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Pharmacological interventions for prevention of weight gain in people with schizophrenia (Protocol)

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[Intervention Protocol]

Pharmacological interventions for prevention of weight gain in people with schizophrenia

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ABSTRACT

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

To determine the effects of pharmacological interventions for preventing weight gain in people with schizophrenia.

BACKGROUND

Description of the condition

Schizophrenia and weight gain

Schizophrenia is a complex and severe neuropsychiatric disorder characterised by delusions, hallucinations, disorganised behaviour and progressive cognitive deficits (Keshavan 2008; van Os 2009). It is also a heterogeneous disorder with psychopathology varying across patients and over the course of the illness (Seaton 2001). The onset is typically in the late adolescence or early adulthood and is marked by episodes of psychosis and severe functional disability (Liversedge 2011). The complexity, phenotypic heterogeneity, and the polygenic nature of the genetic risk for schizophrenia make

it a challenge to treat and investigate, and the etiopathogenesis (the cause and development of a disease or abnormal condition) of schizophrenia is yet to be understood fully (Keshavan 2011). The severity of the disability and lack of knowledge into its aetiology makes it the most disabling among all psychiatric disorders requiring a disproportionate share of mental health services (Mueser 2004); it is the costliest among severe mental disorders in terms of human suffering and expenditure incurred by the society (van Os 2009). The disability and cost to the society are compounded by the common presence of comorbid obesity in this population, a problem that has been exacerbated more recently with the increased use of second-generation antipsychotics, many of which are associated with the risk of weight gain and metabolic disturbances such as diabetes and the metabolic syndrome (Allison 1999; Casey 2004; De Hert 2011; Homel 2002; Rajkumar 2017). The World Health Organization (WHO) defines overweight and

obesity as an 'abnormal or excessive fat accumulation that may impair health'. A person who has a body mass index (BMI) of over 25 is overweight and those with a BMI of over 30 are obese (WHO 2013). The prevalence of obesity in people with schizophrenia has been reported to be anywhere from 1.5 times to 4 times higher than the general population (ADA/APA 2004; Coodin 2001; Gurpegui 2012; Silverstone 1988); the risk may be even higher for long-term inpatients (Ringen 2018). For people with schizophrenia, there is a marked increase in standardised mortality ratios for both natural and unnatural causes of death and much of this increment may be attributed to the increased prevalence of coronary heart disease risk (Cohn 2004; Goff 2005; Henderson 2005; Mackin 2005; Saari 2005; Westman 2017), and related obesity in this population (Annamalai 2017; Coodin 2001; Daumit 2003; Susce 2005). Obesity doubles the risk of all-cause mortality, coronary heart disease, stroke and type 2 diabetes, increases the risk of some cancers, musculoskeletal problems and loss of function, and carries negative psychological consequences (DoH 2004). Being an obese or overweight adult is associated with increases in early mortality and large decreases in life expectancy, and these decreases are similar to those seen with smoking (Peeters 2003). The significance and recognition of this prevalence and its impact on premature mortality and morbidity has led to the development of consensus statements (ADA/APA 2004; De Nayer 2005) and guidelines (Cooper 2016) on its management. Despite this, evidence from a systematic review suggests that the all-cause standardised mortality ratio between persons with schizophrenia and general population has risen steadily since the 1970s (Saha 2007). In stark contrast to the well-recognised risk of metabolic comorbidity in schizophrenia, studies have repeatedly shown extremely low rates of intervention for these risk factors (De Hert 2011; Lappin 2018). Extremely low of intervention for what would be considered 'modifiable" cardiovascular risk factors is also apparent in young, first-episode populations (Correll 2014). In turn, a concurrent body of literature suggests that metabolic risk is accrued early on in illness (De Hert 2006; Ward 2015), later shaving off 15 to 20 years of life (due to cardiovascular disease) (Hoang 2011; Newcomer 2007).

Beyond effects on cardiovascular morbidity and mortality, growing evidence in non-psychiatric populations also suggests that obesity can be associated with structural brain changes, brain perfusion changes and cognitive deficits (Jagust 2007; Sellbom 2012), with observations supporting some similarities to those noted in schizophrenia (Reichenberg 2007). The clinical implications of being overweight or obese on cognitive function in addition to the deficits observed in schizophrenia, remains a relatively unexplored area of research. Emerging evidence has linked cognitive impairment in schizophrenia to metabolic dysfunction (Bora 2017; Friedman 2010; Lindenmayer 2012), which might in turn might suggest that interventions to reduce obesity and cardiometabolic risk could have dual salutary benefits on cardiovascular outcomes and illness-related functional disability. Quality of life is further reduced for people with schizophrenia with a high

BMI (Bueno-Antequera 2018; Faulkner 2007a; Kurzthaler 2001; Strassnig 2003) and those gaining weight (Allison 2003). Furthermore, Weiden and colleagues (Weiden 2004) reported a significant, positive association between obesity, subjective distress from weight gain and medication non-compliance in a sample of people with schizophrenia. People with schizophrenia face the combined challenges of living with the illness, and for many, additional obesity and related illnesses. This combination is a major public health problem (Bueno-Antequera 2018; Wirshing 2004) and carries considerable human cost. Recognition of this has led to growing concern with how best to intervene (Birt 2003; Bueno-Antequera 2018; Catapana 2004; Cooper 2016; Green 2000; Le Fevre 2001; Osborn 2001).

Mechanisms of weight gain in schizophrenia

To date, there is no consensus on what pharmacological factors may be involved in this weight gain particularly regarding the newer antipsychotics. As reviewed elsewhere (Ananth 2004; Jin 2008; Reynolds 2010; Reynolds 2017), a range of potential weight-inducing mechanisms such as dopaminergic blockage; increased appetite due to the interaction of antipsychotic medication with dopamine, serotonin, and histamine neuronal receptors; increased leptin; and increases in systemic levels of various cytokines and soluble cytokine receptors could be implicated. Whether gender influences antipsychotic-related weight gain susceptibility remains a topic of debate; while there are clinical data suggesting that women may be more susceptible to atypical antipsychotic-associated weight gain (Aichhorn 2007; Gebhardt 2009), others have failed to demonstrate this (Basson 2001; Ratzoni 2002). The weight gain story may be further complicated through genetic and/or epigenetic mechanisms, which may modulate risk. In this regard, among others, dopamine, serotonin, and leptin gene polymorphisms have emerged as genetic candidates for antipsychotic-related cardio-metabolic side effects (Correll 2011). In addition, it is important to note that obesity was commonly reported before antipsychotics were widely introduced (Baptista 2002). Compared to the general population, people with schizophrenia also have a poor diet (Dipasquale 2013; McCreadie 1998; Strassnig 2003) and a physically inactive lifestyle (Brown 1999; Cohn 2004; Daumit 2005; Vancampfort 2017) and these lifestyle factors will contribute to weight gain. However, pharmacological intervention strategies may still treat or minimise weight gain associated with poor lifestyle.

Description of the intervention

Pharmacological agents that have been approved for weight loss in the general population, and other medications that may suppress appetite, increase satiety, or increase thermogenesis have been studied to prevent weight gain in people with schizophrenia. These include metformin, topiramate, H2 antagonists such as famotidine and nizatidine, and antidepressants such as fluoxetine and reboxetine. Most clinical trials have been between six and 12 weeks

long. Very few have been for 24 weeks or longer. However, clear evidence regarding the optimal duration of such interventions is lacking (Cooper 2016).

Metformin is a biguanide and is a first-line anti-diabetic agent. It is usually administered in a dose ranging from 500 mg to 2500 mg and is usually administered in divided doses twice a day. Topiramate is an anticonvulsant that has recently approved by the Food and Drug Administration (FDA) in combination with phentermine for weight loss. The dose ranges from 100 mg to 200 mg given in divided doses twice a day. Famotidine (20 mg to 40 mg once a day) and nizatidine (150 mg to 300 mg once a day) are both commonly used in the treatment of peptic ulcer disease and gastroesophageal reflux disease as they block the histamine H2 receptor. Fluoxetine (20 mg once a day) and reboxetine (4 mg once a day) are antidepressants that have also been investigated for their weight loss promoting properties. Reboxetine is a norepinephrine reuptake inhibitor approved as an antidepressant in parts of Europe. Loss of appetite is a side effect of this medication prompting investigation as a weight loss agent. More recently, samidorphan, an opioid modulator that preferentially antagonises the μ-opioid receptor is being investigated for preventing antipsychotic-induced weight gain (Silverman 2018). It is taken orally, the usual dose is 5 mg/day. Common side effects include nausea, sedation and dizziness.

How the intervention might work

Pharmacological interventions may operate on a range of potential mechanisms such as suppressing appetite, increasing satiety, or increasing thermogenesis by modifying central nervous system neurotransmission of norepinephrine, dopamine and serotonin. Metformin lowers liver glucose production and improves whole-body insulin sensitivity. It has variably been associated with weight loss in non-psychiatrically ill populations, and may prevent continual weight gain while improving insulin resistance (Hundal 2003). Hence, it is commonly understood as an peripheral insulin sensitiser. Suppression of appetite is seen commonly with topiramate and may occur by GABA-mediated mechanisms in the central nervous system (Velazquez 2018). With respect to H2 receptor antagonists, it is unclear whether the weight loss action is a direct result of gastric histamine receptor antagonism or if other factors play a role. Histamine is known to mediate leptin action and is involved in energy and feeding regulation (Lett 2012). H2 receptor antagonists can therefore plausibly interact with these medicators to effect weight loss. Fluoxetine and nizatidine modify central nervous system neurotransmission of norepinephrine and serotonin impacting weight. Early studies had shown serotonin blockade to be an effective anorectic strategy (Goldstein 1994) that stimulated interest in studying these agents as weight loss medications.

At the organism level, preventing weight gain avoids all the negative outcomes associated with weight gain and may help engender a healthy lifestyle. Furthermore, sustained changes in health behaviours as a result of such interventions may reduce risk of mortality and morbidity independent of any weight loss (Wei 1999). Indeed, prevention of weight gain has been an area of active enquiry and both older interventions such as metformin (de Silva 2016) and newer molecules such as samidorphan may be useful in achieving this goal (Silverman 2018).

Why it is important to do this review

In the seminal meta-analysis highlighting atypical-antipsychotic related weight gain, every antipsychotic medication except ziprasidone and molindone were associated with some degree of weight increase after just 10 weeks of treatment (Allison 1999). The effects were greatest with olanzapine and clozapine which increased body weight by approximately 4 kg to 4.5 kg, followed by risperidone (mean weight gain 2 kg). Notably, these data were assembled from chronic populations characterised by many years of exposure to medications and illness-related effects. What has become clearer is that factors related to illness chronicity likely result in an underestimation of the impact of antipsychotics on weight gain, and an overestimation of differences between agents. Collectively, data involving both short-term and long-term evidence comparing olanzapine or risperidone in chronic patients to those experiencing a first episode, demonstrate a three to four times larger magnitude of weight gain in those early on in the illness (Alvarez-Jimenez 2008). Furthermore, no antipsychotic medication appears to be devoid of weight gain risk in patients with little prior antipsychotic exposure. For example, one 12-week cohort study enrolling antipsychotic-naive youth assigned to aripiprazole, quetiapine or olanzapine, demonstrated substantial weight gain not only with olanzapine (average 8.5 kg), but also with risperidone, quetiapine as well as aripiprazole (average 4.4 kg; Correll 2009). These findings have since been replicated, including in a recent meta-analysis (Bak 2014). Interestingly, data in previously medication-unexposed individuals also suggests that agents classified as being metabolically neutral may exhibit a more delayed onset of weight gain, with treatments differing by pattern, and not always the final amount of weight increase (Findling 2010; Perez-Iglesias 2008; Zipursky 2005). Morover, results from a nation-wide register-based analysis suggest that all antipsychotics contribute to the risk of diabetes, independently of class (Rajkumar 2017). Obesity is also one of the most important risk factor for the development of dyslipidaemia, diabetes, cardiovascular diseases, leading to premature death (Alberti 2009). Taken together, these emerging data highlight the susceptibility, particularly of first-episode patients, to antipsychotic-related weight gain.This highlights the case for implementing early effective strategies to prevent or decrease metabolic risk accrual which may occur early in the treatment of the illness (Ward 2015).

We believe there is a sufficient volume of material to split the previous Cochrane Review (Faulkner 2007) into separate reviews focusing on behavioural and pharmacological interventions inde-

pendently. Furthermore, given the vast number of pharmacological interventions tried for prevention and treatment of weight gain, we have chosen to split the review on pharmacological interventions to focus on prevention and treatment of weight gain in separate reviews. The current review focuses on pharmacological interventions for the prevention of weight gain. While previous studies have systematically analysed the role of metformin in preventing weight gain (de Silva 2016), no systematic review examining all available pharmacological interventions in a preventive role has been published. This is important as what we consider effective treatments for adult obesity produce modest weight loss (approximately 2 kg to 5 kg) compared to no treatment or usual care. While this degree of weight loss may have a meaningful impact, it is not sufficient to reverse the weight increases associated with antipsychotic treatment (e.g. average 8.5 kg increase in antipsychotic naive patients starting olanzapine Correll 2009). In this regard, prevention strategies may represent the most useful strategy. We are interested in identifying and including all randomised controlled trials (RCTs) of pharmacological agents to prevent weight gain, regardless of aetiology, in all people with schizophrenia or schizophrenia-like illnesses.

OBJECTIVES

To determine the effects of pharmacological interventions for preventing weight gain in people with schizophrenia.

METHODS

Criteria for considering studies for this review

Types of studies

We will consider all relevant randomised controlled trials (RCTs). We will include RCTs meeting our inclusion criteria and reporting useable data. We will consider trials that are described as 'double-blind' - in which randomisation is implied - and include or exclude once we have carried out a sensitivity analysis (see Sensitivity analysis). We will exclude quasi-randomised studies, such as those that allocate intervention by alternate days of the week. Where people are given additional treatments as well as pharmacological strategies for preventing weight gain, we will only include data if the adjunct treatment is evenly distributed between groups and it is only the pharmacological strategy for preventing weight gain that is randomised.

Types of participants

People diagnosed with schizophrenia or schizophrenia-like illnesses (such as schizoaffective disorder, schizophreniform disorder, and delusional disorder) using any diagnostic criteria irrespective of age, nationality or sex of participants. We will include trials regardless of the length of the participant's illness, stage of illness, treatment setting, current clinical state, or symptom cluster.

We are interested in making sure that information is as relevant as possible to the current care of people with schizophrenia, so aim to highlight the current clinical state clearly (acute, early post-acute, partial remission, remission), as well as the stage (prodromal, first episode, early illness, persistent), and whether the studies primarily focused on people with particular problems (for example, negative symptoms, treatment-resistant illnesses).

Types of interventions

1. Pharmacological intervention for preventing weight gain

Pharmacological interventions for preventing weight gain. For people with schizophrenia these 'weight prevention' interventions are typically 'adjunctive' (add-on) interventions to other ongoing routinely prescribed medications such as antipsychotics.

We will consider all types of pharmacological interventions for preventing weight gain, these can include those currently licensed for weight loss, an off-label therapy, withdrawn from the market, or an isolated nutritive supplement.

2. Standard care

We define this as care that the participants receive in the placebo arm of the research trial. This would include regular visits with the psychiatrist, continuing antipsychotic medications, and lifestyle and/or diet advice as mentioned in individual studies.

3. Other behavioural interventions

We will consider an intervention where an additional pharmacological intervention is combined with a behavioural intervention (i.e. diet and/or exercise). We will only consider interventions that compare such a combined intervention strategy with a behavioural intervention alone in order to assess the additive effect of using a pharmacological adjunct.

Types of outcome measures

If possible, we aim to divide all outcomes into short term (less than six months), medium term (seven to 12 months) and long term (over 12 months).

We will endeavour to report binary outcomes recording clear and clinically meaningful degrees of change (e.g. global impression of

much improved, or more than 50% improvement on a rating scale* - as defined within the trials) before any others. Thereafter, we will list other binary outcomes and then those that are continuous.
* For types of scales we will extract data from please see (Data extraction and management)
For outcomes such as 'clinically important change', 'any change', 'relapse' we will use the definition used by each of the trials.

Primary outcomes

1. Weight (or another indicator of body mass e.g. body mass index (BMI), waist measurement, waist-to-hip ratio)

1.1 Clinically important change in weight
1.2 Clinically important change in BMI

2. Leaving the study early

2.1 For any reason

3. Compliance with treatment - as defined by individual studies

4. Adverse effect/events

4.1 Specific

4.1.1 Gastrointestinal effects: nausea

Secondary outcomes

1. Weight (or another indicator of body mass e.g. body mass index (BMI), waist measurement, waist-to-hip ratio)

1.1 Any change in body weight
1.2 Any change in BMI
1.3 Clinically important change in waist circumference (as defined by individual studies)
1.4 Any change in waist circumference
1.5 Clinically important change in waist-to-hip circumference ratio (as defined by individual studies)
1.6 Any change in waist-to-hip circumference ratio
1.7 Clinically important change in percentage body fat
1.8 Any change in percentage body fat

2. Leaving the study early

2.1 For specific reason

3. Global state

3.1 Clinically important change in global state (as defined by individual studies)
3.2 Any change in global state
3.3 Average endpoint/change score on global state scale

4. Mental state

4.1. Clinically important change in general mental state
4.2. Any change in general mental state
4.3. Average endpoint/change score on mental state scale

5. Well-being

5.1 Clinically important change in well-being
5.2 Any change in well-being
5.3 Average endpoint/change score on well-being scale

6. Quality of life

6.1 Clinically important change in quality of life
6.2 Any change in quality of life
6.3 Average endpoint/change score on quality of life scale

7. Adverse effects/event - general or specific

7.1 General

7.1.1 At least one adverse effect/event
7.1.2 Average endpoint/change score on general adverse effect scale

7.2 Specific

7.2.1 Clinically important specific adverse effects (e.g. cardiovascular, gastrointestinal)
7.2.2 Death - suicide and natural causes

8. Physiological

8.1 Cardiovascular measures
8.2 Laboratory measures

9. Economic

9.1 Direct costs
9.2 Indirect costs

'Summary of findings' table

We will use the GRADE approach to interpret findings (Schünemann 2011); and will use GRADEpro GDT to export data from our review to create a 'Summary of findings' table . These tables provide outcome-specific information concerning the overall certainty of evidence from each included study in the comparison, the magnitude of effect of the interventions examined, and the sum of available data on all outcomes we rate as important to patient care and decision making. We aim to select the following main outcomes for inclusion in the 'Summary of findings' table.

1. Weight: clinically important change in weight
2. Weight: clinically important change in BMI
3. Weight: waist circumference: clinically important change in waist circumference
4. Quality of life: clinically important change in quality of life
5. Adverse effect: nausea
6. Leaving the study early: for any reason
7. Compliance with treatment

If data are not available for these pre-specified outdoes but are available for ones that are similar, we will present the closest outcome to the pre-specified one in the table but take this into account when grading the finding.

Search methods for identification of studies

Electronic searches

Cochrane Schizophrenia Group's Study-Based Register of Trials

The Information Specialist will search the register using the following search strategy.
(*{Pharm}* in Intervention) AND (*Weight Gain* in Health Care Condition) of STUDY
In such study-based register, searching the major concept retrieves all the synonyms and relevant studies because all the studies have already been organised based on their interventions and linked to the relevant topics (Shokraneh 2017; Shokraneh 2018).
This register is compiled by systematic searches of major resources (CENTRAL, CINAHL, ClinicalTrials.Gov, Embase, MEDLINE, PsycINFO, PubMed, WHO ICTRP) and their monthly updates, ProQuest Dissertations and Theses A&I and its quarterly update, Chinese databases (CBM, CNKI, and Wanfang) and their annual updates, handsearches, grey literature, and conference proceedings (see Group's website). There is no language, date, document type, or publication status limitations for inclusion of records into the register.

Searching other resources

1. Reference searching

We will inspect references of all included studies for further relevant studies.

2. Personal contact

We will contact the first author of each included study for information regarding unpublished trials. We will note the outcome of this contact in the 'Included studies' or 'Studies awaiting classification' tables.

Data collection and analysis

Selection of studies

Review authors SMA and ZA will independently inspect citations from the searches and identify relevant abstracts; MH will independently re-inspect a random 20% sample of these abstracts to ensure reliability of selection. Where disputes arise, we will acquire the full report for more detailed scrutiny. ZA will then obtain and inspect full reports of the abstracts or reports meeting the review criteria. SMA will re-inspect a random 20% of these full reports in order to ensure reliability of selection. Where it is not possible to resolve disagreement by discussion, we will attempt to contact the authors of the study concerned for clarification.

Data extraction and management

1. Extraction

Review authors MD, ZA, and JL will extract data from all included studies. In addition, to ensure reliability, SMA will independently extract data from a random sample of these studies, comprising 10% of the total. We will attempt to extract data presented only in graphs and figures whenever possible, but will include only if two review authors independently obtain the same result. If studies are multi-centre, then where possible we will extract data relevant to each. We will discuss any disagreement and document our decisions. If necessary, we will attempt to contact study authors through an open-ended request in order to obtain missing information or for clarification. MH will help clarify issues regarding any remaining problems and we will document these final decisions.

2. Management

2.1 Forms

We will extract data onto standard, pre-designed, simple forms.

2.2 Scale-derived data

We will include continuous data from rating scales only if:

a) the psychometric properties of the measuring instrument have been described in a peer-reviewed journal (Marshall 2000);
b) the measuring instrument has not been written or modified by one of the trialists for that particular trial; and
c) the instrument should be a global assessment of an area of functioning and not sub-scores which are not, in themselves, validated or shown to be reliable. However there are exceptions, we will include sub-scores from mental state scales measuring positive and negative symptoms of schizophrenia.

Ideally, the measuring instrument should either be i. a self-report or ii. completed by an independent rater or relative (not the therapist). We realise that this is not often reported clearly; in 'Description of studies' we will note if this is the case or not.

2.3 Endpoint versus change data

There are advantages of both endpoint and change data: change data can remove a component of between-person variability from the analysis; however, calculation of change needs two assessments (baseline and endpoint) that can be difficult to obtain in unstable and difficult-to-measure conditions such as schizophrenia. We have decided primarily to use endpoint data, and only use change data if the former are not available. If necessary, we will combine endpoint and change data in the analysis, as we prefer to use mean differences (MDs) rather than standardised mean differences (SMDs) throughout (Deeks 2011).

2.4 Skewed data

Continuous data on clinical and social outcomes are often not normally distributed. To avoid the pitfall of applying parametric tests to non-parametric data, we will apply the following standards to relevant continuous data before inclusion.
For endpoint data from studies including fewer than 200 participants:

a) when a scale starts from the finite number zero, we will subtract the lowest possible value from the mean, and divide this by the standard deviation (SD). If this value is lower than one, it strongly suggests that the data are skewed and we will exclude these data. If this ratio is higher than one but less than two, there is suggestion that the data are skewed: we will enter these data and test whether

their inclusion or exclusion would change the results substantially. If such data change results we will enter these as 'other data'. Finally, if the ratio is larger than two we will include these data, because it is less likely that they are skewed (Altman 1996; Higgins 2011a).
b) if a scale starts from a positive value (such as the Positive and Negative Syndrome Scale (PANSS), which can have values from 30 to 210 (Kay 1986)), we will modify the calculation described above to take the scale starting point into account. In these cases skewed data are present if $2 SD > (S - S min)$, where S is the mean score and 'S min' is the minimum score.
Please note: we will enter all relevant data from studies of more than 200 participants in the analysis irrespective of the above rules, because skewed data pose less of a problem in large studies. We will also enter all relevant change data, as when continuous data are presented on a scale that includes a possibility of negative values (such as change data), it is difficult to tell whether or not data are skewed.

2.5 Common measurement

To facilitate comparison between trials we aim, where relevant, to convert variables that can be reported in different metrics, such as days in hospital (mean days per year, per week or per month) to a common metric (e.g. mean days per month).

2.6 Conversion of continuous to binary

Where possible, we will make efforts to convert outcome measures to dichotomous data. This can be done by identifying cut-off points on rating scales and dividing participants accordingly into 'clinically improved' or 'not clinically improved'. It is generally assumed that if there is a 50% reduction in a scale-derived score such as the Brief Psychiatric Rating Scale (BPRS) (Overall 1962), or the PANSS (Kay 1986), this could be considered as a clinically significant response (Leucht 2005; Leucht 2005a). If data based on these thresholds are not available, we will use the primary cut-off presented by the original authors.

2.7 Direction of graphs

Where possible, we will enter data in such a way that the area to the left of the line of no effect indicates a favourable outcome for pharmacological intervention for prevention of weight gain. Where keeping to this makes it impossible to avoid outcome titles with clumsy double-negatives (e.g. 'not un-improved') we will report data where the left of the line indicates an unfavourable outcome and note this in the relevant graphs.

Assessment of risk of bias in included studies

Review authors SMA and ZA will work independently to assess risk of bias by using criteria described in the *Cochrane Handbook for Systematic Reviews of Interventions* to assess trial quality (Higgins

2011b). This set of criteria is based on evidence of associations between potential overestimation of effect and the level of risk of bias of the article that may be due to aspects of sequence generation, allocation concealment, blinding, incomplete outcome data and selective reporting, or the way in which these 'domains' are reported.

If the raters disagree, we will make the final rating by consensus. Where inadequate details of randomisation and other characteristics of trials are provided, we will attempt to contact authors of the studies in order to obtain further information. We will report non-concurrence in quality assessment, but if disputes arise regarding the category to which a trial is to be allocated, we will resolve this by discussion.

We will note the level of risk of bias in both the text of the review, Figure 1, Figure 2, and the 'Summary of findings' table/s.

Measures of treatment effect

1. Binary data

For binary outcomes we will calculate a standard estimation of the risk ratio (RR) and its 95% confidence interval (CI), as it has been shown that RR is more intuitive than odds ratios (Boissel 1999); and that odds ratios tend to be interpreted as RRs by clinicians (Deeks 2000). Although the number needed to treat for an additional beneficial outcome (NNTB) and the number needed to treat for an additional harmful outcome (NNTH), with their CIs, are intuitively attractive to clinicians, they are problematic to calculate and interpret in meta-analyses (Hutton 2009). For binary data presented in the 'Summary of findings' table/s we will, where possible, calculate illustrative comparative risks.

2. Continuous data

For continuous outcomes we will estimate MD between groups. We prefer not to calculate effect size measures (SMD). However if scales of very considerable similarity are used, we will presume there is a small difference in measurement, and we will calculate effect size and transform the effect back to the units of one or more of the specific instruments.

Unit of analysis issues

1. Cluster trials

Studies increasingly employ 'cluster randomisation' (such as randomisation by clinician or practice), but analysis and pooling of clustered data poses problems. Authors often fail to account for intra-class correlation in clustered studies, leading to a unit-of-

analysis error whereby P values are spuriously low, CIs unduly narrow and statistical significance overestimated (Divine 1992). This causes type I errors (Bland 1997; Gulliford 1999).

Where clustering has been incorporated into the analysis of primary studies, we will present these data as if from a non-cluster randomised study, but adjust for the clustering effect.

Where clustering is not accounted for in primary studies, we will present data in a table, with a (*) symbol to indicate the presence of a probable unit of analysis error. We will seek to contact first authors of studies to obtain intra-class correlation coefficients (ICCs) for their clustered data and to adjust for this by using accepted methods (Gulliford 1999).

We have sought statistical advice and have been advised that the binary data from cluster trials presented in a report should be divided by a 'design effect'. This is calculated using the mean number of participants per cluster (m) and the ICC) thus design effect = 1 + (m − 1) * ICC (Donner 2002). If the ICC is not reported we will assume it to be 0.1 (Ukoumunne 1999).

If cluster studies have been appropriately analysed and taken ICCs and relevant data documented in the report into account, synthesis with other studies will be possible using the generic inverse variance technique.

2. Cross-over trials

A major concern of cross-over trials is the carry-over effect. This occurs if an effect (e.g. pharmacological, physiological or psychological) of the treatment in the first phase is carried over to the second phase. As a consequence, participants can differ significantly from their initial state at entry to the second phase, despite a wash-out phase. For the same reason, cross-over trials are not appropriate if the condition of interest is unstable (Elbourne 2002). As both carry-over and unstable conditions are very likely in severe mental illness, we will only use data from the first phase of cross-over studies.

3. Studies with multiple treatment groups

Where a study involves more than two treatment arms, if relevant, we will present the additional treatment arms in comparisons. If data are binary, we will simply add these and combine within the two-by-two table. If data are continuous, we will combine data following the formula in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). Where additional treatment arms are not relevant, we will not reproduce these data.

Dealing with missing data

1. Overall loss of credibility

At some degree of loss of follow-up, data must lose credibility (Xia 2009). We choose that, for any particular outcome, should more

than 50% of data be unaccounted for we will not reproduce these data or use them within analyses. If, however, more than 50% of those in one arm of a study are lost, but the total loss is less than 50%, we will address this within the 'Summary of findings' table/s by down-rating quality. Finally, we will also downgrade quality within the 'Summary of findings' table/s should the loss be 25% to 50% in total.

2. Binary

In the case where attrition for a binary outcome is between 0% and 50% and where these data are not clearly described, we will present data on a 'once-randomised-always-analyse' basis (an intention-to-treat (ITT) analysis). Those leaving the study early are all assumed to have the same rates of negative outcome as those who completed. We will use the rate of those who stay in the study - in that particular arm of the trial - and apply this also to those who did not. We will undertake a sensitivity analysis to test how prone the primary outcomes are to change when data only from people who complete the study to that point are compared to the ITT analysis using the above assumptions.

3. Continuous

3.1 Attrition

We will use data where attrition for a continuous outcome is between 0% and 50%, and data only from people who complete the study to that point are reported.

3.2 Standard deviations

If standard deviations (SDs) are not reported, we will try to obtain the missing values from the authors. If these are not available, where there are missing measures of variance for continuous data, but an exact standard error (SE) and CIs available for group means, and either P value or t value available for differences in mean, we can calculate SDs according to the rules described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). When only the SE is reported, SDs are calculated by the formula SD = SE * $\sqrt{}$(n). The *Cochrane Handbook for Systematic Reviews of Interventions* presents detailed formulae for estimating SDs from P, t or F values, CIs, ranges or other statistics (Higgins 2011a). If these formulae do not apply, we will calculate the SDs according to a validated imputation method which is based on the SDs of the other included studies (Furukawa 2006). Although some of these imputation strategies can introduce error, the alternative would be to exclude a given study's outcome and thus to lose information. Nevertheless, we will examine the validity of the imputations in a sensitivity analysis that excludes imputed values.

3.3 Assumptions about participants who left the trials early or were lost to follow-up

Various methods are available to account for participants who left the trials early or were lost to follow-up. Some trials just present the results of study completers; others use the method of last observation carried forward (LOCF); while more recently, methods such as multiple imputation or mixed-effects models for repeated measurements (MMRM) have become more of a standard. While the latter methods seem to be somewhat better than LOCF (Leon 2006), we feel that the high percentage of participants leaving the studies early and differences between groups in their reasons for doing so is often the core problem in randomised schizophrenia trials. We will therefore not exclude studies based on the statistical approach used. However, by preference we will use the more sophisticated approaches, i.e. we will prefer to use MMRM or multiple-imputation to LOCF, and we will only present completer analyses if some kind of ITT data are not available at all. Moreover, we will address this issue in the item 'Incomplete outcome data' of the 'Risk of bias' tool.

Assessment of heterogeneity

1. Clinical heterogeneity

We will consider all included studies initially, without seeing comparison data, to judge clinical heterogeneity. We will simply inspect all studies for participants who are clearly outliers or situations that we had not predicted would arise and, where found, discuss such situations or participant groups.

2. Methodological heterogeneity

We will consider all included studies initially, without seeing comparison data, to judge methodological heterogeneity. We will simply inspect all studies for clearly outlying methods which we had not predicted would arise and discuss any such methodological outliers.

3. Statistical heterogeneity

3.1 Visual inspection

We will inspect graphs visually to investigate the possibility of statistical heterogeneity.

3.2 Employing the I² statistic

We will investigate heterogeneity between studies by considering the I² statistic alongside the Chi² P value. The I² statistic provides an estimate of the percentage of inconsistency thought to be due to

chance (Higgins 2003). The importance of the observed value of I² depends on the magnitude and direction of effects as well as the strength of evidence for heterogeneity (e.g. P value from Chi² test, or a confidence interval for I²). We will interpret an I² estimate greater than or equal to 50% and accompanied by a statistically significant Chi² statistic as evidence of substantial heterogeneity (Chapter 9. *Cochrane Handbook for Systematic Reviews of Interventions*) (Deeks 2011). When substantial levels of heterogeneity are found in the primary outcome, we will explore reasons for heterogeneity (Subgroup analysis and investigation of heterogeneity).

Assessment of reporting biases

Reporting biases arise when the dissemination of research findings is influenced by the nature and direction of results (Egger 1997). These are described in section 10.1 of the *Cochrane Handbook for Systemic reviews of Interventions* (Sterne 2011).

1. Protocol versus full study

We will try to locate protocols of included randomised trials. If the protocol is available, we will compare outcomes in the protocol and in the published report . If the protocol is not available, we will compare outcomes listed in the methods section of the trial report with actually reported results.

2. Funnel plot

We are aware that funnel plots may be useful in investigating reporting biases but are of limited power to detect small-study effects. We will not use funnel plots for outcomes where there are 10 or fewer studies, or where all studies are of similar size. In other cases, where funnel plots are possible, we will seek statistical advice in their interpretation.

Data synthesis

We understand that there is no closed argument for preference for use of fixed-effect or random-effects models. The random-effects method incorporates an assumption that the different studies are estimating different, yet related, intervention effects. This often seems to be true to us and the random-effects model takes into account differences between studies, even if there is no statistically significant heterogeneity. There is, however, a disadvantage to the random-effects model: it puts added weight onto small studies, which often are the most biased ones. Depending on the direction of effect, these studies can either inflate or deflate the effect size. We choose to use a random-effects model for all analyses.

Subgroup analysis and investigation of heterogeneity

1. Subgroup analyses

1.1 Primary outcomes

No subgroup analysis of primary outcomes is anticipated.

2. Investigation of heterogeneity

We will report if inconsistency is high. Firstly, we will investigate whether data have been entered correctly. Secondly, if data are correct, we will inspect the graph visually and remove outlying studies successively to see if homogeneity is restored. For this review we have decided that should this occur with data contributing to the summary finding of no more than 10% of the total weighting, we will present data. If not, we will not pool these data and will discuss any issues. We know of no supporting research for this 10% cut-off but are investigating use of prediction intervals as an alternative to this unsatisfactory state.

When unanticipated clinical or methodological heterogeneity is obvious we will simply state hypotheses regarding these for future reviews or versions of this review. We do not anticipate undertaking analyses relating to these.

Sensitivity analysis

We will carry out sensitivity analyses for primary outcomes only. If there are substantial differences in the direction or precision of effect estimates in any of the sensitivity analyses listed below, we will not add data from the lower-quality studies to the results of the higher-quality trials, but will present these data within a sub-category. If their inclusion does not result in a substantive difference, they will remain in the analyses.

1. Implication of randomisation

If trials are described in some way as to imply randomisation, we will compare data from the implied trials with trials that are randomised.

2. Assumptions for lost binary data

Where assumptions have to be made regarding people lost to follow-up (see Dealing with missing data), we will compare the findings when we use our assumption compared with completer data only. If there is a substantial difference, we will report results and discuss them but continue to employ our assumption.

3. Assumptions for lost continuous data

Where assumptions have to be made regarding missing SDs (see Dealing with missing data), we will compare the findings when we use our assumption compared with data that are not imputed. If there is a substantial difference, we will report results and discuss them but continue to employ our assumption.

4. Risk of bias

We will analyse the effects of excluding trials that are at high risk of bias across one or more of the domains (see Assessment of risk of bias in included studies).

5. Imputed values

We will also undertake a sensitivity analysis to assess the effects of including data from trials where we use imputed values for ICC in calculating the design effect in cluster-randomised trials.

6. Fixed- and random-effects

We will synthesise data using a random-effects model; however, we will also synthesise data for the primary outcome using fixed-effect model to evaluate whether this alters the significance of the results.

REFERENCES

Additional references

ADA/APA 2004
American Diabetes Association, the American Psychological Association, the American Association of Clinical Eendocrinologists, and the North Aamerican Association for the Study of Obesity. Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care* 2004;**27**(2):596–601.

Aichhorn 2007
Aichhorn W, Marksteiner J, Walch T, Zernig G, Hinterhuber H, Stuppaeck C, et al. Age and gender effects on olanzapine and risperidone plasma concentrations in children and adolescents. *Journal of Child and Adolescent Psychopharmacology* 2007;**17**(5):665–74.

Alberti 2009
Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation* 2009;**120**(16):1640–5. [PUBMED: 19805654]

Allison 1999
Allison DB, Mentore JL, Heo M, Chandler LP, Cappelleri JC, Infante MC, et al. Antipsychotic-induced weight gain: A comprehensive research synthesis. *American Journal of Psychiatry* 1999;**156**(11):1686–9.

Allison 2003
Allison DB, Mackell JA, McDonnell DD. The impact of weight gain on quality of life among persons with schizophrenia. *Psychiatric Services* 2003;**54**:565–7.

Altman 1996
Altman DG, Bland JM. Detecting skewness from summary information. *BMJ* 1996;**313**(7066):1200.

Alvarez-Jimenez 2008
Alvarez-Jimenez M, Gonzalez-Blanch C, Crespo-Facorro B, Hetrick S, Rodriguez-Sanchez JM, Perez-Iglesias R, et al. Antipsychotic-induced weight gain in chronic and first-episode psychotic disorders: a systematic critical reappraisal. *CNS Drugs* 2008;**22**(7):547–62.

Ananth 2004
Ananth J, Venkatesh R, Burgoyne K, Gadasalli R, Binford R, Gunatilake S. Atypical antipsychotic induced weight gain: pathophysiology and management. *Annals of Clinical Psychiatry* 2004;**16**:75–85.

Annamalai 2017
Annamalai A, Kosir U, Tek C. Prevalence of obesity and diabetes in patients with schizophrenia. *World Journal of*

Diabetes 2017;**8**(8):390–6. [PUBMED: 28861176]

Bak 2014
Bak M, Fransen A, Janssen J, van Os J, Drukker M. Almost all antipsychotics result in weight gain: a meta-analysis. *PLOS One* 2014;**9**(4):e94112. [PUBMED: 24763306]

Baptista 2002
Baptista T, Kin NM, Beaulieu S, de Baptista EA. Obesity and related metabolic abnormalities during antipsychotic drug administration : Mechanisms, management and research perspectives. *Pharmacopsychiatry* 2002;**35**:205–19.

Basson 2001
Basson BR, Kinon BJ, Taylor CC, Szymanski KA, Gilmore JA, Tollefson GD. Factors influencing acute weight change in patients with schizophrenia treated with olanzapine, haloperidol, or risperidone. *Journal of Clinical Psychiatry* 2001;**62**:231–8.

Birt 2003
Birt J. Management of weight gain associated with antipsychotics. *Annals of Clinical Psychiatry* 2003;**15**:49–58.

Bland 1997
Bland JM. Statistics notes. Trials randomised in clusters. *BMJ* 1997;**315**(7108):600.

Boissel 1999
Boissel JP, Cucherat M, Li W, Chatellier G, Gueyffier F, Buyse M, et al. The problem of therapeutic efficacy indices. 3. Comparison of the indices and their use [Aperçu sur la problématique des indices d'efficacité thérapeutique, 3: comparaison des indices et utilisation. Groupe d'Etude des Indices D'efficacite]. *Therapie* 1999;**54**(4):405–11. [PUBMED: 10667106]

Bora 2017
Bora E, Akdede BB, Alptekin K. The relationship between cognitive impairment in schizophrenia and metabolic syndrome: a systematic review and meta-analysis. *Psychological Medicine* 2017;**47**(6):1030–40. [PUBMED: 28032535]

Brown 1999
Brown S, Birtwhistle J, Roe L, Thompson C. The unhealthy lifestyle of people with schizophrenia. *Psychological Medicine* 1999;**29**:697–701.

Bueno-Antequera 2018
Bueno-Antequera J, Oviedo-Caro MA, Munguia-Izquierdo D. Relationship between objectively measured sedentary behavior and health outcomes in schizophrenia patients: The PsychiActive project. *Schizophrenia Research* 2018;**197**: 87–92. [PUBMED: 29174336]

Casey 2004
Casey DE, Haupt DW, Newcomer JW, Henderson DC, Sernyak MJ, Davidson M, et al. Antipsychotic-induced weight gain and metabolic abnormalities: Implications for increased mortality in patients with schizophrenia. *Journal of Clinical Psychiatry* 2004;**65**(Suppl 7):4–18.

Catapana 2004
Catapana L, Castle D. Obesity in schizophrenia: What can be done about it?. *Australasian Psychiatry* 2004;**12**:23–5.

Cohn 2004
Cohn T, Prud'homme D, Streiner D, Kameh H, Remington G. Characterizing coronary heart disease risk in chronic schizophrenia: High prevalence of the metabolic syndrome. *Canadian Journal of Psychiatry* 2004;**49**:753–60.

Coodin 2001
Coodin S. Body mass index in persons with schizophrenia. *Canadian Journal of Psychiatry* 2001;**46**:549–55.

Cooper 2016
Cooper SJ, Reynolds GP, Barnes T, England E, Haddad PM, Heald A, et al. BAP guidelines on the management of weight gain, metabolic disturbances and cardiovascular risk associated with psychosis and antipsychotic drug treatment. *Journal of Psychopharmacology (Oxford, England)* 2016;**30** (8):717–48. [PUBMED: 27147592]

Correll 2009
Correll CU, Manu P, Olshanskiy V, Napolitano B, Kane JM, Malhotra AK. Cardiometabolic risk of second-generation antipsychotic medications during first-time use in children and adolescents. *JAMA* 2009;**302**(16):1765–73. [PUBMED: 19861668]

Correll 2011
Correll CU, Lencz T, Malhotra AK. Antipsychotic drugs and obesity. *Trends in Molecular Medicine* 2011 Feb;**17**(2): 97–107.

Correll 2014
Correll CU, Robinson DG, Schooler NR, Brunette MF, Mueser KT, Rosenheck RA, et al. Cardiometabolic risk in patients with first-episode schizophrenia spectrum disorders: baseline results from the RAISE-ETP study. *JAMA Psychiatry* 2014;**71**(12):1350–63. [PUBMED: 25321337]

Daumit 2003
Daumit GL, Clark JM, Steinwachs DM, Graham CM, Lehman A, Ford DE. Prevalence and correlates of obesity in a community sample of individuals with severe and persistent mental illness. *Journal of Nervous and Mental Disease* 2003;**191**:799–805.

Daumit 2005
Daumit GL, Goldberg RW, Anthony C, Dickerson F, Brown CH, Kreyenbuhl J, et al. Physical activity patterns in adults with severe mental illness. *Journal of Nervous and Mental Disease* 2005;**193**:641–6.

De Hert 2006
De Hert M, van Winkel R, Van Eyck D, Hanssens L, Wampers M, Scheen A, et al. Prevalence of diabetes, metabolic syndrome and metabolic abnormalities in schizophrenia over the course of the illness: a cross-sectional study. *Clinical Practice and Epidemiology in Mental Health : CP & EMH* 2006;**2**:14. [PUBMED: 16803620]

De Hert 2011
De Hert M, Detraux J, van Winkel R, Yu W, Correll CU. Metabolic and cardiovascular adverse effects associated with antipsychotic drugs. *Nature Reviews Endocrinology* 2011;**8** (2):114–26.

De Nayer 2005

De Nayer A, De Hert M, Scheen A, Van Gaal L, Peuskens J. Belgian consensus on metabolic problems associated with atypical antipsychotics. *International Journal of Psychiatry in Clinical Practice* 2005;**9**:130–7.

de Silva 2016

de Silva VA, Suraweera C, Ratnatunga SS, Dayabandara M, Wanniarachchi N, Hanwella R. Metformin in prevention and treatment of antipsychotic induced weight gain: a systematic review and meta-analysis. *BMC Psychiatry* 2016; **16**(1):341. [PUBMED: 27716110]

Deeks 2000

Deeks J. Issues in the selection for meta-analyses of binary data. Proceedings of the 8th International Cochrane Colloquium; 2000 Oct 25-28; Cape Town. Cape Town: The Cochrane Collaboration, 2000.

Deeks 2011

Deeks JJ, Higgins JP, Altman DG (editors). Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins JP, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.handbook.cochrane.org.

Dipasquale 2013

Dipasquale S, Pariante CM, Dazzan P, Aguglia E, McGuire P, Mondelli V. The dietary pattern of patients with schizophrenia: A systematic review. *Journal of Psychiatric Research* 2013;**47**:197–207.

Divine 1992

Divine GW, Brown JT, Frazier LM. The unit of analysis error in studies about physicians' patient care behavior. *Journal of General Internal Medicine* 1992;**7**(6):623–9.

DoH 2004

Department of Health. *At Least Five a Week. A report from the Chief Medical Officer*. HMSO, London, 2004.

Donner 2002

Donner A, Klar N. Issues in the meta-analysis of cluster randomized trials. *Statistics in Medicine* 2002;**21**(19): 2971–80.

Egger 1997

Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;**315**(7109):629–34.

Elbourne 2002

Elbourne D, Altman DG, Higgins JP, Curtina F, Worthingtond HV, Vaile A. Meta-analyses involving cross-over trials: methodological issues. *International Journal of Epidemiology* 2002;**31**(1):140–9.

Faulkner 2007

Faulkner G, Cohn T, Remington G. Interventions to reduce weight gain in schizophrenia. *Cochrane Database of Systematic Reviews* 2007, Issue 1. DOI: 10.1002/14651858.CD005148.pub2

Faulkner 2007a

Faulkner G, Cohn T, Remington G, Irving H. Body mass index, waist circumference and quality of life in individuals with schizophrenia. *Schizophrenia Research* 2007;**90**(1-3): 174–8.

Findling 2010

Findling RL, Johnson JL, McClellan J, Frazier JA, Vitiello B, Hamer RM, et al. Double-blind maintenance safety and effectiveness findings from the Treatment of Early-Onset Schizophrenia Spectrum (TEOSS) study. *Journal of the American Academy of Child and Adolescent Psychiatry* 2010; **49**(6):583–94.

Friedman 2010

Friedman JI, Wallenstein S, Moshier E, Parrella M, White L, Bowler S, et al. The effects of hypertension and body mass index on cognition in schizophrenia. *American Journal of Psychiatry* 2010;**167**(19):1232–9.

Furukawa 2006

Furukawa TA, Barbui C, Cipriani A, Brambilla P, Watanabe N. Imputing missing standard deviations in meta-analyses can provide accurate results. *Journal of Clinical Epidemiology* 2006;**59**(1):7–10.

Gebhardt 2009

Gebhardt S, Haberhausen M, Heinzel-Gutenbrunner M, Gebhardt N, Remschmidt H, Krieg JC, et al. Antipsychotic-induced body weight gain: predictors and a systematic categorization of the long-term weight course. *Journal of Psychiatric Research* 2009;**43**:620–6.

Goff 2005

Goff DC, Sullivan LM, McEvoy JP, Meyer JM, Nasrallah NA, Daumit GL, et al. A comparison of ten-year cardiac risk estimates in schizophrenia patients from the CATIE study and matched controls. *Schizophrenia Research* 2005; **80**:45–53.

Goldstein 1994

Goldstein DJ, Rampey AH Jr, Enas GG, Potvin JH, Fludzinski LA, Levine LR. Fluoxetine: a randomized clinical trial in the treatment of obesity. *International Journal of Obesity and Related Metabolic Disorders : Journal of the International Association for the Study of Obesity* 1994; **18**(3):129–35. [PUBMED: 8186809]

Green 2000

Green A, Patel J, Goisman R. Weight gain from novel antipsychotic drugs: Need for action. *General Hospital Psychiatry* 2000;**22**:224–35.

Gulliford 1999

Gulliford MC. Components of variance and intraclass correlations for the design of community-based surveys and intervention studies: data from the Health Survey for England 1994. *American Journal of Epidemiology* 1999;**149**(9):876–83.

Gurpegui 2012

Gurpegui M, Martínez-Ortega JM, Gutiérrez-Rojas L, Rivero J, Rojas C, Jurado D. Overweight and obesity in patients with bipolar disorder or schizophrenia compared with a non-psychiatric sample. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 2012;**37**(1): 169–75.

Henderson 2005

Henderson DC, Nguyen DD, Copeland PM, Hayden DL, Borba CP, Louie PM, et al. Clozapine, diabetes mellitus, hyperlipidemia, and cardiovascular risks and mortality: Results of a 10-year naturalistic study. *Journal of Clinical Psychiatry* 2005;**66**:1116–21.

Higgins 2003

Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327** (7414):557–60.

Higgins 2011a

Higgins JP, Green S (editors). Chapter 7: Selecting studies and collecting data. In: Higgins JP, Green S (editors), Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.handbook.cochrane.org.

Higgins 2011b

Higgins JP, Altman DG, Sterne JA (editors). Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.handbook.cochrane.org.

Hoang 2011

Hoang U, Stewart R, Goldacre MJ. Mortality after hospital discharge for people with schizophrenia or bipolar disorder: retrospective study of linked English hospital episode statistics, 1999-2006. *BMJ (Clinical Research ed.)* 2011; **343**:d5422. [PUBMED: 21914766]

Homel 2002

Homel P, Casey D, Allison DB. Changes in body mass index for individuals with and without schizophrenia. *Schizophrenia Research* 2002;**55**:277–84.

Hundal 2003

Hundal RS, Inzucchi SE. Metformin: new understandings, new uses. *Drugs* 2003;**63**(18):1879–94. [PUBMED: 12930161]

Hutton 2009

Hutton JL. Number needed to treat and number needed to harm are not the best way to report and assess the results of randomised clinical trials. *British Journal of Haematology* 2009;**146**(1):27–30. [PUBMED: 19438480]

Jagust 2007

Jagust W. What can imaging reveal about obesity and the brain?. *Current Alzheimer Research* 2007;**4**(2):135–9.

Jin 2008

Jin H, Meyer JM, Mudaliar S, Jeste DV. Impact of atypical antipsychotic therapy on leptin, ghrelin, and adiponectin. *Schizophrenia Research* 2008 Mar;**100**(1-3):70–85.

Kay 1986

Kay SR, Opler LA, Fiszbein A. *Positive and Negative Syndrome Scale (PANSS) Manual*. North Tonawanda, NY: Multi-Health Systems, 1986.

Keshavan 2008

Keshavan MS, Tandon R, Boutros NN, Nasrallah HA. Schizophrenia, "just the facts": what we know in 2008 Part 3: neurobiology. *Schizophrenia Research* 2008;**106**(2-3): 89–107.

Keshavan 2011

Keshavan MS, Nasrallah HA, Tandon R. Schizophrenia, "Just the Facts" 6. Moving ahead with the schizophrenia concept: from the elephant to the mouse. *Schizophrenia Research* 2011;**127**(1-3):3–13.

Kurzthaler 2001

Kurzthaler I, Fleischhacker WW. The clinical implications of weight gain in schizophrenia. *Journal of Clinical Psychiatry* 2001;**62**(Supple 7):32–7.

Lappin 2018

Lappin JM, Wijaya M, Watkins A, Morell R, Teasdale S, Lederman O, et al. Cardio-metabolic risk and its management in a cohort of clozapine-treated outpatients. *Schizophrenia Research* 2018;**99**:367–73. [PUBMED: 29486959]

Le Fevre 2001

Le Fevre PD. Improving the physical health of patients with schizophrenia: Therapeutic nihilism or realism?. *Scottish Medical Journal* 2001;**46**:11–31.

Leon 2006

Leon AC, Mallinckrodt CH, Chuang-Stein C, Archibald DG, Archer GE, Chartier K. Attrition in randomized controlled clinical trials: methodological issues in psychopharmacology. *Biological Psychiatry* 2006;**59**(11): 1001–5. [PUBMED: 16905632]

Lett 2012

Lett TA, Wallace TJ, Chowdhury NI, Tiwari AK, Kennedy JL, Muller DJ. Pharmacogenetics of antipsychotic-induced weight gain: review and clinical implications. *Molecular Psychiatry* 2012;**17**(3):242–66. [PUBMED: 21894153]

Leucht 2005

Leucht S, Kane JM, Kissling W, Hamann J, Etschel E, Engel RR. What does the PANSS mean?. *Schizophrenia Research* 2005;**79**(2-3):231–8. [PUBMED: 15982856]

Leucht 2005a

Leucht S, Kane JM, Kissling W, Hamann J, Etschel E, Engel R. Clinical implications of brief psychiatric rating scale scores. *British Journal of Psychiatry* 2005;**187**:366–71. [PUBMED: 16199797]

Lindenmayer 2012

Lindenmayer JP, Khan A, Kaushik S, Thanju A, Praveen R, Hoffman L, et al. Relationship between metabolic syndrome and cognition in patients with schizophrenia. *Schizophrenia Research* 2012;**142**(1-3):171–6.

Liversedge 2011

Liversedge S, Gilchrist I, Everling S. *The Oxford Handbook of Eye Movements*. OUP Oxford, 2011.

Mackin 2005

Mackin P, Watkinson HM, Young AH. Prevalence of obesity, glucose homeostasis disorders and metabolic

syndrome in psychiatric patients taking typical or atypical antipsychotic drugs: A cross-sectional study. *Diabetologia* 2005;**48**:215–21.

Marshall 2000

Marshall M, Lockwood A, Bradley C, Adams C, Joy C, Fenton M. Unpublished rating scales: a major source of bias in randomised controlled trials of treatments for schizophrenia. *British Journal of Psychiatry* 2000;**176**: 249–52.

McCreadie 1998

McCreadie R, Macdonald E, Blacklock C, Tilak-Singh D, Wiles D, Halliday J, et al. Dietary intake of schizophrenic patients in Nithsdale, Scotland: Case-control study. *BMJ* 1998;**317**:784–5.

Mueser 2004

Mueser KT, McGurk SR. Schizophrenia. *Lancet* 2004;**363** (9426):2063–72.

Newcomer 2007

Newcomer JW, Hennekens CH. Severe mental illness and risk of cardiovascular disease. *JAMA* 2007;**298**(15):1794–6. [PUBMED: 17940236]

Osborn 2001

Osborn DPJ. The poor physical health of people with mental illness. *Western Journal of Medicine* 2001;**175**: 329–32.

Overall 1962

Overall JE, Gorham DR. The brief psychiatric rating scale. *Psychological Reports* 1962;**10**:799–812.

Peeters 2003

Peeters A, Barendregt JJ, Willekens F, Mackenbach JP, Al Mamun A, Bonneux L, et al. Obesity in adulthood and its consequences for life expectancy: a life-table analysis. *Annual of Internal Medicine* 2003;**138**:24–32.

Perez-Iglesias 2008

Perez-Iglesias R, Crespo-Facorro B, Martinez-Garcia O, Ramirez-Bonilla ML, Alvarez-Jimenez M, Pelayo-Teran JM, et al. Weight gain induced by haloperidol, risperidone and olanzapine after 1 year: findings of a randomized clinical trial in a drug-naive population. *Schizophrenia Research* 2008;**99**(1-3):13–22.

Rajkumar 2017

Rajkumar AP, Horsdal HT, Wimberley T, Cohen D, Mors O, Borglum AD, et al. Endogenous and antipsychotic-related risks for diabetes mellitus in young people with schizophrenia: a Danish population-based cohort study. *American Journal of Psychiatry* 2017;**174**(7):686–94. [PUBMED: 28103712]

Ratzoni 2002

Ratzoni G, Gothelf D, Brand-Gothelf A, Reidman J, Kikinzon L, Gal G, et al. Weight gain associated with olanzapine and risperidone in adolescent patients: a comparative prospective study. *Journal of the American Academy of Child and Adolescent Psychiatry* 2002;**41**:337–43.

Reichenberg 2007

Reichenberg A, Harvey PD. Neuropsychological impairments in schizophrenia: Integration of performance-based and brain imaging findings. *Psychological Bulletin* 2007 Sep;**133**(5):833–58.

Reynolds 2010

Reynolds GP, Kirk SL. Metabolic side effects of antipsychotic drug treatment--pharmacological mechanisms. *Pharmacology & Therapeutics* 2010;**125**(1):169–79.

Reynolds 2017

Reynolds GP, McGowan OO. Mechanisms underlying metabolic disturbances associated with psychosis and antipsychotic drug treatment. *Journal of Psychopharmacology (Oxford, England)* 2017;**31**(11):1430–6. [PUBMED: 28892404]

Ringen 2018

Ringen PA, Faerden A, Antonsen B, Falk RS, Mamen A, Rognli EB, et al. Cardiometabolic risk factors, physical activity and psychiatric status in patients in long-term psychiatric inpatient departments. *Nordic Journal of Psychiatry* 2018;**72**(4):296–302. [PUBMED: 29523041]

Saari 2005

Saari KM, Lindeman SM, Viilo KM, Isohanni MK, Jarvelin MR, Lauren LH, et al. A 4-fold risk of metabolic syndrome in patients with schizophrenia: The Northern Finland 1966 birth cohort study. *Journal of Clinical Psychiatry* 2005;**66**: 559–63.

Saha 2007

Saha S, Chant D, McGrath J. A systematic review of mortality in schizophrenia: is the differential mortality gap worsening over time?. *Archives of General Psychiatry* 2007; **64**:1123–31.

Schünemann 2011

Schünemann HJ, Oxman AD, Vist GE, Higgins JP, Deeks JJ, Glasziou P, et al. Chapter 12: Interpreting results and drawing conclusions. In Higgins JPT, Green S (editors), Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Seaton 2001

Seaton BE, Goldstein G, Allen DN. Sources of heterogeneity in schizophrenia: the role of neuropsychological functioning. *Neuropsychology Review* 2001;**11**(1):45–67.

Sellbom 2012

Sellbom KS, Gunstad J. Cognitive function and decline in obesity. *Journal of Alzheimer's Disease* 2012;**30 Suppl 2**: S89–95.

Shokraneh 2017

Shokraneh F, Adams CE. Study-based registers of randomized controlled trials: Starting a systematic review with data extraction or meta-analysis. *BioImpacts* 2017;**7** (4):209–17. DOI: 10.15171/bi.2017.25

Shokraneh 2018

Shokraneh F, Adams CE. Gallstone, snake venom and witchcraft for schizophrenia: the challenges of classifying [schizophrenia] trials. *Evidence-Based Medicine* 2018;**23** (Suppl 1):A18. DOI: 10.1136/bmjebm-2018-111024.36

Silverman 2018

Silverman BL, Martin W, Memisoglu A, DiPetrillo L, Correll CU, Kane JM. A randomized, double-blind, placebo-controlled proof of concept study to evaluate samidorphan in the prevention of olanzapine-induced weight gain in healthy volunteers. *Schizophrenia Research* 2018;**195**:245–51. [PUBMED: 29158012]

Silverstone 1988

Silverstone T, Smith G, Goodall E. Prevalence of obesity in patients receiving depot antipsychotics. *British Journal of Psychiatry* 1988;**153**:214–7.

Sterne 2011

Sterne JA, Egger M, Moher D (editors). Chapter 10: Addressing reporting biases. In: Higgins JP, Green S (editors). *Cochrane Handbook for Systematic Reviews of Intervention.* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.handbook.cochrane.org.

Strassnig 2003

Strassnig M, Brar JS, Ganguli R. Nutritional assessment of patients with schizophrenia: a preliminary study. *Schizophrenia Bulletin* 2003;**29**:393–7.

Susce 2005

Susce MT, Villanueva N, Diaz FJ, de Leon J. Obesity and associated complications in patients with severe mental illnesses: A cross-sectional survey. *Journal of Clinical Psychiatry* 2005;**66**:167–73.

Ukoumunne 1999

Ukoumunne OC, Gulliford MC, Chinn S, Sterne JA, Burney PG. Methods for evaluating area-wide and organisation-based intervention in health and health care: a systematic review. *Health Technology Assessment* 1999;**3**(5): iii–92.

van Os 2009

van Os J, Kapur S. Schizophrenia. *Lancet* 2009;**374**(9690): 635–45.

Vancampfort 2017

Vancampfort D, Firth J, Schuch FB, Rosenbaum S, Mugisha J, Hallgren M, et al. Sedentary behavior and physical activity levels in people with schizophrenia, bipolar disorder and major depressive disorder: a global systematic review and meta-analysis. *World Pychiatry: official journal of the World Psychiatric Association (WPA)* 2017;**16**(3):308–15. [PUBMED: 28941119]

Velazquez 2018

Velazquez A, Apovian CM. Updates on obesity pharmacotherapy. *Annals of the New York Academy of Sciences* 2018;**1411**(1):106–19. [PUBMED: 29377198]

Ward 2015

Ward MC, White DT, Druss BG. A meta-review of lifestyle interventions for cardiovascular risk factors in the general medical population: lessons for individuals with serious mental illness. *Journal of Clinical Psychiatry* 2015;**76**(4): e477–86. [PUBMED: 25919840]

Wei 1999

Wei M, Kampert JB, Barlow CE, Nichaman MZ, Gibbons LW, Paffenbarger RS, et al. Relationship between low cardiorespiratory fitness and mortality in normal weight, overweight and obese men. *JAMA* 1999;**282**:1547–53.

Weiden 2004

Weiden PJ, Mackell JA, McDonnell DD. Obesity as a risk factor for antipsychotic noncompliance. *Schizophrenia Research* 2004;**66**:51–7.

Westman 2017

Westman J, Eriksson SV, Gissler M, Hallgren J, Prieto ML, Bobo WV, et al. Increased cardiovascular mortality in people with schizophrenia: a 24-year national register study. *Epidemiology and Psychiatric Sciences* 2017;**InPress**:InPress. [PUBMED: 28580898]

WHO 2013

World Health Organization. Obesity and overweight fact sheet. http://www.who.int/mediacentre/factsheets/fs311/ en/ March 2013.

Wirshing 2004

Wirshing DA. Schizophrenia and obesity: impact of antipsychotic medications. *Journal of Clinical Psychiatry* 2004;**65**(Suppl 18):13–26.

Xia 2009

Xia J, Adams CE, Bhagat N, Bhagat V, Bhoopathi P, El-Sayeh H, et al. Loss to outcomes stakeholder survey: the LOSS study. *Psychiatric Bulletin* 2009;**33**(7):254–7.

Zipursky 2005

Zipursky RB, Gu H, Green AI, Perkins DO, Tohen MF, McEvoy JP, et al. Course and predictors of weight gain in people with first-episode psychosis treated with olanzapine or haloperidol. *British Journal of Psychiatry* 2005;**187**: 537–43.

References to other published versions of this review

Hahn 2014

Hahn M, Remington G, Duncan MJ, Cohn T, Faulkner GEJ. Pharmacological interventions for reducing weight gain in schizophrenia. *Cochrane Database of Systematic Reviews* 2014, Issue 6. DOI: 10.1002/ 14651858.CD011127

* Indicates the major publication for the study

CONTRIBUTIONS OF AUTHORS

Guy Faulkner, Tony Cohn, and Gary Remington contributed to the original protocol and review of interventions to reduce weight in schizophrenia (Faulkner 2007). Guy Faulkner initiated and conceptualised the initial review (2007). Drs Remington and Faulkner assisted in write-up of the final draft of the current review.

Margaret Hahn and Sri Mahavir Agarwal updated the protocol to reflect the division between behavioural and pharmacological interventions, and between treatment and prevention of weight gain.

Mark Duncan, John Lockhart, Hiroyoshi Takeuchi, and Zohra Ahsan assisted in writing the current protocol.

Vaelrie H Taylor assisted in editing and write-up of the final review draft.

DECLARATIONS OF INTEREST

The review authors have no direct declaration or conflict of interest for conducting this protocol.

Tony Cohn has received speaker fees from Pfizer Canada Inc.

Gary Remington has served as a consultant or speaker for Novartis, Laboratorios Farmacéuticos Rovi, and Roche.

Margaret Hahn has received speaker fees from Alkermes.

Valerie H Taylor has, in the last five years, been on advisory boards for NovoNordisk and Valeant. She has also received honoria from Sunovion and Shire