treatment regarding weight gain in adults, but its effect on psychopathology and in adolescents remains unclear (Han et al., 2022; Himmerich et al., 2023). Five randomised controlled trials (RCTs) examined olanzapine as an SGA for AN. In 2007, Brambilla et al. published the findings of a double-blind, placebo-controlled, multicentre trial of olanzapine in 35 outpatients aged 18–35 years old with AN (Brambilla et al., 2007). In addition to weight, outcomes included scores of the Hamilton Depression Scale (HAM-D) and Yale-Brown-Cornell Eating Disorder Scale (YBC-EDS). Patients with the binge-purging subtype gained weight significantly during olanzapine treatment. The olanzapine group also showed significant improvements in psychopathology, specifically in HAM-D and in compulsive symptoms on the YBC-EDS. In another RCT by Bissada et al. (2008), 34 patients aged 17–41

received either 2.5–10 mg/day olanzapine or placebo for 10 weeks. Olanzapine led to more rapid weight gain, with a greater proportion of patients reaching their target body mass index (BMI), and faster decrease in obsessive symptoms, measured by the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS). Olanzapine lacked any significant effect on the symptoms of depression, anxiety or compulsions. Kafantaris et al. (2011) published a small RCT with 15 young patients (12–21 years) in which the treatment group received 2.5–10 mg/day olanzapine for 10 weeks. There were no significant differences in weight gain, ED symptoms or general psychopathology assessments between groups, as measured using the Eating Disorder Examination Questionnaire (EDE-Q), YBC-EDS, HAM-D and Brief Psychiatric Rating Scale. Attia et al. (2019) published an RCT in 2011 involving 17 outpatients over 16 years old, treated with 2.5–10 mg/day olanzapine or placebo for 8 weeks. Patients on olanzapine achieved a significantly greater increase in body weight, with no differences in several scales measuring ED and general psychopathology. The largest RCT on olanzapine for AN was published in 2019 by Attia et al. (2019) and included 152 outpatients, aged 16–65 years with a BMI of 14–18.5 kg/m^2. The treatment group received 2.5–10 mg/day olanzapine for 16 weeks. Significantly higher weight gain was found in olanzapine group (6.7 kg), compared with the placebo group (4.2 kg) after 16 weeks. There were no significant differences between groups in ED or general psychopathology.

The Olanzapine for young PEople with aNorexia nervosa (OPEN) study will target patients aged 12–24 years, which includes the age range of peak incidence of AN (Solmi et al., 2022) and represents the group at highest risk for developing ED and with the highest chance of remission if treatment is started promptly (Attia et al., 2011).

According to the literature, olanzapine is the SGA with the highest likelihood to restore weight (Borges et al., 2020). It may also treat important psychological and emotional symptoms in AN safely, owing to the following:

- Olanzapine is known to have a beneficial influence on anxiety (Temmingh & Stein, 2015) and sleep (Kluge et al., 2014). A survey of 36 patients with AN and 37 carers demonstrated they would welcome pharmacological treatment to help with anxiety and sleep disturbances (Dessain et al., 2019).
- Olanzapine is shown to increase appetite (Himmerich et al., 2015), and in patients with schizophrenia, clozapine and olanzapine cause the most weight gain among antipsychotic agents (Tek et al., 2016). However, clozapine can have severe side effects and requires stricter monitoring.

Thus, we have decided to test olanzapine in this feasibility study. However, all previous studies of olanzapine in AN had shortcomings, including small samples, focusing mainly on weight gain rather than changes in psychopathology and the quality of life of patients and carers, and lack of economic measures.

2 | STUDY AIMS

The primary aim is to assess the feasibility of a future definitive trial on olanzapine in young people with AN, looking at primary feasibility parameters: rates of participant recruitment, adherence to olanzapine, completion of study assessments at five timepoints, quality of adverse event (AE) reporting, and the acceptability of the intervention and study design by participants and their family/carers.

The secondary aims are to test the feasibility of specific data collection procedures at each timepoint and assess willingness to participate in a future blinded, placebo-controlled RCT.

3 | METHODS AND ANALYSIS

The study is protocolised and will be reported in accordance with Standard Protocol Items: Recommendations for Interventional Trials guidance and the Consolidated Standards of Reporting Trials statement extension for randomised pilot and feasibility trials (Eldridge et al., 2016).

3.1 | Study design

OPEN is an open-label feasibility study of 55 participants with AN who will be treated with olanzapine and followed up for 12 months. Outcomes will be assessed at baseline, 8 weeks, 16 weeks, 6 months and 12 months after starting olanzapine. Due to the one-arm open treatment design, there will be no randomisation, blinding, placebo or comparator.

3.2 | Participants

3.2.1 | Recruitment

Recruitment will take place in Children and Adolescent and Adult specialist eating disorder (ED) services in inpatient, outpatient and day-care settings at 11 NHS Trusts in England, which offer local and national ED services.

Patients identified as suitable candidates will receive written and verbal information about the study. Following providing informed written consent, participants will be screened for inclusion; eligible participants will carry on with baseline assessment and will be prescribed olanzapine by their treating psychiatrists or general practitioner.

3.2.2 | Eligibility criteria

Participants will be screened for eligibility to enter the study. The inclusion and exclusion criteria are listed in Table 1.

Serious self-harm will include any of following:

- Recent (within the last 12 months) self-harm with suicidal intent;
- Recent self-harm with risk to life (e.g., drug intake, deep cutting, burning, swallowing sharp items);
- Recent self-harm which could lead, or has led, to long lasting impairment of health and functioning.

Serious medical comorbidities that will be considered contraindications for olanzapine will mean any of following:

- Coronary heart disease;
- Cerebrovascular disease;
- Parkinson's disease, parkinsonism or dementia;
- Hepatic or renal impairment.

3.3 | Sample size

A reasonable sample size for a feasibility study can lie between 30 and more than 50 participants (Arain et al., 2010; Sim & Lewis, 2012). To address the aims, the feasibility study should cover: willingness to accept and adhere to the intervention; a demonstration that adherence can be

TABLE 1 Olanzapine for young PEople with aNorexia nervosa inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
• Adolescent or young adults (12–24 years old)	• Serious self-harm, suicidality, psychotic disorder, serious medical comorbidities (detailed below) that are contraindications for olanzapine
• Receiving inpatient, day-care or outpatient treatment	• Current alcohol or substance use disorder
• Diagnosed with AN, or atypical AN, according to DSM-5	• On major tranquilliser or opioids
• Having gained <2 kg within at least 1 month of treatment as usual (TAU). Outpatients should have attended ≥4 therapeutic sessions	• Electrocardiogram (ECG) changes representing contraindications for olanzapine: QTc interval >450 milliseconds (ms) on two separate ECGs
• The patient can read and write in English	• Alerting liver function tests or white blood cell (WBC) count (Treasure, 2004): - Bilirubin >40 μmol/L - Alkaline phosphatase (ALP) >200 U/L - Aspartate aminotransferase (AST) >80 U/L - Alanine aminotransferase (ALT) >90 U/L - Gamma-glutamyl transferase (GGT) >90 U/L - White blood cells (WBC) <2.0 × 109/L - Mean corpuscular volume (MCV) >120 fL
• Written informed consent provided	• On other psychopharmacological medication at stable dose for <4 weeks • On medication interacting with olanzapine • Pregnancy or breastfeeding • Of childbearing potential and unwilling to have pregnancy tests • Objecting to taking effective contraceptive measures • Insufficient understanding of the trial/lack of capacity to agree to the trial procedures as assessed by the responsible clinician • Hypersensitivity to olanzapine or any of its excipients • Taking part in another pharmacological trial for AN • Involvement in research that includes contraindications for treatment with olanzapine

measured; estimated numbers of young people potentially eligible for recruitment; key parameters of a potential future trial to include a justification of the choice and timing of an appropriate primary outcome measure.

A sample size calculation was made based on estimating the feasibility parameter 'rate of adherence': assuming that 70% of patients took olanzapine for at least 16 weeks, a sample size of 55 patients can estimate a 95% confidence interval (CI) for this parameter with 12.2% margin of error (i.e., expected CI from 57.8% to 82.2%; for a more extreme attrition rate of 50% the margin of error increases to 13.3%).

3.4 | Intervention

In this study, olanzapine will be prescribed off-label for AN. Olanzapine will be used open-label in form of tablets or dispersible tablets, of 2.5, 5, 7.5 or 10 mg, from any brand/manufacturer with a marketing authorisation, in original packaging.

Olanzapine will be initiated at 1.25 or 2.5 mg/day in adolescents. In adults, the starting dose will be 2.5 mg/day. Patients can maintain this dose if clinically deemed sufficient. This dosage is within the British National Formulary limits. A slow titration schedule of weekly increments of 1.25 or 2.5 mg/day for adolescents and 2.5 mg/day for adults, up to a maximum of 10 mg/day for both, will be followed. This dose range would also apply in an RCT. A similar down-titration schedule should apply at the end of treatment with olanzapine to improve patient safety. However, it will be a clinical decision whether patients continue or stop olanzapine.

3.5 | Concomitant care

Olanzapine will be added to treatment as usual (TAU). TAU is currently defined by NICE Guidelines on ED (National Institute for Health and Care Excellence, 2017) and Quality Network for Eating Disorders Quality Standards for Community Eating Disorder Services (Royal College of Psychiatrists, 2022).

TAU will include:

- Specialist treatment by ED services;
- Psychoeducation and psychological treatment, for example, cognitive-behavioural therapy for eating disorders, family therapy for anorexia nervosa, the Maudsley Model of Anorexia Nervosa Treatment for Adults, specialist supportive clinical management, adolescent-focused therapy for anorexia nervosa, focal psychodynamic therapy;
- Monitoring of weight, mental and physical health;
- Family members' or carers' involvement;
- Dietary advice.

TAU will not necessarily include psychopharmacological medication. For this study, there will be no specific requirements for TAU, and TAU elements will be logged for each participant.

3.6 | Trial procedure

Participants will be screened and if found eligible, will take part in study assessments at five timepoints. Participants will be invited to participate in a qualitative interview at baseline and after 16 weeks. All assessments will be conducted by study researchers and the patients' clinical teams. During study-related activities and olanzapine treatment, a trusted adult (e.g., parent, carer or clinical staff member) will accompany children aged 12–15 years. The study schedule is presented in Figure 1.

3.7 | Outcome assessment

Figure 2 outlines the schedule of events at each timepoint in detail.

3.7.1 | Primary feasibility parameters

The following parameters will be used to assess the feasibility of a future definitive trial:

- *Participant recruitment*: This will be assessed by the proportion of people who are recruited out of the total sample size required, as well as the proportion of people who are recruited out of people that were approached and screened. This will inform ability to recruit sufficient numbers for a future definitive trial.
- *Adherence to olanzapine treatment*: This will be measured at each follow up time point (8 weeks, 16 weeks, 6 months and 12 months) using several different measures (self-reported adherence, pill count and olanzapine plasma levels) and reported as proportion of the sample who adhered to treatment according to each measure. This will inform the acceptability of treatment through adherence.
- *Completion of baseline and follow up assessments*: Completion and withdrawal (from treatment and/or data collection) rates will be reported for each assessment. This will inform the feasibility of timing of primary outcome and sample size calculation for a future trial.

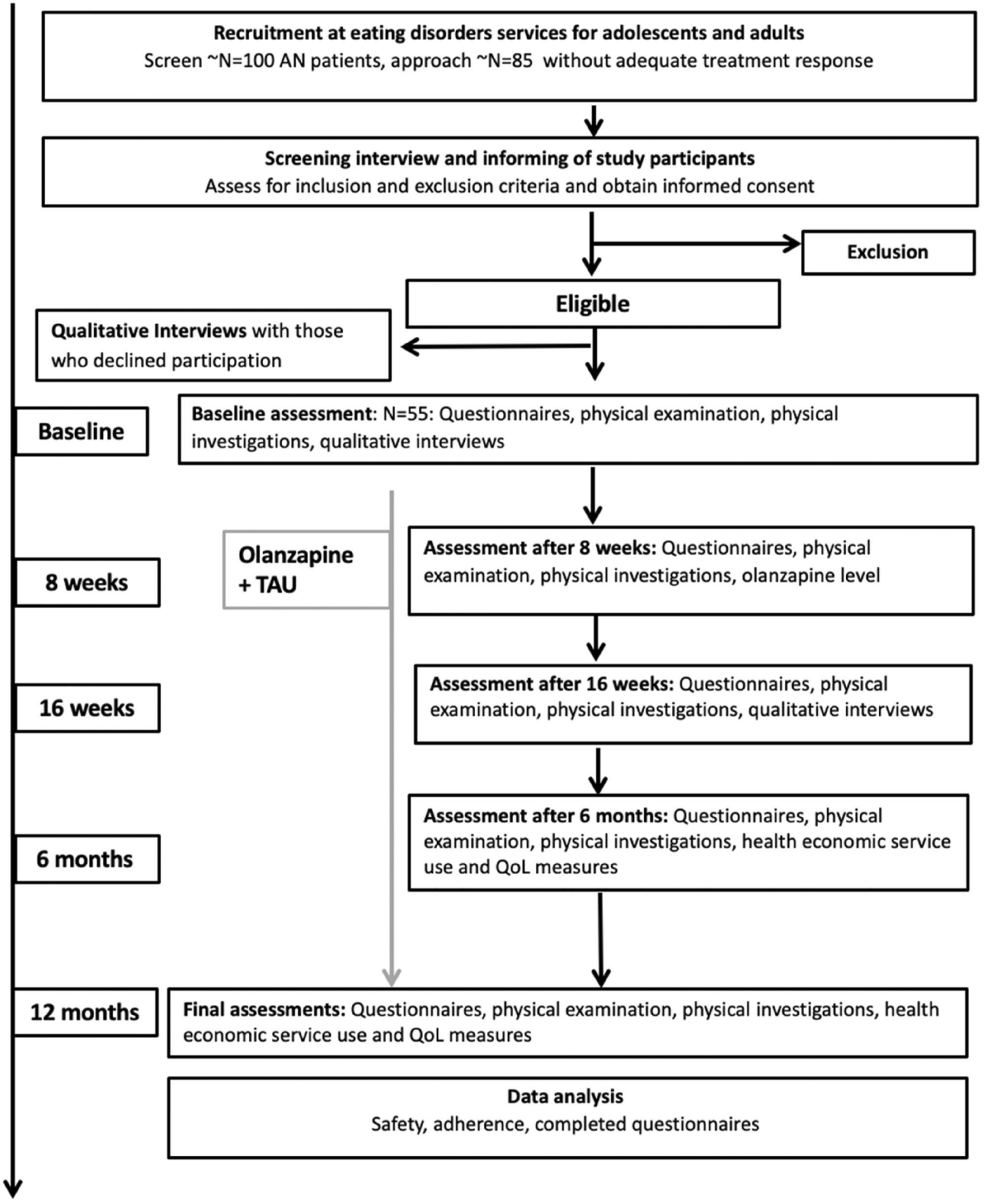

FIGURE 1 Olanzapine for young PEople with aNorexia nervosa time schedule of participants.

- *Quality of AE reporting*: This will be examined by reporting rates of AEs over time (and comparing rates to similar studies) and the completeness of supporting information.

Feasibility measures will be broken down by different recruitment settings (adolescent/adult, outpatient/inpatient/day-care) to inform potential settings for the future trial.

Methods/Assessments	Screening	Baseline (≤ 7-10 days following Screening)	8 weeks (±7 days)	16 weeks (±7 days)	6 months (±7 days)	12 months (±7 days)
Informed Consent	X†					
Clinical Examinations						
- Inclusion/Exclusion Criteria	X†					
- Psychiatric and physical examination	X†,‡		X†,‡	X†,‡	X†,‡	X†,‡
- Weight, height, blood pressure (BP), body temperature	X†,‡	X†,‡	X†,‡	X†,‡	X†,‡	X†,‡
- Laboratory parameters	X†,‡		X†,‡	X†,‡	X†,‡	X†,‡
- Electrocardiogram (ECG)	X†,‡		X†,‡	X†,‡	X†,‡	X†,‡
- Concomitant Medications	X†	X†	X†	X†	X†	X†
- Serum Pregnancy Test	X†,‡		X†,‡	X†,‡	X†,‡	X†,‡
IMP dispensing		X†,‡	X†,‡	X†,‡	X†,‡	
Screening for Drug or Alcohol Abuse Disorders						
- Alcohol, Smoking and Substance Involvement Screening Test (ASSIST)		X†				
Treatment as Usual						
- Treatment elements checklist		X†	X†	X†	X†	X†
Adherence measures						
- Olanzapine plasma level			X†,‡			
- Pill count			X†,‡	X†,‡	X†,‡	X†,‡
AE recording/reporting			X†	X†	X†	X†
- UKU Side Effects Rating Scale			X†	X†	X†	X†
Eating Disorders Psychopathology						
- Eating Disorder Examination-Questionnaire (EDE-Q)		X†	X†	X†	X†	X†
- Revised Beliefs about Voices Questionnaire (BAVQ-R)		X†	X†	X†	X†	X†
- Self-regulation of Eating Behaviour Questionnaire (SREBQ)		X†	X†	X†	X†	X†
General Psychopathology						
- Depression Anxiety Stress Scales (DASS/RCADS)		X†	X†	X†	X†	X†
- Yale-Brown Obsessive-Compulsive Scale (Y-BOCS/CY-BOCS)		X†	X†	X†	X†	X†
- Columbia Suicide Severity Rating Scale (C-SSRS)		X†	X†	X†	X†	X†
Rating and Documentation of Side Effects						
- Epworth Sleepiness Scale (ESS/ESS-CHAD)		X†	X†	X†	X†	X†
Health Economic and Quality of Life						
- EQ-5D-Y™		X†			X†	X†
- Child, Adolescent and Adult Service Use Schedule (CAA-SUS)		X†			X†	X†
- Eating Disorders Symptom Impact Scale (EDSIS)		X†			X†	X†
Qualitative Research						
- Patient experience: Interview with those who consent to trial participation		X§				
- Patient experience: Interview with those who declined to participate in trial		X§				
- Experience of treatment and the trial (including adherence/nonadherence)				X§		
Questions on RCT						
- Willingness to take part in an RCT (double-blind)		X†			X†	X†

FIGURE 2 Olanzapine for young PEople with aNorexia nervosa study schedule of events. The superscript numbers indicate who will perform the assessments †, researcher; ‡, patient's clinical team; §, qualitative researcher. [Colour figure can be viewed at wileyonlinelibrary.com]

3.7.2 | Secondary feasibility parameters

(i) Feasibility (rates of completeness) of recording the following measures, when applicable, at baseline, 8 weeks, 16 weeks, 6 months and 12 months:
- Demographics and the Alcohol, Smoking and Substance Involvement Screening Test
- Height, weight and BMI
- ED psychopathology questionnaires
- General psychopathology questionnaires
- Health economic and quality of life assessments
- Olanzapine plasma level
- Physical examination measures
- ECG, laboratory parameters
- Measure of sleepiness

This will be separate to the overall completeness of assessments as participants may not complete all measures at each assessment.

(ii) Willingness to participate in a future blinded, placebo-controlled RCT: Participants will be asked this at baseline and at the end of the study; the proportion willing will be reported.

3.7.3 | Additional measures

- *TAU*: TAU elements will be logged for each participant, including frequency, length and setting.
- Concomitant medications will be logged so the commonly used medications and comorbidities can be explored and any impact on action of olanzapine discussed.

3.7.4 | Qualitative feasibility measures

Participants' experience of recruitment and treatment, acceptability, reluctance to take olanzapine and reasons for adherence and non-adherence: these will be ascertained in qualitative interviews.

3.8 | Measures

3.8.1 | Body weight and BMI

Weight and height will be measured objectively, and BMI calculated at baseline, 8 weeks, 16 weeks, 6 months and 12 months and adjusted for age and gender in adolescent patients.

3.8.2 | ED psychopathology

Eating Disorder Examination Questionnaire (EDE-Q): EDE-Q will be used to assess key behavioural features and associated psychopathology of ED (Luce & Crowther, 1999). It includes four subscales: restraint, weight concern, shape concern and eating concern.

Revised Beliefs About Voices Questionnaire (BAVQ-R; >15 years): BAVQ-R is a self-report measure of a patient's beliefs, emotions and behaviour about auditory hallucinations (Chandwick et al., 2000). People with AN often report experiencing an internal 'anorexic voice' that comments on the individual's eating, weight and shape, and instructs them to restrict eating or compensate for it (Pugh & Waller, 2017). BAVQ-R will provide information about patients' emotional and behavioural reactions to these voices, and allow conclusions not only about the content and form, but also about the meaning given to these hallucinations (Pugh & Waller, 2017).

Self-regulation of Eating Behaviour Questionnaire (SREBQ): SREBQ is a self-report measure of a patient's capacity for management of behaviour, thoughts, feelings, attention and environment in the pursuit of personal goals and measuring change in response to self-regulation interventions in adults (Boekaerts et al., 2005). It will give additional information on food cravings, dietary restraint and capacity for self-regulation (Kliemann et al., 2016).

3.8.3 | General psychopathology

As AN is associated with mood disorders, anxiety disorders and OCD (Tan et al., 2023) and shows an overlap with schizophrenia on a symptomatic and genetic level (Bulik-Sullivan et al., 2015), we will include scales for general psychopathology.

Depression Anxiety Stress Scale (DASS): DASS (Brown et al., 1997) is a 42-item instrument designed to measure the three related negative emotional states of depression, anxiety and stress. It is widely used in research and evaluated in large clinical samples (Brown et al., 1997).

For adolescents, we will use the *Revised Children's Anxiety and Depression Scale (RCADS)* which is a 47-item questionnaire measuring the frequency of various symptoms of anxiety and low mood. It produces a total anxiety and depression score, and separately scores sub-scales of separation anxiety, social phobia, generalised anxiety, panic, obsessive compulsive, total anxiety and low mood (Chorpita et al., 2005). It is commonly used in adolescent studies.

Yale-Brown Obsessive-Compulsive Scale (Y-BOCS): Y-BOCS (Goodman et al., 1989) is a clinician-administered 10-item scale designed to measure the severity and type of symptoms of OCD. It is sensitive to changes in OCD symptoms and used extensively in clinical studies (Costa et al., 2017). For adolescents, we will use the adapted version, Children's Yale-Brown Obsessive-Compulsive Scale.

Columbia Suicide Severity Rating Scale (C-SSRS): C-SSRS is a suicidal ideation rating scale created to evaluate suicidality in adolescents and adults (from 12 years) (Posner et al., 2011). It is used successfully for research in both adolescent and adult populations (van Duijin et al., 2017; Wolfe et al., 2019).

3.8.4 | Health economic and quality of life assessment of patients and carers

EQ-5D™: is a standardised instrument developed by the EuroQol Group as a measure of health-related quality-of-life that can be used in a wide range of health conditions and treatments. It has a descriptive system, comprising five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. It has been widely used (Batóg et al., 2018; Wille et al., 2010). In OPEN, we will use the youth version of the three-level EQ-5D adapted for children and young people, the EQ-5D-Y (Byford, 2013).

Child and Adolescent Service Use Schedule (CA-SUS) and Adult Service Use Schedule (AD-SUS): Are measures designed to record service use in mental health populations and have been used successfully in several mental health trials (Kuyken et al., 2015). For OPEN, a combined child, adolescent and adult version (CAA-SUS) was designed to cover the age range of the study. The CAA-SUS will cover the number and duration of hospital and community-based health and social care contacts. It will be collected at baseline, 6 and 12 months. At baseline, information will cover the previous 3 months. At each follow-up, service use since the previous assessment will be recorded.

Eating Disorders Symptom Impact Scale (EDSIS): This was developed to assess the specific caregiving burden of AN and bulimia nervosa (Sepulveda et al., 2008).

3.8.5 | Drug adherence measures

Olanzapine plasma level: This will be measured at 8 weeks after starting olanzapine (Hiemke et al., 2011). An independent physician with immediate access to results will inform the study team if any results exceed the upper limit (Hiemke et al., 2018).

Pill count: The number of dosage units taken/not taken at each follow-up visit will be counted and used as an indirect measure of adherence. In outpatients, this will be a self-reported measure. We are aware that removal of a dosage unit does not mean that the medication was taken, that it does not characterise the adherence pattern and that it is unable to identify causes of adherence or non-adherence. Therefore, pill count will be used in addition to olanzapine plasma level (Lam & Fresco, 2015).

3.8.6 | Drug safety measures

Adverse effects: We will measure possible adverse effects in a structured, standardised manner. As there are no existing guidelines concerning use of antipsychotics in AN, we included the clinical outcome measures of adverse effects based on the World Federation of Societies of Biological Psychiatry Guidelines for Biological Treatment of Schizophrenia (Hasan et al., 2013).

- *Physical examination*:
  - Weight
  - Blood pressure and pulse
  - Body temperature
- *ECG*: A QTc interval >450 ms confirmed by a second ECG or an otherwise seriously abnormal ECG (Arain et al., 2010) will be an exclusion criterion. A QTc interval >500 ms or a rise by >60 ms from baseline or other severe cardiac side effects will stop participation of that patient. A QTc interval >500 ms or rises by >60 ms from baseline or other severe cardiac side effects in more than one patient will lead to a stop of recruitment into the study.
- *Laboratory parameters*: Alterations are common in AN, including electrolytes, liver enzymes, kidney parameters, leucocyte count and haemoglobin. Additionally, medical problems secondary to AN, or due to treatment itself, may cause abnormalities. Olanzapine may change metabolic parameters, including cholesterol, glucose, and blood fats (Himmerich et al., 2015). Therefore, the following will be checked at baseline, 8, 16 weeks, 6 and 12 months:
  - Electrolytes and salt/water balance
  - Kidney function
  - Liver function
  - Blood count
  - Glucose and lipid profile
  - Pregnancy test in women
- *UKU-Side Effect Rating Scale (UKU-SERS)*: This is a general rating scale for a broad range of side effects of psychotropic medication (Lingjærde et al., 1987), developed by the task force of Scandinavian College of Neuropsychopharmacology on the development of rating scales and methodological issues in psychopharmacological research.
- *Epworth Sleepiness Scale (ESS)*: Is a self-administered questionnaire measuring the general level of daytime sleepiness (Johns, 1991) and is used in clinical studies. Starvation results in the fragmentation of sleep and a reduction of slow-wave sleep, and thus abnormalities in sleep efficiency and architecture (Lauer & Krieg, 2004). On one hand, daytime sleepiness is a common side effect of antipsychotics, and olanzapine specifically is known to induce moderate somnolence (Lauer & Krieg, 2004), on the other hand, it has been shown to lead to an improvement of sleep (Himmerich et al., 2015) and may thus reduce AN-associated daytime sleepiness.

3.8.7 | Qualitative examination of acceptability

Qualitative interviews will examine the acceptability of the intervention and study design, both in principle and in practice, from the perspective of young people with AN, family members and healthcare professionals across treatment settings. We will invite young people with AN who either decline or agree to participate in OPEN study to take part in a qualitative interview. Our intention will be to explore perspectives across a range of participant characteristics, including gender, age, ethnicity, recruitment source, BMI at baseline and adherence. Recruitment will continue until we have achieved information power, providing sufficiently rich and diverse data to answer our research question (Malterud et al., 2016).

At recruitment, participants will be asked why they chose to take part or not. Interviews will examine the decision-making process and the perceived risks and advantages of taking olanzapine within the study. Those who are recruited to OPEN will also be interviewed after the 16-week assessment about their subsequent experiences of olanzapine treatment and study design, including the perceived burden of completing outcome measures and attitudes towards randomisation in a future clinical trial. We will offer interviews to people who adhered to olanzapine as well as people who chose to discontinue. Carers/parents will be invited to contribute their views after the 16 weeks assessment, with the participant's consent. A further 10–15 interviews with healthcare professionals across settings will explore the perceived challenges and facilitators to recruitment and retention. The data will provide insight into the barriers of trial inclusion, ways in which trial procedures could be improved to optimise recruitment and retention, and the value and

expectations that patients, families and healthcare professionals place on olanzapine as a treatment for AN.

Figure 2 provides a synopsis and schedule of all assessments. We have listed many outcome parameters; however, given the multiple comorbidities of AN and potential side effects of olanzapine, these parameters make sense clinically.

3.9 | Data analysis

Feasibility outcomes will be analysed with mixed-methods analysis utilising summary statistics and qualitative analysis.

3.9.1 | Feasibility parameter estimation

Summary statistics will be presented for feasibility parameters and may include estimation of CIs where appropriate:

- Number of patients approached, screened and included in study (including the proportion of people who are recruited of the total sample size required as well as the proportion of people who are recruited of people that were approached and screened)
- Adherence, measured separately by a self-reported questionnaire, pill counts and olanzapine plasma levels (reported as rates and continuous measures)
- Retention, that is, rates of withdrawal from olanzapine treatment and from data collection
- Completion of assessments at each timepoint (including completion of individual measures)
- Number of AEs and serious adverse events (SAEs) reported

Summary statistics for feasibility parameters will be broken down by different recruitment settings (adolescent/adult and outpatient/inpatient/day-care).

3.9.2 | Reporting of descriptives

Summary statistics will be reported for the following measures at each timepoint: demographics, alcohol, smoking and substance use, body weight and BMI, ED psychopathology, general psychopathology, service use and quality-of-life life assessments, laboratory parameters (kidney function, liver function, blood count, glucose, and lipid profile), drug adherence and safety.

Additional safety outcomes which will be reported include:

- Summary statistics on 'concerning' and 'alerting' laboratory and ECG parameters;
- Descriptives of other safety parameters;
- Summary of reported AEs and SAEs.

Additionally, elements of TAU will be described.

3.9.3 | Exploratory analyses

We will perform exploratory analyses looking at change over time in weight, BMI, eating psychopathology and other measures to inform a future definitive study design. Appropriate longitudinal modelling approaches will be used.

3.9.4 | Qualitative analysis

Qualitative analysis will use the Framework Approach (Ritchie et al., 1994) to facilitate analysis within and between individual cases and groups of participants. The thematic framework will draw on a priori issues around the acceptability of the intervention and study design, but also be responsive to emergent themes.

3.10 | Patient and public involvement

Before this study, we recruited two people with lived experience of AN, one being a co-applicant; had two independent focus groups; spoke to service users individually; recorded statements, developed questionnaires with experts by experience of AN to assess patient and carer views and conducted a survey (Dessain et al., 2019).

Patient and public involvement made significant contribution to ideas (e.g., extending the recruitment to outpatient and day-care services), decisions and drawing up of the study proposal, and will continue to guide the study until publication and presentation of the results as members of the Trial Management Group (TMG) and Trial Steering Committee (TSC). Furthermore, one of the qualitative researchers involved in the study has lived experience of AN.

4 | TRIAL MANAGEMENT

The trial management duties will be fulfiled by TMG for day-to-day running of the trial; TSC for monitoring trial progress and conduct; Data Monitoring and Ethics Committee for reviewing progress and safety and providing advice to TSC on the conduct of the trial.

5 | PROGRESSION FROM A FEASIBILITY STUDY TO A RANDOMISED CONTROLLED TRIAL

Progression will be considered in the following conditions:

- If (Go Criteria):
  - 55 participants are recruited, treated and followed up for 12 months
  - ≥41 (~75%) patients say that they would take part in an RCT
  - ≥41 (~75%) patients continue in the study for 12 months
  - Olanzapine is well tolerated
  - Assessments can be performed as planned or can be easily modified
  - The mean increase in BMI over 12 months is at least 1 kg/m^2; this parameter will define treatment response because it is associated with improved quality of life
- Not if: >1 patient fulfils one of the stop criteria as described under safety outcomes.

6 | DISCUSSION

In clinical practice, olanzapine is widely used off-label for AN, including for weight restoration (Beykloo et al., 2019; Mutwalli et al., 2023). This is not reciprocated in clinical guidelines as olanzapine is not currently recommended for weight restoration in AN by the most recent guidelines for ED treatment (Association of the Scientific Medical Societies in Germany, 2010; Dutch Foundation for Quality Development in Mental Healthcare, 2017; Hay et al., 2014; National Institute for Health and Care Excellence, 2017). There is a limited evidence base for the use of pharmacological treatment in AN (Attia et al., 2019). The OPEN study was designed to assess the feasibility of exploring the safety and efficacy of pharmacotherapy in adolescents and young adults with AN, having designated olanzapine as the agent with the highest likelihood of success. The OPEN study will inform a future RCT to bridge the gap in knowledge on olanzapine for weight restoration in AN.

This study has strengths and limitations. Most importantly, it will provide useful insight into the feasibility of conducting an RCT on use of olanzapine for treatment of AN in adolescents and young adults. Being a non-commercial study funded by NIHR and relying on the contributions of NHS ED services that underwent severe strain throughout the COVID-19 pandemic, we anticipate difficulties with achieving recruitment targets in a timely fashion. This might impact our study size, which was already relatively modest due to being a feasibility study with limited resources. OPEN will include participants from various treatment settings (inpatient, outpatient and day-care). While the aim of this approach is to maximise participant recruitment, we are aware that the needs and differences in therapeutic interventions applied in different treatment settings could influence the study results.

Additionally, although this study's exploratory aims are to assess weight change, general and ED psychopathology, health economic and quality of life outcomes of olanzapine treatment, it is not designed to investigate the possible mechanisms of action and efficacy of olanzapine. Instead, the primary objective is to assess the feasibility of recruitment and treatment of participants to target. Therefore, while patients will be included into the study according to the inclusion and exclusion criteria, as the study was designed in a real-world approach, we have chosen not to question established ED diagnoses. Instead, we will use EDE-Q as a standardised measure of ED psychopathology and not as a tool to check patients' respective ED diagnosis. Similarly, we will not use standardised diagnostic assessments to diagnose comorbid psychopathology (e.g., the Kiddie Schedule for Affective Disorders and Schizophrenia for children or Structured Clinical Interview for DSM I or II for adults).

From the perspective of safety, several risk mitigation strategies will be in place. As a precaution, we will exclude patients with known serious self-harm or suicidality from the study. This decision is based on the report by Attia that three patients in the olanzapine arm were withdrawn due to suicidal ideation or a suicide attempt compared to none in the placebo arm (Attia et al., 2011). Additionally, throughout the study, we will monitor the participants in terms of suicidal ideation and behaviour using a standardized tool (C-SSRS) to mitigate the risks around suicidality.

We have included a single olanzapine plasma level measurement as a drug safety and adherence measure and as per the real-life setting of the study. In patients with AN, the therapeutic olanzapine plasma levels are unknown. However, a recently published study by Karwautz et al. reports therapeutic drug monitoring in adolescents with AN treated with adjunct olanzapine (Karwautz et al., 2023). Therefore, we have used the general clinical guidance on Therapeutic Drug Monitoring by the Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie e.V. (AGNP) to identify a range for plasma level (Hiemke et al., 2018). According to the AGNP guidelines, the olanzapine plasma level should be between 20 and 80 ng/mL (Hiemke et al., 2018). Due to budget limitations, we have

included a measurement of olanzapine plasma levels after 8 weeks of treatment even though it would potentially be beneficial to measure plasma levels more frequently from a pharmacokinetic perspective. Plasma levels of psychopharmacological medications have been largely neglected in research and would potentially constitute an excellent focus of future studies.

The assessments of the proposed study take place at baseline, 8, 16 weeks, 6, and 12 months. The complete length of previous RCTs testing olanzapine in AN were 8 weeks (National Institute for Health and Care Excellence, 2017), 10 weeks (Bissada et al., 2008), 3 months (Brambilla et al., 2007) and 16 weeks (Attia et al., 2019). After 16 weeks, only 55% were still taking olanzapine (Attia et al., 2019). Therefore, we added only two more time points to our study protocol, at 6 months and at 12 months after baseline which means that there is a substantial gap between 6 and 12 months. However, the researchers will document the date when study participants stop olanzapine if they decide to do so with their clinicians and carers. Additionally, patients will be regularly seen, and the medication will be continuously reviewed by their clinicians. According to the termination of olanzapine over time during this feasibility study, we will review whether an additional time point after 9 months might be scientifically relevant for a full RCT.

AUTHOR CONTRIBUTIONS

The chief investigators are Hubertus Himmerich for the UK and Sloane Madden for Australia. All authors were involved in study conception and design. Olena Said, Ece Sengun Filiz, Dominic Stringer, Briana Applewhite and Hubertus Himmerich drafted the study protocol. The study protocol was based on the application (written by Dasha Nicholls, Mima Simic, Dilveer Sually, Jessica Bentley, Allan H. Young, Sarah Byford, Sabine Landau, Vanessa Lawrence, Janet Treasure, Ulrike Schmidt, Hubertus Himmerich and Sloane Madden) in response to the UK's NIHR HTA call 19/76 'Antipsychotics for anorexia nervosa' and the application (written by Sloane Madden and Hubertus Himmerich) in response to the 2019 NHMRC-NIHR Collaborative Research Grant Scheme. All authors reviewed the paper, informed subsequent drafts and approved its final version.

ACKNOWLEDGEMENTS

US, JT, SL and HH receive salary support from NIHR Biomedical Research Centre at South London and Maudsley NHS Foundation Trust (SLaM) and KCL. SL is also supported by the Applied Research Collaboration (ARC), South London. DN is supported by the NIHR ARC Northwest London, and the NIHR Imperial BRC. The views expressed are those of the authors and not necessarily those of the NIHR, the National Health Service (NHS), the Department of Health and Social Care, or the NHMRC. We thank the NIHR Research Design Service London for their advice on the study design. We additionally thank the members of the Data Monitoring Committee (Dr. John Roche, Dr. Charlotte Scott, Ms. Rebecca Woolley) and the Trial Steering Committee (Dr. Helen E. Bould, Prof Paul Robinson, Dr. Michael Kluge, Dr. Stephany Fulda, Ms. Jessica Bentley, Ms. Aylin Unlu) for contributing their time and valuable expertise to the oversight of the project. This study has been funded by the National Institute for Health Research (NIHR) Evaluation, Trials and Studies Coordinating Centre (NETSCC) Health Technology Assessment (HTA) Programme (project reference NIHR130780). King's College London (KCL) is the lead sponsor and South London and Maudsley NHS Foundation Trust (SLaM) is the co-sponsor for this study. The sponsors act as data controllers. OPEN has a separate sister study planned in Australia, which aims to recruit 15 participants. The study was planned in two countries to allow for differences in healthcare systems and care processes to be explored. The study protocols are largely similar, with separate ethics approval, funding and sponsorship. The Australian part of the study was approved by the Sydney Children Hospitals Network Human Research Ethics Committee (HREC reference 2021/ETH01321) on 20 September 2021 and has been funded by the National Health and Medical Research Council (NHMRC). The sponsor is the University of Sydney. The current protocol article refers exclusively to the OPEN study performed in the UK.

CLINICAL TRIAL REGISTRATION

This study has been registered with the International Standard Randomised Controlled Trial Number (ISRCTN) register and has the unique identification number ISRCTN80075010. Current Protocol version 1.3; 2 December 2022.

CONFLICT OF INTEREST STATEMENT

No competing interests have been declared.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Olena Said https://orcid.org/0000-0003-1090-839X
Ece Sengun Filiz https://orcid.org/0000-0002-8779-3351
Janet Treasure https://orcid.org/0000-0003-0871-4596
Hubertus Himmerich https://orcid.org/0000-0003-1209-6073

REFERENCES

Arain, M., Campbell, M. J., Cooper, C. L., & Lancaster, G. A. (2010). What is a pilot or feasibility study? A review of current practice and editorial policy. *BMC Medical Research Methodology*, *10*(1), 1–7. https://doi.org/10.1186/1471-2288-10-67

Association of the Scientific Medical Societies in Germany. (2010). Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften, AWMF. *S3-guideline for the assessment and therapy of eating disorders [S3 Leitlinie Diagnostik und Therapie von Essstörungen]*, 051–26.

Attia, E., Kaplan, A. S., Walsh, B. T., Gershkovich, M., Yilmaz, Z., Musante, D., & Wang, Y. (2011). Olanzapine versus placebo for out-patients with anorexia nervosa. *Psychological Medicine*, *41*(10), 2177–2182. https://doi.org/10.1017/s0033291711000390

Attia, E., Steinglass, J. E., Walsh, B. T., Wang, Y., Wu, P., Schreyer, C., Wildes, J., Yilmaz, Z., Guarda, A. S., Kaplan, A. S., & Marcus, M. D. (2019). Olanzapine versus placebo in adult outpatients with anorexia nervosa: A randomized clinical trial. *American Journal of Psychiatry*, *176*(6), 449–456. https://doi.org/10.1176/appi.ajp.2018.18101125

Batóg, P., Rencz, F., Péntek, M., Gulácsi, L., Filipiak, K. J., Prevolnik Rupel, V., Simon, J., Brodszky, V., Baji, P., Závada, J., Petrova, G., Rotar, A., & Golicki, D. (2018). EQ-5D studies in cardiovascular diseases in eight Central and Eastern European countries: A systematic review of the literature. *Kardiologia Polska*, *76*(5), 860–870. https://doi.org/10.5603/kp.a2018.0033

Beykloo, M., Nicholls, D., Simic, M., Brauer, R., Mills, E., & Wong, I. C. (2019). Survey on self-reported psychotropic drug prescribing practices of eating disorder psychiatrists for the treatment of young people with anorexia nervosa. *BMJ Open*, *9*, e031707.

Birmingham, C. L., & Treasure, J. (2019). *Medical management of eating disorders*. Cambridge University Press.

Bissada, H., Tasca, G. A., Barber, A. M., & Bradwejn, J. (2008). Olanzapine in the treatment of low body weight and obsessive thinking in women with anorexia nervosa: A randomized, double-blind, placebo-controlled trial. *American Journal of Psychiatry*, *165*(10), 1281–1288. https://doi.org/10.1176/appi.ajp.2008.07121900

Boekaerts, M., Maes, S., & Karoly, P. (2005). Self-regulation across domains of applied psychology: Is there an emerging consensus? *Applied Psychology*, *54*(2), 149–154. https://doi.org/10.1111/j.1464-0597.2005.00201.x

Borges, K., Lewis, Y. D., Bentley, J., & Himmerich, H. (2020). *Use of antipsychotics in the treatment of eating disorders BT – Neuro-Psychopharmacotherapy* (P. Riederer, G. Laux, T. Nagatsu, W. Le, & C. Riederer, Eds., pp. 1–14). Springer International Publishing.

Brambilla, F., Garcia, C. S., Fassino, S., Daga, G. A., Favaro, A., Santonastaso, P., Ramaciotti, C., Bondi, E., Mellado, C., Borriello, R., & Monteleone, P. (2007). Olanzapine therapy in anorexia nervosa: Psychobiological effects. *International Clinical Psychopharmacology*, *22*(4), 197–204. https://doi.org/10.1097/yic.0b013e328080ca31

Brown, T. A., Chorpita, B. F., Korotitsch, W., & Barlow, D. H. (1997). Psychometric properties of the Depression Anxiety Stress Scales (DASS) in clinical samples. *Behaviour Research and Therapy*, *35*(1), 79–89. https://doi.org/10.1016/s0005-7967(96)00068-x

Bulik-Sullivan, B., Finucane, H. K., Anttila, V., Gusev, A., Day, F. R., & Loh, P. R. (2015). ReproGen Consortium; Psychiatric Genomics Consortium; Genetic Consortium for Anorexia Nervosa of the Wellcome Trust Case Control Consortium, Duncan L, Perry JR, Patterson N, Robinson EB, Daly MJ, Price AL, Neale BM. An atlas of genetic correlations across human diseases and traits. *Nature Genetics*, *47*(11), 1236–1241. https://doi.org/10.1038/ng.3406

Byford, S. (2013). The validity and responsiveness of the EQ-5D measure of health-related quality of life in an adolescent population with persistent major depression. *Journal of Mental Health*, *22*(2), 101–110. https://doi.org/10.3109/09638237.2013.779366

Chandwick, P., Lees, S., & Birchwood, M. (2000). The revised Beliefs About Voices Questionnaire (BAVQ-R). *British Journal of Psychiatry*, *177*(3), 229–232. https://doi.org/10.1192/bjp.177.3.229

Chorpita, B. F., Moffitt, C. E., & Gray, J. (2005). Psychometric properties of the Revised Child Anxiety and Depression Scale in a clinical sample. *Behaviour Research and Therapy*, *43*(3), 309–322. https://doi.org/10.1016/j.brat.2004.02.004

Costa, D. L. C., Diniz, J. B., Requena, G., Joaquim, M. A., Pittenger, C., Bloch, M. H., Miguel, E. C., & Shavitt, R. G. (2017). Randomized, double-blind, placebo-controlled trial of N-acetylcysteine augmentation for treatment-Resistant obsessive-compulsive disorder. *The Journal of Clinical Psychiatry*, *78*(7), 766–773. https://doi.org/10.4088/jcp.16m11101

Dessain, A., Bentley, J., Treasure, J., Schmidt, U., & Himmerich, H. (2019). Patients' and carers' perspectives of psychopharmacological interventions targeting anorexia nervosa symptoms. In H. Himmerich (Ed.), *Jáuregui Lobera I (Hrg.): Anorexia and bulimia nervosa*. InTech Open.

Dutch Foundation for Quality Development in Mental Healthcare. (2017). *Practice guideline for the treatment of eating disorders [Zorgstandaard Eetstoornissen]*. Netwerk Kwaliteitsontwikkeling GGz.

Eddy, K. T., Tabri, N., Thomas, J. J., Murray, H. B., Keshaviah, A., Hastings, E., Edkins, K., Krishna, M., Herzog, D. B., Keel, P. K., & Franko, D. L. (2017). Recovery from anorexia nervosa and bulimia nervosa at 22-year follow-up. *The Journal of Clinical Psychiatry*, *78*(02), 184–189. https://doi.org/10.4088/jcp.15m10393

Eldridge, S. M., Chan, C. L., Campbell, M. J., Bond, C. M., Hopewell, S., Thabane, L., & Lancaster, G. A. (2016). CONSORT 2010 statement: Extension to randomised pilot and feasibility trials. *BMJ*, 355.

Goodman, W. K., Price, L. H., Rasmussen, S. A., Mazure, C., Fleischmann, R. L., Hill, C. L., Heninger, G. R., & Charney, D. S. (1989). The Yale-Brown Obsessive Compulsive Scale. I. Development, use, and reliability. *Archives of General Psychiatry*, *46*, 1006–1011. https://doi.org/10.1001/archpsyc.1989.01810110048007

Han, R., Bian, Q., & Chen, H. (2022). Effectiveness of olanzapine in the treatment of anorexia nervosa: A systematic review and meta-analysis. *Brain Behav*, *12*(2), e2498. https://doi.org/10.1002/brb3.2498

Hasan, A., Falkai, P., Wobrock, T., Lieberman, J., Glenthoj, B., Gattaz, W. F., Thibaut, F., & Möller, H. J. (2013). WFSBP Task force on Treatment Guidelines for Schizophrenia. World Federation of Societies of Biological Psychiatry (WFSBP)

guidelines for biological treatment of schizophrenia, part 2: Update 2012 on the long-term treatment of schizophrenia and management of antipsychotic-induced side effects. *World Journal of Biological Psychiatry*, *14*(1), 2–44. https://doi.org/10.3109/15622975.2012.739708

Hay, P., Chinn, D., Forbes, D., Madden, S., Newton, R., Sugenor, L., Touyz, S., & Ward, W. (2014). Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the treatment of eating disorders. *Australian and New Zealand Journal of Psychiatry*, *48*(11), 977–1008. https://doi.org/10.1177/0004867414555814

Hiemke, C., Baumann, P., Bergemann, N., Conca, A., Dietmaier, O., Egberts, K., Fric, M., Gerlach, M., Greiner, C., Gründer, G., Haen, E., Havemann-Reinecke, U., Jaquenoud Sirot, E., Kirchherr, H., Laux, G., Lutz, U. C., Messer, T., Müller, M. J., Pfuhlmann, B, … Zernig, G. (2011). AGNP consensus guidelines for therapeutic drug monitoring in psychiatry: Update 2011. *Pharmacopsychiatry*, *44*(06), 195–235. https://doi.org/10.1055/s-0031-1286287

Hiemke, C., Bergemann, N., Clement, H., Conca, A., Deckert, J., Domschke, K., Eckermann, G., Egberts, K., Gerlach, M., Greiner, C., Gründer, G., Haen, E., Havemann-Reinecke, U., Hefner, G., Helmer, R., Janssen, G., Jaquenoud, E., Laux, G., Messer, T., … Baumann, P. (2018). Consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology: Update 2017. *Pharmacopsychiatry*, *51*(1–02), 9–62. https://doi.org/10.1055/s-0043-116492

Himmerich, H., Lewis, Y. D., Conti, C., Mutwalli, H., Karwautz, A., Sjögren, J. M., Uribe Isaza, M. M., Tyszkiewicz-Nwafor, M., Aigner, M., McElroy, S. L., Treasure, J., Kasper, S., Bailer, U., Bulik, C. M., Zwaan, M. D., Favaro, A., Fernandez-Aranda, F., Fetissov, S., … Yoshiuchi, K. (2023). World Federation of Societies of Biological Psychiatry (WFSBP) guidelines update 2023 on the pharmacological treatment of eating disorders. *World Journal of Biological Psychiatry*, *24*(8), 1–64. https://doi.org/10.1080/15622975.2023.2179663

Himmerich, H., Minkwitz, J., & Kirkby, K. C. (2015). Weight gain and metabolic changes during treatment with antipsychotics and antidepressants. *Endocrine, Metabolic & Immune Disorders: Drug Targets*, *15*(4), 252–260. https://doi.org/10.2174/1871530315666150623092031

Johns, M. W. (1991). A new method for measuring daytime sleepiness: The Epworth sleepiness scale. *Sleep*, *14*(6), 540–545. https://doi.org/10.1093/sleep/14.6.540

Kafantaris, V., Leigh, E., Hertz, S., Berest, A., Schebendach, J., Sterling, W. M., Saito, E., Sunday, S., Higdon, C., Golden, N. H., & Malhotra, A. K. (2011). A placebo-controlled pilot study of adjunctive olanzapine for adolescents with anorexia nervosa. *Journal of Child and Adolescent Psychopharmacology*, *21*(3), 207–212. https://doi.org/10.1089/cap.2010.0139

Karwautz, A., Zeiler, M., Schwarzenberg, J., Mairhofer, D., Mitterer, M., Truttmann, S., Philipp, J., Koubek, D., Glüder, M., Wagner, G., Malcher, A., Schöfbeck, G., Laczkovics, C., Rock, H. W., Zanko, A., Imgart, H., Banaschewski, T., Fleischhaker, C., Correll, C. U., … Gerlach, M. (2023). Therapeutic drug monitoring in adolescents with anorexia nervosa for safe treatment with adjunct olanzapine. *European Eating Disorders Review*, 1–14. https://doi.org/10.1002/erv.3022

Keski-Rahkonen, A., & Mustelin, L. (2016). Epidemiology of eating disorders in Europe: Prevalence, incidence, comorbidity, course, consequences, and risk factors. *Current Opinion in Psychiatry*, *29*(6), 340–345. https://doi.org/10.1097/yco.0000000000000278

Kliemann, N., Beeken, R. J., Wardle, J., & Johnson, F. (2016). Development and validation of the Self-Regulation of Eating Behaviour Questionnaire for adults. *International Journal of Behavioral Nutrition and Physical Activity*, *13*(1), 1–11. https://doi.org/10.1186/s12966-016-0414-6

Kluge, M., Schacht, A., Himmerich, H., Rummel-Kluge, C., Wehmeier, P. M., Dalal, M., Hinze-Selch, D., Kraus, T., Dittmann, R. W., Pollmächer, T., & Schuld, A. (2014). Olanzapine and clozapine differently affect sleep in patients with schizophrenia: Results from a double-blind, polysomnographic study and review of the literature. *Schizophrenia Research*, *152*(1), 255–260. https://doi.org/10.1016/j.schres.2013.11.009

Kuyken, W., Hayes, R., Barrett, B., Byng, R., Dalgleish, T., Kessler, D., Lewis, G., Watkins, E., Brejcha, C., Cardy, J., Causley, A., Cowderoy, S., Evans, A., Gradinger, F., Kaur, S., Lanham, P., Morant, N., Richards, J., Shah, P, … Byford, S. (2015). Effectiveness and cost-effectiveness of mindfulness-based cognitive therapy compared with maintenance antidepressant treatment in the prevention of depressive relapse or recurrence (PREVENT): A randomised controlled trial. *Lancet*, *386*(9988), 63–73. Epub 2015 Apr 20. Erratum for: Lancet. 2016 Oct 1;388 (10052):1376. PMID: 25907157. https://doi.org/10.1016/S0140-6736(14)62222-4

Lam, W. Y., & Fresco, P. (2015). Medication adherence measures: An overview. *BioMed Research International*, *2015*, 217047. https://doi.org/10.1155/2015/217047

Lauer, C. J., & Krieg, J. C. (2004). Sleep in eating disorders. *Sleep Medicine Reviews*, *8*(2), 109–118. https://doi.org/10.1016/s1087-0792(02)00122-3

Lingjærde, O., Ahlfors, U. G., Bech, P., Dencker, S. J., & Elgen, K. (1987). The UKU side effect rating scale. A new comprehensive rating scale for psychotropic drugs and a cross-sectional study of side effects in neuroleptic-treated patients. *Acta Psychatr Scand*, *76*(Suppl 334), 1–100. https://doi.org/10.1111/j.1600-0447.1987.tb10566.x

Luce, K. H., & Crowther, J. H. (1999). The reliability of the Eating Disorder Examination-Self-Report Questionnaire Version (EDE-Q). *International Journal of Eating Disorders*, *25*(3), 349–351. https://doi.org/10.1002/(sici)1098-108x(199904)25:3<349::aid-eat15>3.3.co;2-d

Malterud, K., Siersma, V. D., & Guassora, A. D. (2016). Sample size in qualitative interview studies: Guided by information power. *Qualitative Health Research*, *26*(13), 1753–1760. https://doi.org/10.1177/1049732315617444

Mutwalli, H., Lewis, Y. D., Conti, C., Treasure, J., & Himmerich, H. (2023). *Pharmacological treatment and eating disorders BT – Eating disorders: An international comprehensive view* (P. Robinson, T. Wade, B. Herpertz-Dahlmann, F. Fernandez-Aranda, J. Treasure, & S. Wonderlich, Eds., pp. 1–22). Springer International Publishing. https://doi.org/10.1007/978-3-030-97416-9_72-1

National Institute for Health and Care Excellence. (2017). *Eating disorders: Recognition and treatment*. Published May 2017, updated December 2020. (Clinical guideline [NG69]). NICE.

Retrieved July 4, 2022, from https://www.nice.org.uk/guidance/ng69

Posner, K., Brown, G. K., Stanley, B., Brent, D. A., Yershova, K. V., Oquendo, M. A., Currier, G. W., Melvin, G. A., Greenhill, L., Shen, S., & Mann, J. J. (2011). The Columbia-Suicide Severity Rating Scale: Initial validity and internal consistency findings from three multisite studies with adolescents and adults. *American Journal of Psychiatry*, *168*(12), 1266–1277. https://doi.org/10.1176/appi.ajp.2011.10111704

Pugh, M., & Waller, G. (2017). Understanding the 'Anorexic Voice' in anorexia nervosa. *Clinical Psychology & Psychotherapy*, *24*(3), 670–676. https://doi.org/10.1002/cpp.2034

Ritchie, J., & Spencer, L. (1994). Qualitative data analysis for applied policy research. In A. Bryman & R. G. Burgess (Eds.), *Analyzing qualitative data*. Routledge.

Royal College of Psychiatrists. (2022). *Quality network for eating disorders (QED) quality standards for adult community eating disorder services [Internet]*. (CCQI 393). RCPsych. Retrieved September 14, 2022, from https://www.rcpsych.ac.uk/docs/default-source/improving-care/ccqi/quality-networks/eating-disorders-qed/qed-community-standards---third-edition.pdf?sfvrsn=e8b3aebc_4

Schmidt, U., Adan, R., Böhm, I., Campbell, I. C., Dingemans, A., Ehrlich, S., Elzakkers, I., Favaro, A., Giel, K., Harrison, A., Himmerich, H., Hoek, H. W., Herpertz-Dahlmann, B., Kas, M. J., Seitz, J., Smeets, P., Sternheim, L., Tenconi, E., van Elburg, A., van Furth, E., & Zipfel, S. (2016). Eating disorders: The big issue. *The Lancet Psychiatry*, *3*(4), 313–315. https://doi.org/10.1016/s2215-0366(16)00081-x

Sepulveda, A. R., Whitney, J., Hankins, M., & Treasure, J. (2008). Development and validation of an Eating Disorders Symptom Impact Scale (EDSIS) for carers of people with eating disorders. *Health and Quality of Life Outcomes*, *6*(1), 28. https://doi.org/10.1186/1477-7525-6-28

Sim, J., & Lewis, M. (2012). The size of a pilot study for a clinical trial should be calculated in relation to considerations of precision and efficiency. *Journal of Clinical Epidemiology*, *65*(3), 301–308. https://doi.org/10.1016/j.jclinepi.2011.07.011

Solmi, M., Radua, J., Olivola, M., Croce, E., Soardo, L., Salazar de Pablo, G., Il Shin, J., Kirkbride, J. B., Jones, P., Kim, J. H., Kim, J. Y., Carvalho, A. F., Seeman, M. V., Correll, C. U., & Fusar-Poli, P. (2022). Age at onset of mental disorders worldwide: Large-scale meta-analysis of 192 epidemiological studies. *Molecular Psychiatry*, *27*(1), 281–295. https://doi.org/10.1038/s41380-021-01161-7

Tan, E. J., Raut, T., Le, L. K.-D., Hay, P., Ananthapavan, J., Lee, Y. Y., & Mihalopoulos, C. (2023). The association between eating disorders and mental health: An umbrella review. *Journal of Eating Disorders*, *11*(1), 51. https://doi.org/10.1186/s40337-022-00725-4

Tek, C., Kucukgoncu, S., Guloksuz, S., Woods, S. W., Srihari, V. H., & Annamalai, A. (2016). Antipsychotic-induced weight gain in first-episode psychosis patients: A meta-analysis of differential effects of antipsychotic medications. *Early Intervention in Psychiatry*, *10*(3), 193–202. https://doi.org/10.1111/eip.12251

Temmingh, H., & Stein, D. J. (2015). Anxiety in patients with schizophrenia: Epidemiology and management. *CNS Drugs*, *29*(10), 819–832. https://doi.org/10.1007/s40263-015-0282-7

Treasure, J. (2004). *A guide to the medical risk assessment for eating disorders*. King's College London, Section of Eating Disorders, Institute of Psychiatry. Retrieved July 5, 2022, from http://www.iop.kcl.ac.uk/sites/edu. Accessed 05 July 2022.

van Duijn, E., Vrijmoeth, E. M., Giltay, E. J., & Bernhard Landwehrmeyer, G. (2017). REGISTRY investigators of the European Huntington's Disease Network. Suicidal ideation and suicidal behavior according to the C-SSRS in a European cohort of Huntington's disease gene expansion carriers. *Journal of Affective Disorders*, *228*, 194–204.

Wille, N., Badia, X., Bonsel, G., Burström, K., Cavrini, G., Devlin, N., Egmar, A. C., Greiner, W., Gusi, N., Herdman, M., Jelsma, J., Kind, P., Scalone, L., & Ravens-Sieberer, U. (2010). Development of the EQ-5D-Y: A child-friendly version of the EQ-5D. *Quality of Life Research*, *19*(6), 875–886. https://doi.org/10.1007/s11136-010-9648-y

Wolfe, K. L., Nakonezny, P. A., Owen, V. J., Rial, K. V., Moorehead, A. P., Kennard, B. D., & Emslie, G. J. (2019). Hopelessness as a predictor of suicide ideation in depressed male and female adolescent youth. *Suicide and Life-Threatening Behavior*, *49*(1), 253–263. https://doi.org/10.1111/sltb.12428

How to cite this article: Said, O., Sengun Filiz, E., Stringer, D., Applewhite, B., Kellermann, V., Mutwalli, H., Bektas, S., Akkese, M. N., Kumar, A., Carter, B., Simic, M., Sually, D., Bentley, J., Young, A. H., Madden, S., Byford, S., Landau, S., Lawrence, V., Treasure, J., … Himmerich, H. (2024). Olanzapine for young PEople with aNorexia nervosa (OPEN): A protocol for an open-label feasibility study. *European Eating Disorders Review*, *32*(3), 532–546. https://doi.org/10.1002/erv.3060