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Interventions for the management of obesity in people with bipolar disorder (Protocol)

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[Intervention Protocol]

Interventions for the management of obesity in people with bipolar disorder

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ABSTRACT

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

To assess the effectiveness of interventions for the management of obesity in people with bipolar disorder.

BACKGROUND

Bipolar disorder is a serious mental illness characterised by mood instability and results in marked impairment in overall functioning and health-related quality of life (De Hert 2011; Klienman 2003). Bipolar disorder is the sixth leading cause of disability worldwide in people aged 15 to 44 years (Klienman 2003) and has a worldwide prevalence of 2.4% (Merikangas 2011). Globally, bipolar disorder affects approximately 60 million people (WHO 2015).

Weight gain and obesity has long been recognised in mental health practice as of significant concern (Baptista 1999; McIntyre 2001; McIntyre 2010). Bipolar disorder individuals are more frequently overweight (body mass index (BMI) 25.0 to 29.9), obese (BMI $\geq$ 30), or have a higher prevalence of central obesity, or both, compared with the general population (McElroy 2004). Analysis of data from the United States (US) National Comorbidity Survey Replication demonstrated that obesity is associated with a significant increase in lifetime diagnosis of bipolar disorder (Simon 2006).

Clinical research suggests that approximately 68% of treatment-seeking bipolar disorder individuals are overweight or obese (McElroy 2004). Traditionally, the issue of weight gain in people with mental illness was perceived as less important than mental wellness (Fontaine 2001). However, clinicians today recognise that obesity has the potential to contribute to other physical health conditions in people with bipolar disorder, including diabetes, hypertension, metabolic syndrome (MetS), cardiovascular disease and coronary heart disease (De Hert 2011). Cardiovascular disease is the leading cause of premature death in bipolar disorder, occurring a decade or more earlier, on average, than in the general population (Goldstein 2014).

Weight gain is a commonly reported side effect of medications used in the treatment of bipolar disorder and is associated with lower quality of life in this population. Factors contributing to

obesity in the bipolar disorder population are diverse but generally stem from illness-related factors (mood-related factors i.e. mania or depression), treatment-related factors (weight implications and other side effects of medications) or lifestyle factors (physical inactivity, poor diet, smoking, substance abuse) (De Hert 2011; Newcomer 2007; Stahl 2009; Ussher 2011), or a combination of some or all of these factors. Obesity and related physical illnesses are associated with aggravation of depression, morbid course of illness, non-adherence with treatment regimes, poor treatment outcomes, and an increased prevalence of suicide in people with bipolar disorder (Fagiolini 2003).

Bipolar disorder leads to a significant economic burden on both the individual and society as a whole. Indirect physical health costs account for most of this burden. This is due largely to lost work productivity of people with bipolar disorder and their carers. Hospitalisation and emergency department services, psychiatric visits, and the costs of medication are the main contributors to direct costs (Guvstavsson 2011).

Description of the condition

Bipolar disorder is a recurrent and sometimes chronic mental illness. The term 'bipolar disorder' refers to a group of affective or mood disorders, typically characterised by episodes of depression and either mania (elated or irritable mood or both), manifested as increased energy and reduced need for sleep, or hypomania, whose symptoms are less severe or less protracted than are those of mania. The fifth edition of the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM-V) (APA 2013) identifies four subtypes of bipolar disorder:

1. bipolar disorder type I is defined as episodes of depression and at least one episode of mania;
2. bipolar disorder type II is numerous, longer episodes of depression and at least one hypomanic episode but no manic episodes;
3. cyclothymic disorder, that is, a number of episodes of hypomanic and depressive symptoms, where the depressive symptoms do not meet criteria for depression; and
4. bipolar disorder not otherwise specified (NOS), that is, depressive and hypomanic episodes that may change rapidly, yet not meeting full diagnostic criteria for any of the other illnesses.

The World Health Organization (WHO 1992) International Classification of Diseases (ICD-10) defines bipolar disorder as characterised by two or more episodes, where the individual's mood and activity levels are very disturbed and may involve an elevation of mood with increased energy and activity (hypomania or mania) and at other times a lowering of mood and decreased energy and activity (depression). Repeated episodes of hypomania or mania only are classified as bipolar disorder.

Description of the intervention

There is a diversity of interventions available for treatment of obesity. The main interventions can be classified into non-pharmacological, pharmacological and surgical.

Non-pharmacological interventions

Non-pharmacological interventions include four types of approaches:

Dietary interventions

This approach focuses on lifestyle modification, generally encompassing diet changes, whereby there is an attempt to enhance dietary restraint by providing adaptive dietary strategies and by discouraging maladaptive dietary practices (Shaw 2005). This approach also includes self-monitoring.The aim is to achieve weight loss by reducing daily intake of food (Harvey 2004; Shaw 2005; McElroy 2012).

Exercise interventions

This approach aims to increase daily expenditure of energy via increased physical activity (Harvey 2004, Shaw 2005). These types of physical activity include jogging and brisk walking (De Hert 2011).

Behaviour-change interventions

The aim of behaviour-change strategies is to elicit behaviour change by enabling individuals to explore and resolve mixed feelings they may have about change. Interventions such as motivational interviewing, which is a grounded in a client-centred approach, help individuals to move to a greater readiness to change behaviour (Rollnick 1995). Another approach is cognitive behavioural therapies that teach individuals behavioural and cognitive strategies, for example, breaking negative behaviour cycles with the focus on achieving and maintaining lifestyle changes (Beck 1979). This can be achieved by stimulus control, goal setting, and self-monitoring. All of these interventions can be delivered at an individual or group level.

Multi-component interventions

Multi-component interventions may contain one or more components of any of the three interventions described above.

Pharmacological interventions

Pharmacological interventions may involve one of two approaches:

Weight-loss medication interventions

This approach involves the taking of drugs that inhibit appetite or food absorption, or both, or that act centrally. Obesity guidelines currently recommend that drug therapy be considered for patients with a BMI of 30 kg/m² or more (Lau 2007; Padwal 2007). There are five anti-obesity drugs commonly used, namely orlistat, lorcaserin, phentermine/topiramate, naloxone/bupropion and liraglutide (Patel 2015).

Medication-switching interventions

Weight gain is a well-recognised side effect of some of the medications used in the treatment for bipolar disorder (Narasimhan 2007). For example, second generation, atypical anti-psychotic drugs such as olanzapine have the propensity to induce weight gain (McIntyre 2001; Lieberman 2005). The mood-stabilising drug, lithium is also associated with weight gain (Shrivastava 2010). Consequently, the second pharmacological approach for managing weight gain in bipolar disorder involves the switching of antipsychotic or mood-stabilising medications to alternative antipsychotic or mood-stabilising medications with less potential for weight gain (Weiden 2007; White 2013).

Surgical interventions

Bariatric surgery (weight-loss surgery), is considered almost exclusively for patients with a BMI of 40 kg/m² or more. It may also be considered for patients with a BMI of 35 kg/m² in the presence of an associated serious physical illness, such as diabetes (NICE 2006).

How the intervention might work

Non-pharmacological interventions

Common to all non-pharmacological interventions for weight management is the concept of lifestyle modification to diet, physical exercise or behaviour, or a combination of these approaches (McElroy 2009; Patel 2015). A central aim of lifestyle-change approaches is to achieve and maintain weight loss by reducing caloric intake and increasing physical activity. The behavioural component seeks to inspire behaviour change toward food intake and physical activity. Weight loss, however modest, can have positive effects on overall well-being and is considered a successful outcome especially if maintained over time. A weight loss of between 5% and 15% has been shown to improve lipid levels, reduce low-density lipoprotein (LDL), total cholesterol, blood pressure and risk of cardiovascular disease (Aucott 2005; Wing 2011). Weight loss of 10 kg has been shown to decrease systolic blood pressure by 5 mmHg and diastolic blood pressure by 6 mmHg (Aucott 2005). Weight loss has also been reported to improve psychological well-being and quality of life, and to facilitate a more active lifestyle, which can help to maintain or increase weight loss.

Pharmacological interventions

The five most commonly used weight-loss drugs are orlistat, lorcaserin, phentermine/topiramate, naloxone/bupropion and liraglutide (Patel 2015). Orlistat acts peripherally by preventing intestinal fat absorption by inhibiting the pancreatic lipase enzyme (Heck 2000). Lorcaserin is a selective agonist of 5-HT2C receptors (Hurren 2011). Phentermine/topiramate is a combination treatment that consists of phentermine, which increases central noradrenaline levels, and topiramate is a central modulator of the inhibitory neurotransmitter GABA (Khorassani 2015). Another combination therapy is the mu-opioid receptor antagonist naloxone and bupropion (Yanovski 2015). Finally, liraglutide is a glucagon-like peptide 1 (GLP-1) receptor agonist that was originally developed to treat type 2 diabetes mellitus but has now been approved for long-term weight management. The drug therapies that are no longer used focused on centrally acting agents that have targeted the catecholaminergic or serotonergic systems, or both (such as sibutramine, mazindol, diethylpropion, benzphetamine and phendimetrazine), or the cannabinoid receptor antagonist, rimonabant. Due to the safety concerns of previous therapeutic approaches, great care is advised in the treatment of weight reduction with the current drugs (American College of Cardiology 2014). Medication switching involves changing from the prescribing of drugs associated with weight gain to the prescribing of drugs associated with less weight gain. A Cochrane Review (Mukundan 2010) evaluating the effects of antipsychotic switching for people with schizophrenia who have neuroleptic-induced weight gain concluded that patients switched to aripiprazole or quetiapine from olanzapine lost weight, had a reduced BMI and had improved profiles of fasting glucose and lipids.

Surgical interventions

Bariatric surgery for obesity includes a variety of approaches. Weight loss is achieved by reducing the size of the stomach so that food intake is restricted and weight loss is induced (Colquitt 2014). Surgical approaches include gastric bypass, gastric bands, biliopancreatic diversion and vertical banded gastroplasty.

Why it is important to do this review

A previous systematic review evaluated interventions targeting physical health comorbidities in people with serious mental illness (Cabassa 2010). However, the term 'serious mental illness', is an umbrella term, incorporating schizophrenia, major depressive disorder and bipolar disorder. Our proposed systematic review seeks to focus only on people with bipolar disorder. Given the prevalence and devastating effects of obesity in this population, as well as the

enormous economic burden to society, any intervention that is effective in addressing the problem of obesity in bipolar disorder would have a major impact. Psychological and health-related quality of life improvements have been shown in people with bipolar disorder following weight loss. Moreover, weight loss allows for improved psychological functioning, a more active lifestyle and increased physical activity, which in turn may induce further weight loss, weight maintenance or both.

OBJECTIVES

To assess the effectiveness of interventions for the management of obesity in people with bipolar disorder.

METHODS

Criteria for considering studies for this review

Types of studies

In this review we will include randomised controlled trials (RCTs), randomised at the level of the individual or cluster. We will include studies employing a cross-over design, using data from the first active treatment only, that is, prior to the first cross-over. Non-randomised controlled studies, in which assignment to treatment group is decided through non-random methods, will not be eligible for inclusion. We will include studies regardless of their publication status.

Types of participants

Participant characteristics

We will include studies where participants have a clinical diagnosis of bipolar disorder and comorbid obesity. We will not exclude studies on the basis of participants' type of bipolar disorder, stage of the illness, age or sex.

Diagnosis

Diagnosis of bipolar disorder must be made using criteria laid out by the American Psychiatric Association (APA 1994) in the DSM-IV or DSM-V (APA 2013)) or, criteria specified by the WHO in the ICD-10 (WHO 1992). Participants must have a clinical diagnosis of obesity, defined in the context of this review as a BMI of 30 kg/m² or more. We anticipate that there will be few studies where all participants have a clinical diagnosis of bipolar disorder and comorbid obesity. Therefore, we will include all studies where 80% or more of the participants have both bipolar disorder and comorbid obesity.

Comorbidities

Comorbid obesity, but participants will be included regardless of any other diagnosed comorbidities.

Setting

There will be no restriction on the treatment setting**.**

Types of interventions

Experimental interventions

We will consider all interventions aimed at improving health outcomes for people with obesity and bipolar disorder, including the following.

1. Non-pharmacological interventions (i.e. lifestyle modifications). To include the following approaches:
   1. diet
   2. exercise
   3. behavioural
   4. multi-component lifestyle interventions, which may include, one or more of the components detailed in 1, 2 and 3 above

There will be no restriction on who delivers the intervention, where the intervention is delivered, or on frequency, intensity or duration of the intervention.

2. Pharmacological interventions. To include the following approaches:
   1. weight-loss drugs
   2. medication switching

There will be no restriction on type of drug, dose, frequency of delivery, route of delivery or length of exposure.

3. Surgical interventions. To include the following approaches:
   1. gastric bypass
   2. gastric banding
   3. biliopancreatic diversion
   4. vertical banded gastroplasty

There will be no restriction on the type of surgical procedure or length of follow-up.

Comparator interventions

1. Inactive comparator, which can be:
   1. no treatment
   2. treatment as usual (TAU), also called standard care or usual care;

3. placebo (inactive/dummy), defined as a control condition that is regarded by researchers as inactive but regarded as active by participants.

2. Active comparator, which can be:
   1. a dietary intervention versus a different dietary intervention
   2. an exercise intervention versus a different exercise intervention
   3. a behavioural intervention versus a different behavioural intervention
   4. a medication-switching intervention versus a different medication switching intervention
   5. a weight-loss medication intervention versus a different weight-loss medication intervention
   6. a surgical intervention versus a different surgical intervention

Types of outcome measures

We will include studies that meet the inclusion criteria irrespective of whether measured outcome data are reported in a 'usable way'. Studies where outcome data are not reported in a usable way will not be included in the meta-analyses, however we will discuss their omission.

Primary outcomes

1. Changes in body mass, measured as change in BMI
2. Patient-reported adverse events (e.g. pain, distress)
3. Quality of life measured by the following validated quality-of-life measurement scales: the Quality of life in Bipolar Disorder (QOL-BD) scale (Michalak 2010) and the suite of Short Form (SF) Health Surveys, originating from the SF-36 tool (Ware 1993).

Secondary outcomes

1. Mood measured by validated measurement scales, for example, the Hamilton Depression Rating Scale (HDRS) (Hamilton 1960) may be used to indicate depression and severity of depression. The Young Mania Rating Scale (YMRS) (Young 1978) may be used to assess severity of manic episodes
2. Global functioning measured by validated measurement scales, for example, Global Assessment of Functioning (GAF) (Jones 1995) and the Clinical Global Impression Bipolar (CGI-BP) scale (Spearing 1997)
3. Clinician-reported adverse events (e.g. infection, drug toxicity)
4. Blood pressure
5. Total cholesterol
6. LDLs
7. Blood glucose levels

Keeley and colleagues (Keeley 2015) are currently developing a core outcome set for use in research involving service users with schizophrenia or bipolar disorder managed in a community setting. If this core outcome set is published before we start screening citations for this review, we will review our primary and secondary outcomes in light of the published core outcome set.

Timing of outcome assessment

We anticipate that study authors will report response rates at various time points during and postintervention. Therefore, we will subdivide the timing of outcome assessment as follows:

1. short-term effects, measured up to 12 months after the end of the intervention, which will be the primary time point reported in the 'Summary of findings' table;
2. sustained effects, measured at least 12 months after the end of the intervention.

If studies provide data at more than one time point, we will include one set of data in short-term effects meta-analysis, choosing the time point nearest 12 months, and one set of data in the sustained-effects meta-analysis, choosing the longest data collection period possible.

Hierarchy of outcome measures

Where available, we will measure data on the primary outcome, change in body mass, and included them in meta-analysis using BMI only.

If data on change in quality of life is available from studies that are sufficiently similar to allow a meta-analysis, we will do one meta-analysis using data measured by QOL-BD and a separate meta-analysis using data from the SF suite of scales and will report both of these in our 'Summary of findings' table.

For our secondary outcomes, we will include data from HDRS and BDI in our meta-analysis for depressed mood, and data from the YMRS in the meta-analysis of mania. We will conduct separate meta-analysis for overall global assessment using data from GAF and CGI-BP. We will not report on secondary outcomes in our 'Summary of findings' table.

If a study reports an outcome in more than one way, we will include relevant data in each meta-analysis.

Search methods for identification of studies

Cochrane Common Mental Disorders' Specialised Register (CCMDCTR)

The Cochrane Common Mental Disorders Group (CCMD) maintains two archived clinical trials registers at its editorial base in York, UK: a references register and a studies-based register. The CCMDCTR-References Register contains over 40,000 reports of RCTs in depression, anxiety and neurosis. Approximately 50% of these references have been tagged to individual, coded trials.

The coded trials are held in the CCMDCTR-Studies Register and records are linked between the two registers through the use of unique Study ID tags. Coding of trials is based on the EU-Psi coding manual, using a controlled vocabulary (please contact the CCMD Information Specialists for further details). Reports of trials for inclusion in the Group's registers were collated from routine (weekly), generic searches of MEDLINE (1950 to 2016), Embase (1974 to 2016) and PsycINFO (1967 to 2016); quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL) and review-specific searches of additional databases. Reports of trials were sourced from international trial registers via the World Health Organization's trials portal (the International Clinical Trials Registry Platform (ICTRP)), pharmaceutical companies, the handsearching of key journals, conference proceedings and other (non-Cochrane) systematic reviews and meta-analyses. Details of CCMD's generic search strategies (used to identify RCTs) can be found on the Group's website. The Group's Specialised Register had fallen out of date with the Editorial Group's move from Bristol to York in the summer of 2016.

Electronic searches

1. We will search the CCMDCTR-Studies Register using the following controlled search terms: ((bipolar) and (obes* or BMI):stc,sco
2. We will search the CCMDCTR-References Register using a more sensitive set of terms to identify additional untagged/uncoded reports of RCTs: #1 (bipolar or cyclothymi* or "rapid cycling" or psychos* or *psychotic* or *mani* or schizoaffective): ti,ab,kw,ky,emt,mh#2 (*weight* or obes* or "body mass" or BMI or fatness or diet or metabol*): :ti,ab,kw,ky,emt,mh#3 (#1 and # 2). (Key to search fields: ti: title; ab: abstract; kw: keywords; ky: additional keywords; emt: EMTREE headings; mh: MeSH headings; stc: target condition; sco: healthcare condition.)
3. We will conduct searches in Cocharne CENTRAL, MEDLINE (Ovid interface), Embase (Ovid interface) and PsycINFO (Ovid interface). The search strategy is reported in Appendix 2.
4. We will search international trials registries via the World Health Organization's trials portal (ICTRP) and ClinicalTrials.gov to identify unpublished or ongoing studies. We will not apply any restrictions on date, language or publication status to the searches.

Searching other resources

Grey literature

We will search the following sources of grey literature:

1. Guidelines, via the National Guideline Clearing House
2. Theses via PsycINFO (Appendix 3); the British Library e-theses online service (EthOS) and the DART-Europe E-theses Portal

We will search citations within identified studies from the search strategy described above. We will contact authors of the identified studies about published and unpublished data.

Data collection and analysis

Selection of studies

After merging search results and discarding duplicates, two review authors (AT, FJ) will independently assess the titles and abstracts of documents retrieved, using predetermined eligibility criteria. We will classify the citations into three groups: 'exclude', 'include' and 'unclear'. We will exclude citations classified by both authors as 'exclude'. The two authors will meet to resolve differences in decisions. We will resolve any disagreements between the authors through discussion, and if required, we will consult another review author (SS).

We will retrieve full-text versions of all 'include' and 'unclear' citations, where possible, for definitive assessment of eligibility. We will make every effort to obtain sufficient translations of non-English citations to allow us to judge whether to include or exclude the studies. For conference abstracts, we will search for related publications and if we are not able to find any, we will contact the study authors to see whether there are any further unpublished data available. If it is not possible to evaluate a study due to lack of published information, we will make a decision based on the information available. Two review authors (SS, YC) will independently screen the full texts against the inclusion criteria. After screening the first 20 full-text citations, the pair of authors will meet to resolve differences in decisions through discussion, and if required, will consult another review author (JG or DD). We will record our screening process using a PRISMA flow chart (Liberati 2009). We will present studies excluded at the full-text stage and reasons for their exclusion in a 'Characteristics of excluded studies table'.

Data extraction and management

We will design an electronic data extraction form and pilot it on two studies initially and then five studies in the review. Two review authors (SS, EM) will use this form to extract study characteristics and outcome data from included studies. Where available, we will extract the following data from each study.

1. Methods: study design, date of, total duration of and length of time each participant is part of the study, details of any 'run-in' period, number of study centres and location, study setting, and date of study

2. Participants: inclusion criteria and exclusion criteria, method of recruitment, number of participants eligible and number randomised, reasons for not including eligible participants, baseline imbalances, and withdrawals and numbers lost to follow-up in each arm. Participant characteristics: age, sex, duration and severity of condition, race, diagnostic criteria, occupational status

3. Intervention(s): details of intervention (name, intervention components, including any materials used by study personnel or given to participants, dose, location, timing and mode of administration, duration, providers, scope for and details of modifications during the study)

4. Comparison (including definition of usual care where appropriate): concomitant medications, and excluded medications

5. Outcomes: unit of analysis, primary and secondary outcomes specified and collected, time points reported, scales used to measure outcomes, person/method of recording outcome; baseline and end of intervention data on outcomes of interest. Data to assess risk of bias of each study, as required by the Cochrane 'Risk of bias' tool

6. Notes: funding for study, and notable conflicts of interest of study authors, any other study-specific information of importance not already captured above.

We will resolve disagreements in data extraction by consensus or by consultation with a third review author (DD). Where data are missing or unclear, we will contact the original study author for additional information. One review author (FJ) will enter all extracted data into Review Manager 5 (RevMan 5) (RevMan 2014) and a second review author (AT) will check them for accuracy and consistency against the data extraction sheets.

Main comparisons

Main comparisons reported in 'Summary of findings' tables, will be:

1. dietary interventions versus inactive comparator;
2. exercise interventions versus inactive comparator;
3. behavioural interventions versus inactive comparator;
4. multi-component lifestyle interventions versus inactive comparator;
5. medication-switching interventions versus inactive comparator;
6. weight-loss medication interventions versus inactive comparator;
7. surgical interventions versus inactive comparator.

Assessment of risk of bias in included studies

We will assess risk of bias in included studies using Cochrane's tool for assessing risk of bias as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017) and contained in RevMan 5 (RevMan 2014). We will contact study authors for clarification of or further detail of methodologies where appropriate.

Two review authors (AT and FJ) will assess risk of bias independently for each study. We will resolve any disagreements by consultation with a third review author (EM or DD).

For randomised studies, we will base our assessment on the following domains.

1. Random sequence generation
2. Allocation concealment
3. Blinding of participants and personnel
4. Blinding of outcome assessment
5. Incomplete outcome data
6. Selective outcome reporting
7. Other bias

We will judge each potential source of bias as having high, low, or unclear risk and will provide a supporting quotation from the study report together with a justification for our judgement in the 'Risk of bias' table. We will summarise risk of bias judgements across different studies for each of the domains listed. When information on risk of bias is related to unpublished data or correspondence with a study author, we will note this in the 'Risk of bias' table.

For cluster-randomised studies, we will assess these additional sources of bias as detailed in section 16.3.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

1. Recruitment bias
2. Baseline imbalance

We will judge each additional source of bias as having high, low, or unclear risk and will provide a supporting quotation from the study report together with a justification for our judgement in the 'Risk of bias' table.

Measures of treatment effect

For continuous data, where the included studies measured outcomes using the same scale or in the same way, we will use the mean difference (MD) with 95% confidence intervals (CIs). We will use the standardised mean difference (SMD) with 95% CIs if studies measured the same outcomes using different measurement scales, but in a manner that allows us to combine data (Deeks 2017). We will use change-from-baseline data, or, if this is not available, final value scores. Adverse events will be the only dichotomous outcome and for dichotomous data, we will present results as summary risk ratios (RR) with 95% CIs.

Unit of analysis issues

We envisage that, for most studies, we shall be able to extract data from baseline and end point data. However, if the study design is a cluster-randomised, cross-over or multiple-arm study, we shall address unit of analysis issues as detailed below.

Cluster-randomised studies

We will include cluster-randomised studies in the analyses along with individually randomised studies. We will make an adjustment to the sample size in these studies for each intervention based on the method described in Deeks 2017, using an estimate of the intra-cluster correlation coefficient (ICC) derived from the study (where available) or from a similar study or from a study of a similar population. If we use ICCs from other studies, we will conduct sensitivity analyses to explore the effect of variation in ICC values. We will include studies with data from more than one time point, selecting data from one clinically important time point for inclusion in a meta-analysis if appropriate.

Cross-over studies

If any included study has a cross-over design, we will consider only results from the first randomisation period, that is, prior to the first cross-over.

Studies with multiple treatment groups

If the study has three (or more) arms testing relevant active interventions versus an inactive control, for continuous outcomes, we will pool means, SDs and number of participants for each active treatment group across treatment arms, or we will divide the number of participants in the control group between the treatment arms. For dichotomous outcomes, we will pool data from relevant active intervention arms into a single arm for comparison or we will divide data from the comparator arm equally between the treatment arms.

Dealing with missing data

We will record missing and unclear data for each included study. If possible, we will perform all analyses using an intention-to-treat approach, that is, we will analyse all participants and their outcomes within the groups to which they were allocated, regardless of whether they received the intervention. If necessary, we will contact study authors to request missing data.

Assessment of heterogeneity

If meta-analysis of data is possible, we will evaluate heterogeneity by visually inspecting point effect estimates and confidence intervals in the forest plots, and by using the Tau², Chi² test and I² statistic (Higgins 2003), as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2017). We will interpret the I² statistic as follows: 0% to 40% might not be important; 30% to 60% may represent moderate heterogeneity; 50% to 90% may represent substantial heterogeneity; 75% to 100% represents considerable heterogeneity.

Assessment of reporting biases

If 10 or more studies are included in the meta-analysis, we will prepare funnel plots and examine them for asymmetry. If asymmetry is noted, we will explore possible reasons (Sterne 2017).

Data synthesis

We will use RevMan 5 (RevMan 2014) to conduct statistical analysis. When it is reasonable to assume that studies are homogeneous, that is, examining the same intervention in similar populations using the same methods, we will use a fixed-effect meta-analysis to combine data. If there is clinical heterogeneity (due to variations in participants, interventions or outcomes), we will use random-effects meta-analysis to produce an overall summary if it is reasonable to assume that an average treatment effect across the included studies is clinically meaningful. If not, we will not perform a meta-analysis and instead will present a narrative synthesis. If we use a random-effects model, we will present the results as the average treatment effect with 95% CIs. Irrespective of the model used, we will report estimates of Tau², Chi² test and I² statistics. We anticipate that we will find few studies of sufficient homogeneity to warrant use of a fixed-effect model and therefore we anticipate using a random-effects model.

Subgroup analysis and investigation of heterogeneity

If we identify substantial heterogeneity, we will explore it using subgroup analyses. To explain anticipated heterogeneity among study results, we define three a priori hypotheses on which we will base subgroup analyses. We will perform the following subgroup analyses on our primary outcomes:

1. bipolar disorder type I versus bipolar disorder type II;
2. duration of treatment (up to 12 months and longer than 12 months);
3. setting (community versus hospital).

Sensitivity analysis

We will repeat the analyses including high-quality studies only. For the purpose of this review, we will classify studies judged as 'low risk of bias' for sequence generation and allocation concealment as high-quality studies.

'Summary of findings' table

For each of the main comparators (detailed under the 'Main comparators' heading), we will prepare a 'Summary of findings' table using GRADEpro GDT 2015 software. We will include the three primary outcomes i.e. changes in body mass as measured by change in BMI, patient reported adverse events and quality of life. Short-term effects, measured up to 12 months after the end of the intervention, which will be the primary time point reported in

the 'Summary of findings' table. We will grade the quality of the evidence according to the GRADE approach (Guyatt 2008). We will assign one of four levels of quality, high, moderate, low, or very low, based on overall risk of bias of the included studies, the directness of the evidence, the inconsistency of results, the precision of the estimates and risk of publication bias.

Ensuring relevance to decisions in health care

The principle of assessing healthcare interventions using outcomes that matter to people making choices in health care underpins our approach to defining the outcomes for this review. We consulted with a consumer group of people living with bipolar disorder on what outcomes matter to this population and the primary and secondary outcomes of this review reflect their input. We will continue to consult with this consumer group throughout the process of carrying out this systematic review.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. CCMDCTR core MEDLINE search

CCMD's core search strategy used to inform the Group's Specialised Register: OVID MEDLINE

A search alert based on condition + RCT filter only

1. *[MeSH Headings]:*

eating disorders/ or anorexia nervosa/ or binge-eating disorder/ or bulimia nervosa/ or female athlete triad syndrome/ or pica/ or hyperphagia/ or bulimia/ or self-injurious behavior/ or self mutilation/ or suicide/ or suicidal ideation/ or suicide, attempted/ or mood disorders/ or affective disorders, psychotic/ or bipolar disorder/ or cyclothymic disorder/ or depressive disorder/ or depression, postpartum/ or depressive disorder, major/ or depressive disorder, treatment-resistant/ or dysthymic disorder/ or seasonal affective disorder/ or neurotic disorders/ or depression/ or adjustment disorders/ or exp antidepressive agents/ or anxiety disorders/ or agoraphobia/ or neurocirculatory asthenia/ or obsessive-compulsive disorder/ or obsessive hoarding/ or panic disorder/ or phobic disorders/ or stress disorders, traumatic/ or combat disorders/ or stress disorders, post-traumatic/ or stress disorders, traumatic, acute/ or anxiety/ or anxiety, castration/ or koro/ or anxiety, separation/ or panic/ or exp anti-anxiety agents/ or somatoform disorders/ or body dysmorphic disorders/ or conversion disorder/ or hypochondriasis/ or neurasthenia/ or hysteria/ or munchausen syndrome by proxy/ or munchausen syndrome/ or fatigue syndrome, chronic/ or obsessive behavior/ or compulsive behavior/ or behavior, addictive/ or impulse control disorders/ or firesetting behavior/ or gambling/ or trichotillomania/ or stress, psychological/ or burnout, professional/ or sexual dysfunctions, psychological/ or vaginismus/ or Anhedonia/ or Affective Symptoms/ or *Mental Disorders/

2. *[Title/ Author Keywords]:*

(eating disorder* or anorexia nervosa or bulimi* or binge eat* or (self adj (injur* or mutilat*)) or suicide* or suicidal or parasuicid* or mood disorder* or affective disorder* or bipolar i or bipolar ii or (bipolar and (affective or disorder*)) or mania or manic or cyclothymic* or depression or depressive or dysthymi* or neurotic or neurosis or adjustment disorder* or antidepress* or anxiety disorder* or agoraphobia or obsess* or compulsi* or panic or phobi* or ptsd or posttrauma* or post trauma* or combat or somatoform or somati# ation or medical* unexplained or body dysmorphi* or conversion disorder or hypochondria* or neurastheni* or hysteria or munchausen or chronic fatigue* or gambling or trichotillomania or vaginismus or anhedoni* or affective symptoms or mental disorder* or mental health).ti,kf.

3. *[RCT filter]:*

(controlled clinical trial.pt. or randomized controlled trial.pt. or (randomi#ed or randomi#ation).ab,ti. or randomly.ab. or (random* adj3 (administ* or allocat* or assign* or class* or control* or determine* or divide* or distribut* or expose* or fashion or number* or place* or recruit* or subsitut* or treat*)).ab. or placebo*.ab,ti. or drug therapy.fs. or trial.ab,ti. or groups.ab. or (control* adj3 (trial* or study or studies)).ab,ti. or ((singl* or doubl* or tripl* or trebl*) adj3 (blind* or mask* or dummy*)).mp. or clinical trial, phase ii/ or clinical trial, phase iii/ or clinical trial, phase iv/ or randomized controlled trial/ or pragmatic clinical trial/ or (quasi adj (experimental or random*)).ti,ab. or ((waitlist* or wait* list* or treatment as usual or TAU) adj3 (control or group)).ab.)

4. (1 and 2 and 3)

Records are screened for reports of RCTs within the scope of the Cochrane Common Mental Disorders Group. Secondary reports of RCTs are tagged to the appropriate study record.

Similar search alerts are also conducted on OVID EMBASE and PsycINFO, using relevant subject headings (controlled vocabularies) and search syntax, appropriate to each resource.

Appendix 2. Cochrane CENTRAL and MEDLINE (Ovid) search strategy

We will use the following terms to search the Cochrane Library.
ID Search Hits
#1 MeSH descriptor: [Bipolar Disorder] explode all trees
#2 (Bipolar or cyclothymi*):ti,ab,kw (Word variations have been searched)
#3 ((Mani* or major) and (depres* or disorder*)):ti,ab,kw (Word variations have been searched)
#4 #1 or #2 or #3
#5 MeSH descriptor: [Obesity] explode all trees
#6 Obes*:ti,ab,kw (Word variations have been searched)
#7 MeSH descriptor: [Body Mass Index] this term only
#8 (body mass or BMI):ti,ab,kw (Word variations have been searched)
#9 #5 or #6 or #7 or #8
#10 #4 and #9
We will use the following terms to search MEDLINE (Ovid interface)

#	Searches	Results
1	Bipolar Disorder/	36872
2	(Bipolar or cyclothymi*).ti,ab,kw,ot.	55522
3	((Mani$ or major) and (depres$ or disorder$)).ti,ab,kw.	184134
4	1 or 2 or 3	237605
5	exp Obesity/	183198
6	Obes$.ti,ab,kw,ot.	256668
7	*Overweight/	11947
8	*body mass index/	17350
9	(body mass or BMI).ti,ab,kw,ot.	224315
10	5 or 6 or 7 or 8 or 9	445401
11	randomized controlled trial.pt.	457132
12	controlled clinical trial.pt.	92290
13	(randomized or randomised).ab.	487026
14	placebo.ab.	187645
15	clinical trials as topic.sh.	183110
16	randomly.ab.	287705

(*Continued*)

17	trial.ti.	179972
18	11 or 12 or 13 or 14 or 15 or 16 or 17	1172169
19	4 and 10 and 18	542
20	exp animals/ not humans.sh.	4440009
21	19 not 20	528

Appendix 3. OVID PsycINFO search

We will use the following terms to search OVID PsycINFO.

1	bipolar disorder/
2	(Bipolar or cyclothymi*).ti,ab.
3	((Mani$ or major) and (depres$ or disorder$)).ti,ab.
4	1 or 2 or 3
5	exp OBESITY/
6	Obes$.ti,ab.
7	exp OVERWEIGHT/
8	exp Body Mass Index/
9	(body mass or BMI).ti,ab.
10	5 or 6 or 7 or 8 or 9
11	4 and 10
12	random$.ti,ab. or DISSERTATION ABSTRACT.pt
13	11 and 12

CONTRIBUTIONS OF AUTHORS

AT, ED, SS, YC and FJ drafted the review protocol. DD and John Geddes (JG) reviewed the protocol, provided feedback on individual drafts and contributed to the final version. John Kelly (JK) informed the Pharmacological interventions section. AT and SS were responsible for project management. Sarah Dawson prepared the search strategy. FJ was responsible for the submission of the protocol to the Editorial team.

DECLARATIONS OF INTEREST

Agnes Tully: no known conflicts of interest to declare

Edel Murphy: no known conflicts of interest to declare

Siobhan Smyth: no known conflicts of interest to declare

Yvonne Conway: no known conflicts of interest to declare

John Geddes: no known conflicts of interest to declare

Declan Devane: no known conflicts of interest to declare

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