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[Intervention Protocol]

Antipsychotic drugs for anorexia nervosa

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To assess the effects of antipsychotic drugs (both first- and second-generation antipsychotics) compared to placebo on body weight gain, psychological symptoms, acceptability, and adverse events for people with anorexia nervosa.

BACKGROUND

Description of the condition

Anorexia nervosa is an eating disorder typified by body image distortions, an excessive desire to be thin, and diet restriction (APA 2013). Anorexia nervosa presents in two subtypes: restricting or binge-eating/purging types (APA 2013). A diagnosis of anorexia nervosa in the *International Classification of Diseases,* Tenth Revision (ICD-10) requires a minimum 15% body weight reduction below expected values or a body mass index (BMI) of 17.5 or less (WHO 1992). The *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5) describes the severity classification of anorexia nervosa by BMI to be extreme (BMI < 15 kg/m^2), severe (BMI 15 to 15.99 kg/m^2), moderate (BMI 16 to 16.99 kg/m^2), or mild (BMI > 17 kg/m^2) (APA 2013). Anorexia nervosa is not a rare mental illness, having a lifetime prevalence of 0.48% to 0.80% (Hudson 2007; Preti 2009; Udo 2018). Mortality is considerably high compared to other mental illnesses, with a crude mortality rate of 5.1% and a standard mortality ratio of 5.86 (Arcelus 2011; Chesney 2014). Death in people with anorexia nervosa is often caused by malnutrition-related somatic complications, such as arrhythmia and severe infections due to weight loss. Additionally, suicide is another major concern, accounting for about 20% of deaths in people with anorexia nervosa (Arcelus 2011). The etiology of anorexia nervosa is not yet fully elucidated, but multiple factors involving genetic, neurobiological, developmental, psychological, psychosocial, and behavioral factors are considered to be involved with the underlying mechanisms (Treasure 2020; Zipfel 2015).

Description of the intervention

In the treatment of anorexia nervosa, reaching a healthy body weight or BMI through weight gain is one of the primary indicators of treatment success for clinicians/treating teams. Weight gain is key in supporting other physical, psychological, and quality of life changes that are necessary for recovery (NICE 2017). Many intervention approaches are used to gain body weight or BMI. Psychotherapeutic approaches are recommended as the first-line choice, according to treatment guidelines (APA 2006; APA 2012; NICE 2017; RANZCP 2014). A selective network meta-analysis, in which low-quality studies were excluded, suggests that family therapy is the most studied therapy in young people, while individual psychotherapy is the most studied in adults (Zeeck 2018). It also concludes that there is no benefit of one therapeutic approach over another. The methodology of this network meta-analysis made assumptions about treatment efficacy comparisons that have not been directly tested head-to-head in empirical studies (Zeeck 2018). A Cochrane review found some weak evidence to indicate that family therapy might be more efficacious than treatment as usual in the short term (Fisher 2019). However, there is no evidence to support one specific psychological therapy over another (Fisher 2019; Van den Berg 2019). On the contrary, specific psychological therapies are generally no more efficacious than treatment as usual or active control conditions (Fisher 2019; Van den Berg 2019).

Nutritional approaches are also recommended for the treatment of anorexia nervosa in all major treatment guidelines (APA 2006; APA 2012; NICE 2017; RANZCP 2014). However, nutritional counseling alone is considered insufficient because it does not address symptomatic cognitive dysfunction (Pike 2003; Serfaty 1999). While nasogastric feeding and parenteral medication may be urgent treatment options for people in life-threatening conditions due to starvation (Rizzo 2019), such treatments are invasive and often against the individual's will. Because psychotherapies and nutritional therapies have limitations, providers have turned to unconventional alternatives.

Antipsychotic pharmacotherapy is not an approved indication for anorexia nervosa and not officially recommended in the treatment guidelines (APA 2006; APA 2012; NICE 2017; RANZCP 2014). Yet, off-label use (i.e. not licensed by regulatory authorities) of second-generation antipsychotic drugs (SGAs), and especially olanzapine, is not uncommon for adjunctive therapy in clinical settings (Beykloo 2019; Fazeli 2012; Parsons 2009). However, the efficacy of antipsychotic interventions remains unclear.

Antipsychotic drugs are roughly divided into two types. Older or “typical” first-generation antipsychotic drugs (FGAs) include chlorpromazine and haloperidol. Newer or “atypical” second-generation antipsychotics include drugs such as olanzapine, risperidone, and quetiapine. While FGAs strongly block the dopaminergic system, SGAs inhibit dopaminergic, serotonergic, and other neuronal systems. Antipsychotic drugs were used initially for people with schizophrenia spectrum disorders. Because of their broad spectrum of efficacy, SGAs came to be used off-label for the treatment of other mental disorders, such as anxiety disorders, obsessive-compulsive disorder (Maher 2011), autism spectrum disorder (Jobski 2017), and dementia (Gitlin 2012). Compared to FGAs, SGAs are known to be more effective for negative symptoms (absence of things normally present) and are associated with fewer extrapyramidal side effects, a group of adverse drug reactions arising from dysfunction of the extrapyramidal tract, such as dystonia, akathisia, drug-induced Parkinsonism, and tardive dyskinesia.

Weight gain is recognized as one of the side effects of antipsychotic drugs and is seen transdiagnostically (Allison 1999; Bak 2014; Barton 2020; Musil 2015). Antipsychotic-induced weight gain typically occurs quickly in the first few weeks (Tarricone 2010), and reaches a plateau after several months (Hasnain 2012). In addition, weight gain in this early period after initiating antipsychotic drugs predicts longer-term weight gain, especially with females and those with a lower baseline BMI (Pillinger 2020; Vandenberghe 2016).

How the intervention might work

In general, the mechanism of antipsychotic-induced weight gain has not been clearly identified but is considered to be multifactorial. Likewise, in people with anorexia nervosa, antipsychotic drugs are thought to increase body weight for multiple reasons. One rationale suggests antipsychotic drugs affect the improvement of obsessive-compulsive and delusional thoughts, especially those related to body image and food refusal (Dold 2015). Another suggests SGAs combine actions on histaminergic, serotoninergic, and adrenergic receptors, leading to increased appetite and weight gain (Montastruc 2015). This weight gain is usually regarded as a serious side effect for those who aim to keep a healthy body weight but may be beneficial for those with anorexia nervosa. There was insufficient evidence to determine the efficacy of SGAs on increasing body weight in people with anorexia nervosa in a recent meta-analysis (Dold 2015). However, the lack of evidence may be due to the small sample size. Although weight gain has been reported more often for SGAs than for FGAs, the

effects of each type cannot be clearly separated (Alonso-Pedrero 2019; Leucht 2009; Leucht 2013).

Why it is important to do this review

In a previous systematic review comprehensively examining the association between SGAs and weight gain in people with anorexia nervosa, no statistically significant effect was observed in efficacy and acceptability in the pooled or subgroup analyses for olanzapine, quetiapine, and risperidone compared to placebo (Dold 2015). However, a randomised controlled trial (RCT) published in 2019 showed a significant increase in body weight with olanzapine compared to placebo (Attia 2019). Moreover, a recent systematic review and meta-analysis focusing on the effectiveness of olanzapine for anorexia nervosa indicated that olanzapine might increase BMI in adults with anorexia nervosa compared to placebo (Han 2022). However, the review did not evaluate safety and other outcomes, and did not assess the risk of bias in the included studies with a validated scale, such as the Cochrane risk of bias tool for randomized trials (RoB 2) (Higgins 2023a). In another recent systematic scoping review exploring the effectiveness and safety of SGAs for anorexia nervosa, an updated meta-analysis was not conducted, and the review did not include FGAs (Thorey 2023). In contrast, in this Cochrane systematic review and meta-analysis, we aim to estimate the advantages and disadvantages of all types of antipsychotic drugs in people with anorexia nervosa more comprehensively and more precisely with a larger sample size. There are potential benefits and harms associated with the use of antipsychotic drugs in the treatment of anorexia nervosa. This review aims to provide a full picture of the associated benefits and harms. We also expect to provide evidence for or against the frequent off-label use of antipsychotic drugs in the treatment of anorexia nervosa.

OBJECTIVES

To assess the effects of antipsychotic drugs (both first- and second-generation antipsychotics) compared to placebo on body weight gain, psychological symptoms, acceptability, and adverse events for people with anorexia nervosa.

METHODS

Criteria for considering studies for this review

Types of studies

We will include all randomized controlled trials (RCTs) meeting the inclusion criteria. We will exclude cluster-randomized and cross-over trials because such study designs are not appropriate for this topic. We will not use the review outcomes listed below as criteria for including or excluding studies.

Types of participants

Participant characteristics

We will exclude studies that include pregnant women if separate subgroup results for non-pregnant women are not reported. Otherwise, we will impose no restrictions in terms of age, gender, ethnicity, initial BMI, or the subtypes of anorexia nervosa (restricting or binge-eating/purging type).

Diagnosis

People with anorexia nervosa will be eligible if diagnosed according to any defined criteria, including Russell's (Russell 1970), the tenth revision of the *International Classification of Diseases* (ICD-10) (WHO 1992), and the *Diagnostic and Statistical Manual of Mental Disorders,* Third Edition (DSM-III), Third Revised Edition (DSM-III-R), Fourth Edition (DSM-IV), Text Revision of the Fourth Edition (DSM-IV-TR), or Fifth Edition (DSM-5) (APA 2013).

Setting

We will include both inpatient and outpatient settings.

Comorbidities

Participants with comorbid physical disorders and other psychological disorders will be eligible for inclusion, as long as the primary diagnosis was anorexia nervosa.

When only a subset of participants in a study is eligible for inclusion and this subset's data are reported separately, we will include these data in the analysis. If separate subgroup results are not reported, we will not use the data for analysis.

Types of interventions

We will include studies that examine the efficacy of FGAs and SGAs compared with placebo for people with anorexia nervosa. Treatment should last at least one week. A concurrent stable dose of medication other than antipsychotic drugs, or any psychotherapy including family therapy or group therapy, will be allowed so long as both study arms receive the same co-interventions.

Types of outcome measures

Primary outcomes

- Body weight gain: as measured by body mass index (BMI = weight in kilograms divided by height in meters squared)
- Anorexia-related psychological symptoms change: as measured by the change in scores of any validated and recognized continuous scale, such as the Yale-Brown-Cornell Eating Disorders Scale (YBC-EDS) (Mazure 1994), the Eating Disorders Inventory (EDI) (Garner 1991), and the Eating Disorder Examination (EDE) (Cooper 1989)
- Acceptability: as measured by the proportion of dropouts due to any reason

Secondary outcomes

- Adverse events, as measured by:
  - the proportion of dropouts due to adverse events;
  - the proportion of specific adverse events.
- Mortality: as measured by the proportion of deaths due to any reason
- Quality of life
- Depressive symptoms
- Anxiety symptoms

Quality of life, depressive symptoms, and anxiety symptoms must be measured by the change in any validated or recognized continuous scale.

Selection of measurement scales

For four of our prespecified outcomes (anorexia-related psychological symptoms, quality of life, depressive symptoms, and anxiety symptoms), studies may use different measurement scales or may report multiple scales for the same outcome. Where a study reports multiple scales for the same outcome (for example, if a study assesses anorexia-related psychological symptoms with the Yale-Brown-Cornell Eating Disorders Scale (YBC-EDS) and the Eating Disorders Inventory (EDI)), we will select one scale per outcome and use the data for the analysis, using the following hierarchy:

- the scale with the longest follow-up time point;
- if multiple scales have equally long follow-up time points, we will select the scale designated as the study's primary outcome measure;
- if no scale or multiple scales meet the above criteria, we will select the scale used for the study's sample size calculation.

Timing of outcome assessment

We will assess the review's outcomes at three time points, as follows:

- Short-term: one month (range one to seven weeks). When multiple time point measures are available, we will prioritize the time point closest to four weeks.
- Medium-term: three months (range eight to 16 weeks). When multiple time point measures are available, we will prioritize the time point closest to 12 weeks. If there are two time points equally close to 12 weeks, we will select the longer time point. For example, if an outcome was assessed at 10 weeks and 14 weeks and not assessed between the two time points, we will select the outcome at 14 weeks for the medium-term outcome.
- Long-term: more than 16 weeks. When multiple time point measures are available, we will prioritize the time point with the longest follow-up.

Search methods for identification of studies

See Appendix 1 for the detailed search strategies.

Electronic searches

We will search for relevant studies in the following databases:

- Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library;
- MEDLINE Ovid;
- Embase Ovid;
- PsycINFO Ovid.

We will perform additional searches in the following trial registers to find any unpublished and ongoing studies:

- World Health Organization International Clinical Trials Registry Platform (WHO ICTRP; https://www.who.int/clinical-trials-registry-platform/the-ictrp-search-portal);
- ClinicalTrials.gov (https://clinicaltrials.gov/).

There will be no restriction on date, language (Egger 1997a), or publication status.

Searching other resources

We will examine the reference lists of all the included studies, and any systematic reviews from the search above for further relevant publications. We will also conduct a citation search on the Web of Science (https://www.webofscience.com/wos/woscc/basic-search) to identify additional reports citing any of the included studies.

Data collection and analysis

Selection of studies

Three pairs of review authors (KY, HI, ES, YL, SK, YT), working independently, will screen the titles and abstracts of the records obtained in the searches. We will identify and discard duplicate records and records that are clearly irrelevant to the review. Of the remaining records, we will code those that clearly do not meet the review's inclusion criteria as 'do not retrieve', and those that meet or potentially meet the inclusion criteria as 'retrieve'. We will collate multiple reports of the same study, so that each study, rather than each report, is the unit of interest in the review (Lefebvre 2023). We will retrieve full-text publications for those records coded as 'retrieve' for closer inspection, checking the study's eligibility and the quality of the methodology. When there are conflicts of opinion, we will discuss discrepancies among the review authors. We will consult a seventh review author as needed. We will calculate the inter-rater reliability (kappa) of our inclusion/exclusion judgments. We will record the selection process in sufficient detail to complete a PRISMA flow diagram and 'Characteristics of excluded studies' table, which will identify studies that may appear to some readers to meet the eligibility criteria, but which we will exclude with reasons (Cumpston 2023; Liberati 2009). We will manage the results of our search using Rayyan software (Ouzzani 2016).

Data extraction and management

Three pairs of review authors (KY, HI, ES, YL, SK, YT), working independently, will extract data from each study (see below) and input it into a data extraction sheet. One of the review author pairs will transcribe data into Review Manager (RevMan) software (RevMan 2023). Another review author will double-check all data entered into RevMan to minimize transcription errors. We will extract the following data:

- eligibility criteria: inclusion and exclusion criteria;
- study methods: study duration, study year, study setting, masking, and withdrawals;
- participants: anorexia type, how the diagnosis was made, number, age, gender, baseline body weight, baseline eating disorder scale measure and its score, mental and physical comorbidities, and previous treatment for anorexia nervosa;
- interventions: number of intervention groups, type and dose of antipsychotic drugs, duration of intervention, and co-intervention (e.g. psychotherapy and concurrent medication);
- outcomes: measures, definition of thresholds, and time of assessment.

Assessment of risk of bias in included studies

Three pairs of review authors (KY, HI, ES, YL, SK, YT), working independently, will assess the methodological quality of each included study using Cochrane's risk of bias tool for randomized trials (RoB 2) (Higgins 2023a). We will apply the RoB 2 tool to assess

the following outcomes and time points, which will be included in the summary of findings table:

- body weight gain: in the short term (one month), medium term (three months), and long term (more than 16 weeks);
- anorexia-related psychological symptoms change: in the medium term (three months) and long term (more than 16 weeks);
- acceptability, measured by all-cause dropouts: in the medium term (three months) and long-term (more than 16 weeks).

We are interested in the effect of assignment to the interventions at baseline, regardless of whether the interventions are received as intended (the 'intention-to-treat effect'). Based on our answers to the signaling questions and RoB 2 tool algorithms, we will assign a rating of 'high risk' of bias, 'some concerns', or 'low risk' for the following domains: the randomization process, intended interventions, missing outcome data, measurement of the outcome, and selection of the reported results (Higgins 2023a). The overall risk of bias for each outcome will be judged as follows:

- low risk of bias: a 'low risk of bias' judgment for all domains;
- some concerns: 'some concerns' judgment in at least one domain and no 'high risk of bias' judgment in any domain;
- high risk of bias: a 'high risk of bias' judgment in at least one domain, or 'some concerns' for multiple domains.

We will resolve any disagreement by discussion and consultation with a seventh review author. We will use the RoB 2 Excel tool to implement the RoB 2 assessment, and present the consensus decisions for the signaling questions as supplementary materials. We will use the overall RoB 2 judgment for each outcome to determine the GRADE risk of bias domain assessment. We will conduct the primary analysis including all eligible studies, and conduct sensitivity analyses excluding trials with a high overall risk of bias.

Measures of treatment effect

For continuous outcomes, we will calculate the mean differences (MD) with 95% confidence intervals (CI) when outcomes are on the same scale. When outcomes are on different scales but measure the same concept, we will calculate the standardized mean difference (SMD) based on Hedge's g statistic with 95% CIs. According to the rule of thumb, an SMD of 0.2 indicates a small effect, 0.5 a moderate effect, and 0.8 a large effect (Cohen 1988). For dichotomous outcomes, we will calculate risk ratios (RR) with 95% CIs.

Unit of analysis issues

If we include a study with more than one relevant intervention arm in a meta-analysis, we will distribute the control group evenly among the comparisons, in order to avoid double-counting participants (Higgins 2023b).

Dealing with missing data

We will attempt to contact the original investigators of any studies with missing data. If we are unsuccessful in obtaining missing data or further information, we will use the data as presented in the original articles. We will analyze data using the intention-to-treat (ITT) principle whenever possible.

For continuous data, we will indicate the missing data imputation method used in the analyses (e.g. last observation carried forward [LOCF], multiple imputation [MI], or mixed-effects models for repeated measures [MMRM]). We will not exclude studies based on the statistical method used for imputing missing data, but will investigate the impact of imputation in a sensitivity analysis. When the standard deviations (SD) of continuous measure scores are not reported, and we are unsuccessful in obtaining them from the original investigators, we will calculate the standard deviation from the standard error (SE), confidence interval (CI), t statistic, or P value (Altman 1996; Higgins 2023c). If these approaches are not possible, we will impute the standard deviation (SD) according to a validated imputation method (Furukawa 2006).

For dichotomous data, we will use the available data, which will be the proportion of participants who experienced the events of interest (i.e. dropouts, specific adverse events, and death). We do not anticipate that there will be any missing data for these dichotomous outcomes, and thus, we do not plan to use sensitivity analyses.

Assessment of heterogeneity

We will assess heterogeneity between the studies with the Chi^2 test and I^2 statistic. The Chi^2 test provides evidence of variation in effect estimates beyond chance. We will set the significance level at 0.10 because the Chi^2 test is underpowered when a meta-analysis includes few studies or includes studies with a small sample size (Deeks 2023).

The I^2 statistic calculates the percentage of variability due to heterogeneity rather than chance. We will interpret the heterogeneity as follows (Deeks 2023):

- 0 to 40%: might not be important;
- 30 to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

We will also calculate the Tau^2 statistic to estimate the between-study variance in a random-effects meta-analysis, represented in a forest plot created in RevMan. The Tau^2 statistic gives an indication of the spread of true intervention effects.

Assessment of reporting biases

We will visually assess reporting bias by drawing a funnel plot for the primary outcomes (Egger 1997b), when at least 10 studies are included in an analysis. We will not use a test for funnel plot asymmetry when there are fewer than 10 studies, as, in this case, the test has insufficient power to detect the effects of the studies with a small sample size (Sterne 2011). We will also not use the test when sample sizes of the included studies are similar (Sterne 2011).

Data synthesis

We will use the random-effects model of DerSimonian and Laird to calculate treatment effects because it takes the heterogeneity of the included studies into account (DerSimonian 1986). We will use RevMan software to conduct meta-analytic calculations (RevMan 2023). When a meta-analysis of effect estimates is not possible due to incompletely reported data, we will narratively summarize the data and visually display the results using methods such as forest plots without a combined effect estimate (i.e. the summary

diamond), and albatross plots if P values are reported (McKenzie 2023).

Subgroup analysis and investigation of heterogeneity

We will perform subgroup analyses for the following a priori defined factors that may be effect modifiers:

- mean participant age: younger than 18 years old or others (i.e. adults);
- mean baseline BMI: meta-regression analysis;
- subtypes of anorexia nervosa: restrictive subtype or binge-purge subtype;
- types of antipsychotic drugs:
  - FGA or SGA;
  - specific medication.

We will conduct these analyses using the same methods as for the main analyses.

Sensitivity analysis

We will conduct sensitivity analyses of the primary outcomes to assess the robustness of our findings by excluding:

- studies with a high overall risk of bias as assessed by RoB 2;
- studies which do not report the results following the ITT principle;
- studies where there are missing data and only the available data were included in the analysis or missing outcome data were imputed with replacement values without considering uncertainty (e.g. LOCF) in the main analyses;
- studies in which the SDs are imputed to calculate treatment effect.

Summary of findings and assessment of the certainty of the evidence

Three pairs of review authors (KY, HI, ES, YL, SK, YT), working independently, will assess each outcome in the summary of findings table regarding the certainty of the body of evidence, using the GRADE approach, which assesses five domains (risk of bias, imprecision, indirectness, inconsistency, and publication bias) (Guyatt 2011). We will resolve any disagreement about our GRADE assessments through discussion and by consulting a seventh review author, if necessary. We will create a summary of findings table and report the results of the following outcomes:

- body weight gain: in the short term (one month), medium term (three months), and long-term (more than 16 weeks);
- anorexia-related psychological symptoms change: in the medium term (three months) and long term (more than 16 weeks);
- acceptability, measured by all-cause dropouts: in the medium term (three months) and long-term (more than 16 weeks).

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- Managing Editor (selected peer reviewers, collated peer-reviewer comments, provided editorial guidance to authors, edited the article): Jessica Hendon, CCMD, Centre for Reviews and Dissemination, University of York; Anupa Shah, Cochrane Central Editorial Service.
- Information Specialist (search review, provided editorial guidance to authors, edited the article): Sarah Dawson, CCMD and University of Bristol; Jo Platt (Cochrane Central Editorial Service Team).
- Peer reviewers (provided comments and recommended an editorial decision): Caroline Fisher, Royal Melbourne Hospital, Melbourne, Australia & The Melbourne Clinic, Melbourne, Australia. (clinical/content review); Verity Westgate, University of Oxford (consumer review); Gillian Worthy (methods review); Jen Hilgart (methods review).
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APPENDICES

Appendix 1. Preliminary search strategy

Cochrane Central Register of Controlled Trials (CENTRAL)

1. (Acepromazine or Acetophenazine or Amisulpride or Aripiprazole or Asenapine or Benperidol or Blonanserin or Brexpiprazole or Bromperidol or Butaperazine Cariprazine or or Carpipramine or Chlorproethazine or Chlorpromazine or Chlorprothixene or Clocapramine or Clopenthixol or Clopentixol or Clothiapine or Clotiapine or Clozapine or Cyamemazine or Cyamepromazine or Dixyrazine or Droperidol or Fluanisone or Flupehenazine or Flupenthixol or Flupentixol or Fluphenazine or Fluspirilen or Fluspirilene or Haloperidol or Iloperidone or Levomepromazine or Levosulpiride or Loxapine or Loxapinsuccinate or Lumateperone or Lurasidone or Melperone or Mepazine or Mesoridazine or Methotrimeprazine or Molindone or Moperone or Mosapramine or Olanzapine or Oxypertine or Paliperidone or Penfluridol or Perazine or Periciazine or Pericyazine or Perospirone or Perphenazine or Pimozide or Pipamperone or Pipothiazine or Pipotiazine or Prochlorperazine or Promazine or Promethazine or Prothipendyl or Quetiapine or Remoxipiride or Reserpine or Riospirone or Risperdal or Risperidone or Seroquel or Sertindole or Stelazine or Sulpiride or Sultopride or Thiopropazate or Thioproperazine or Thioridazine or Tiospirone or Thiothixene or Tiapride or Tiotixene or Trifluoperazine or Trifluperidol or Trifluoperidol or Triflupromazine or Trifluperazine or Veralipride or Ziprasidone or Zotepine or Zuclopenthixol):ti,ab,kw
2. (Antipsychoti* or Anti-psychotic* or Neurolepic* or Neurolept*):ti,ab,kw
3. MeSH descriptor: [Antipsychotic Agents] explode all trees
4. #1 or #2 or #3
5. MeSH descriptor: [Feeding and Eating Disorders] explode all trees
6. (eat* near/3 disorder*)
7. MeSH descriptor: [Anorexia] this term only
8. anorexi*
9. #5 or #6 or #7 or #8
10. #4 and #9

Ovid MEDLINE

1. (Acepromazine or Acetophenazine or Amisulpride or Aripiprazole or Asenapine or Benperidol or Blonanserin or Brexpiprazole or Bromperidol or Butaperazine or Cariprazine or Carpipramine or Chlorproethazine or Chlorpromazine or Chlorprothixene or Clocapramine or Clopenthixol or Clopentixol or Clothiapine or Clotiapine or Clozapine or Cyamemazine or Cyamepromazine or Dixyrazine or Droperidol or Fluanisone or Flupehenazine or Flupenthixol or Flupentixol or Fluphenazine or Fluspirilen or Fluspirilene or Haloperidol or Iloperidone or Levomepromazine or Levosulpiride or Loxapine or Loxapinsuccinate or Lumateperone or Lurasidone or Melperone or Mepazine or Mesoridazine or Methotrimeprazine or Molindone or Moperone or Mosapramine or Olanzapine or Oxypertine or Paliperidone or Penfluridol or Perazine or Periciazine or Pericyazine or Perospirone or Perphenazine or Pimozide or Pipamperone or Pipothiazine or Pipotiazine or Prochlorperazine or Promazine or Promethazine or Prothipendyl or Quetiapine or Remoxipiride or Reserpine or Riospirone or Risperdal or Risperidone or Seroquel or Sertindole or Stelazine or Sulpiride or Sultopride or Thiopropazate or Thioproperazine or Thioridazine or Tiospirone or Thiothixene or Tiapride or Tiotixene or Trifluoperazine or Trifluperidol or trifluoperidol or Triflupromazine or trifluperazine or Veralipride or Ziprasidone or Zotepine or Zuclopenthixol).mp.
2. (Antipsychoti$ or Anti-psychotic$ or Neurolepic$ or Neurolept$).mp.
3. Antipsychotic Agents/
4. 1 or 2 or 3
5. Anorexia/
6. exp “Feeding and Eating Disorders”/
7. (eat* adj3 disorder*).mp.
8. 5 or 6 or 7
9. exp randomized controlled trial/
10. controlled clinical trial.pt.
11. randomized.ab.
12. placebo.ab.
13. drug therapy.fs.
14. randomly.ab.

15.trial.ab.
16.groups.ab.
17.9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
18.exp animals/ not humans.sh.
19.17 not 18
20.4 and 8 and 19

Ovid Embase

1. (Acepromazine or Acetophenazine or Amisulpride or Aripiprazole or Asenapine or Benperidol or Blonanserin or Brexpiprazole or Bromperidol or Butaperazine or Cariprazine or Carpipramine or Chlorproethazine or Chlorpromazine or Chlorprothixene or Clocapramine or Clopenthixol or Clopentixol or Clothiapine or Clotiapine or Clozapine or Cyamemazine or Cyamepromazine or Dixyrazine or Droperidol or Fluanisone or Flupehenazine or Flupenthixol or Flupentixol or Fluphenazine or Fluspirilen or Fluspirilene or Haloperidol or Iloperidone or Levomepromazine or Levosulpiride or Loxapine or Loxapinsuccinate or Lumateperone or Lurasidone or Melperone or Mepazine or Mesoridazine or Methotrimeprazine or Molindone or Moperone or Mosapramine or Olanzapine or Oxypertine or Paliperidone or Penfluridol or Perazine or Periciazine or Pericyazine or Perospirone or Perphenazine or Pimozide or Pipamperone or Pipothiazine or Pipotiazine or Prochlorperazine or Promazine or Promethazine or Prothipendyl or Quetiapine or Remoxipiride or Reserpine or Riospirone or Risperdal or Risperidone or Seroquel or Sertindole or Stelazine or Sulpiride or Sultopride or Thiopropazate or Thioproperazine or Thioridazine or Tiospirone or Thiothixene or Tiapride or Tiotixene or Trifluoperazine or Trifluperidol or trifluoperidol or Triflupromazine or trifluperazine or Veralipride or Ziprasidone or Zotepine or Zuclopenthixol).mp.
2. (Antipsychoti$ or Anti-psychotic$ or Neurolepic$ or Neurolept$).mp.
3. neuroleptic agent/
4. or/1-3
5. exp Eating Disorders/
6. (eat* adj3 disorder*).mp.
7. Anorexia Nervosa/
8. or/5-7
9. exp randomized controlled trial/
10. controlled clinical trial/
11. random$.ti,ab.
12. randomization/
13. intermethod comparison/
14. placebo.ti,ab.
15. (compare OR compared OR comparison).ti,ab.
16. ((evaluated OR evaluate OR evaluating OR assessed OR assess) AND (compare OR compared OR comparing OR comparison))
17. (open adj label).ti,ab.
18. ((double OR single OR doubly OR singly) adj (blind OR blinded OR blindly)).ti,ab.
19. double blind procedure/
20. parallel group$1.ti,ab.
21. (crossover OR cross over).ti,ab.
22. ((assign$ OR match OR matched OR allocation) adj5 (alternate OR group$1 OR intervention$1 OR patient$1 OR subject$1 OR participant $1)).ti,ab.
23. (assigned OR allocated).ti,ab.
24. (controlled adj7 (study OR design OR trial)).ti,ab.
25. (volunteer OR volunteers).ti,ab.
26. human experiment/
27. trial.ti.
28. or/9-27
29. (random$ adj sampl$ adj7 ("cross section$" OR questionnaire$1 OR survey$ OR database$1)).ti,ab. NOT (comparative study/ OR controlled study/ OR randomi?ed controlled.ti,ab. OR randomly assigned.ti,ab.)
30. cross-sectional study/de NOT (exp randomized controlled trial/ OR controlled clinical trial/ OR controlled study/ OR randomi?ed controlled.ti,ab. OR control group$1.ti,ab.)
31. ((case adj control$) AND random$.ti,ab.) NOT randomi?ed controlled.ti,ab.
32. (systematic review.ti,ab. NOT (trial OR study)).ti.
33. (nonrandom$ NOT random$).ti,ab.

34. "random field$".ti,ab.
35. (random cluster adj3 sampl$).ti,ab.
36. (review.ab. AND review.pt.) NOT trial.ti.
37. ("we searched".ab. AND (review.ti. OR review.pt.))
38. "update review".ab.
39. (databases adj4 searched).ab.
40. (rat OR rats OR mouse OR mice OR swine OR porcine OR murine OR sheep OR lambs OR pigs OR piglets OR rabbit OR rabbits OR cat OR cats OR dog OR dogs OR cattle OR bovine OR monkey OR monkeys OR trout OR marmoset$1).ti. AND animal experiment/
41. animal experiment/ NOT (human experiment/ OR human/)
42. or/29-41
43. 28 NOT 42
44. 4 and 8 and 43

Ovid PsycINFO

1. (Acepromazine or Acetophenazine or Amisulpride or Aripiprazole or Asenapine or Benperidol or Blonanserin or Brexpiprazole or Bromperidol or Butaperazine or Cariprazine or Carpipramine or Chlorproethazine or Chlorpromazine or Chlorprothixene or Clocapramine or Clopenthixol or Clopentixol or Clothiapine or Clotiapine or Clozapine or Cyamemazine or Cyamepromazine or Dixyrazine or Droperidol or Fluanisone or Flupehenazine or Flupenthixol or Flupentixol or Fluphenazine or Fluspirilen or Fluspirilene or Haloperidol or Iloperidone or Levomepromazine or Levosulpiride or Loxapine or Loxapinsuccinate or Lumateperone or Lurasidone or Melperone or Mepazine or Mesoridazine or Methotrimeprazine or Molindone or Moperone or Mosapramine or Olanzapine or Oxypertine or Paliperidone or Penfluridol or Perazine or Periciazine or Pericyazine or Perospirone or Perphenazine or Pimozide or Pipamperone or Pipothiazine or Pipotiazine or Prochlorperazine or Promazine or Promethazine or Prothipendyl or Quetiapine or Remoxipiride or Reserpine or Riospirone or Risperdal or Risperidone or Seroquel or Sertindole or Stelazine or Sulpiride or Sultopride or Thiopropazate or Thioproperazine or Thioridazine or Tiospirone or Thiothixene or Tiapride or Tiotixene or Trifluoperazine or Trifluperidol or trifluoperidol or Triflupromazine or trifluperazine or Veralipride or Ziprasidone or Zotepine or Zuclopenthixol).mp.
2. (Antipsychoti$ or Anti-psychotic$ or Neurolepic$ or Neurolept$).mp.
3. neuroleptic drugs/
4. or/1-3
5. exp Eating Disorders/
6. (eat* adj3 disorder*).mp.
7. Anorexia Nervosa/
8. or/5-7
9. ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).mp.
10. (random$ adj5 (assign$ or allocat$)).mp.
11. randomi$.mp.
12. or/9-11
13. 4 and 8 and 12

WHO ICTRP

Acepromazine and anorexia

Acetophenazine and anorexia

Amisulpride and anorexia

Aripiprazole and anorexia

Asenapine and anorexia

Benperidol and anorexia

Blonanserin and anorexia

Brexpiprazole and anorexia

Bromperidol and anorexia

Butaperazine and anorexia

Cariprazine and anorexia

Carpipramine and anorexia

Chlorproethazine and anorexia

Chlorpromazine and anorexia

Chlorprothixene and anorexia

Clocapramine and anorexia

Clopenthixol and anorexia

Clopentixol and anorexia

Clothiapine and anorexia

Clotiapine and anorexia

Clozapine and anorexia

Cyamemazine and anorexia

Cyamepromazine and anorexia

Dixyrazine and anorexia

Droperidol and anorexia

Fluanisone and anorexia

Flupehenazine and anorexia

Flupenthixol and anorexia

Flupentixol and anorexia

Fluphenazine and anorexia

Fluspirilen and anorexia

Fluspirilene and anorexia

Haloperidol and anorexia

Iloperidone and anorexia

Levomepromazine and anorexia

Levosulpiride and anorexia

Loxapine and anorexia

Loxapinsuccinate and anorexia

Lumateperone and anorexia

Lurasidone and anorexia

Melperone and anorexia

Mepazine and anorexia

Mesoridazine and anorexia

Methotrimeprazine and anorexia

Molindone and anorexia

Moperone and anorexia

Mosapramine and anorexia

Olanzapine and anorexia

Oxypertine and anorexia

Paliperidone and anorexia

Penfluridol and anorexia

Perazine and anorexia

Periciazine and anorexia

Pericyazine and anorexia

Perospirone and anorexia

Perphenazine and anorexia

Pimozide and anorexia

Pipamperone and anorexia

Pipothiazine and anorexia

Pipotiazine and anorexia

Prochlorperazine and anorexia

Promazine and anorexia

Promethazine and anorexia

Prothipendyl and anorexia

Quetiapine and anorexia

Remoxipiride and anorexia

Reserpine and anorexia

Riospirone and anorexia

Risperdal and anorexia

Risperidone and anorexia

Seroquel and anorexia

Sertindole and anorexia

Stelazine and anorexia

Sulpiride and anorexia

Sultopride and anorexia

Thiopropazate and anorexia

Thioproperazine and anorexia

Thioridazine and anorexia

Tiospirone and anorexia

Thiothixene and anorexia

Tiapride and anorexia

Tiotixene and anorexia

Trifluoperazine and anorexia

Trifluperidol and anorexia

Trifluoperidol and anorexia

Triflupromazine and anorexia

Trifluperazine and anorexia

Veralipride and anorexia

Ziprasidone and anorexia

Zotepine and anorexia

Zuclopenthixol and anorexia

Antipsychotic* and anorexia

ClinicalTrials.gov

Intervention Acepromazine / Condition Anorexia

Intervention Acetophenazine / Condition Anorexia

Intervention Amisulpride / Condition Anorexia

Intervention Aripiprazole / Condition Anorexia

Intervention Asenapine / Condition Anorexia

Intervention Benperidol / Condition Anorexia

Intervention Blonanserin / Condition Anorexia

Intervention Brexpiprazole / Condition Anorexia

Intervention Bromperidol / Condition Anorexia

Intervention Butaperazine / Condition Anorexia

Intervention Cariprazine / Condition Anorexia

Intervention Carpipramine / Condition Anorexia

Intervention Chlorproethazine / Condition Anorexia

Intervention Chlorpromazine / Condition Anorexia

Intervention Chlorprothixene / Condition Anorexia

Intervention Clocapramine / Condition Anorexia

Intervention Clopenthixol / Condition Anorexia

Intervention Clopentixol / Condition Anorexia

Intervention Clothiapine / Condition Anorexia

Intervention Clotiapine / Condition Anorexia

Intervention Clozapine / Condition Anorexia

Intervention Cyamemazine / Condition Anorexia

Intervention Cyamepromazine / Condition Anorexia

Intervention Dixyrazine / Condition Anorexia

Intervention Droperidol / Condition Anorexia

Intervention Fluanisone / Condition Anorexia

Intervention Flupehenazine / Condition Anorexia

Intervention Flupenthixol / Condition Anorexia

Intervention Flupentixol / Condition Anorexia

Intervention Fluphenazine / Condition Anorexia

Intervention Fluspirilen / Condition Anorexia

Intervention Fluspirilene / Condition Anorexia

Intervention Haloperidol / Condition Anorexia

Intervention Iloperidone / Condition Anorexia

Intervention Levomepromazine / Condition Anorexia

Intervention Levosulpiride / Condition Anorexia

Intervention Loxapine / Condition Anorexia

Intervention Loxapinsuccinate / Condition Anorexia

Intervention Lumateperone / Condition Anorexia

Intervention Lurasidone / Condition Anorexia

Intervention Melperone / Condition Anorexia

Intervention Mepazine / Condition Anorexia

Intervention Mesoridazine / Condition Anorexia

Intervention Methotrimeprazine / Condition Anorexia

Intervention Molindone / Condition Anorexia

Intervention Moperone / Condition Anorexia

Intervention Mosapramine / Condition Anorexia

Intervention Olanzapine / Condition Anorexia

Intervention Oxypertine / Condition Anorexia

Intervention Paliperidone / Condition Anorexia

Intervention Penfluridol / Condition Anorexia

Intervention Perazine / Condition Anorexia

Intervention Periciazine / Condition Anorexia

Intervention Pericyazine / Condition Anorexia

Intervention Perospirone / Condition Anorexia

Intervention Perphenazine / Condition Anorexia

Intervention Pimozide / Condition Anorexia

Intervention Pipamperone / Condition Anorexia

Intervention Pipothiazine / Condition Anorexia

Intervention Pipotiazine / Condition Anorexia

Intervention Prochlorperazine / Condition Anorexia

Intervention Promazine / Condition Anorexia

Intervention Promethazine / Condition Anorexia

Intervention Prothipendyl / Condition Anorexia

Intervention Quetiapine / Condition Anorexia

Intervention Remoxipiride / Condition Anorexia

Intervention Reserpine / Condition Anorexia

Intervention Riospirone / Condition Anorexia

Intervention Risperdal / Condition Anorexia

Intervention Risperidone / Condition Anorexia

Intervention Seroquel / Condition Anorexia

Intervention Sertindole / Condition Anorexia

Intervention Stelazine / Condition Anorexia

Intervention Sulpiride / Condition Anorexia

Intervention Sultopride / Condition Anorexia

Intervention Thiopropazate / Condition Anorexia

Intervention Thioproperazine / Condition Anorexia

Intervention Thioridazine / Condition Anorexia

Intervention Tiospirone / Condition Anorexia

Intervention Thiothixene / Condition Anorexia

Intervention Tiapride / Condition Anorexia

Intervention Tiotixene / Condition Anorexia

Intervention Trifluoperazine / Condition Anorexia

Intervention Trifluperidol / Condition Anorexia

Intervention Trifluoperidol / Condition Anorexia

Intervention Triflupromazine / Condition Anorexia

Intervention Trifluperazine / Condition Anorexia

Intervention Veralipride / Condition Anorexia

Intervention Ziprasidone / Condition Anorexia

Intervention Zotepine / Condition Anorexia

Intervention Zuclopenthixol / Condition Anorexia

Intervention Antipsychotic* / Condition Anorexia

CONTRIBUTIONS OF AUTHORS

KY conceived and designed the study, and wrote the first draft of the protocol.

HI reviewed and provided feedback on the draft protocol and approved it before submission.

ES reviewed and provided feedback on the draft protocol and approved it before submission.

YL reviewed and provided feedback on the draft protocol and approved it before submission.

SK reviewed and provided feedback on the draft protocol and approved it before submission.

YT reviewed and provided feedback on the draft protocol and approved it before submission.

IM reviewed and provided feedback on the draft protocol and approved it before submission.

TAF reviewed and provided feedback on the draft protocol and approved it before submission.

NW reviewed and provided feedback on the draft protocol and approved it before submission.

DECLARATIONS OF INTEREST

KY has no known conflict of interest.
HI received an honorarium for a lecture from Otsuka Pharmaceutical Co., Ltd.
ES has no known conflict of interest.
YL reports two research grants from Japan Society for the Promotion of Science KAKENHI (grant number JP22K21112, JP23K16355) outside this work.
SK has no known conflict of interest.
YT reports grants from Japan Society for the Promotion of Science, Kyoto University, and Pfizer Foundation, outside the submitted work. In addition, YT is a board member of Cochrane Japan and works as a physician at Oku Medical Clinic.
IM has no known conflicts of interest.
TAF reports personal fees from Boehringer-Ingelheim, Daiichi Sankyo, DT Axis, Kyoto University Original, Micron, Shionogi, SONY and UpToDate, and a grant from DT Axis and Shionogi, outside the submitted work. In addition, TAF has a patent 7448125 and a pending patent 2022-082495, and has licensed intellectual properties for Kokoro-app to Mitsubishi-Tanabe.

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  Authors' host institution

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