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Oestrogen (adjunct) versus placebo for women with schizophrenia (Protocol)

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[Intervention Protocol]

Oestrogen (adjunct) versus placebo for women with schizophrenia

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To evaluate the clinical efficacy and safety of oestrogen as an adjunctive treatment versus placebo, in women with schizophrenia or schizophrenia-like illnesses.

BACKGROUND

Description of the condition

Schizophrenia is a serious mental disorder that affects approximately 0.7% of the population worldwide. The prevalence in men and women is approximately equal (McGrath 2008). It emerges in young adulthood and is frequently disabling and often a life-long condition. It is one of the leading causes of disability worldwide. The Global Burden of Disease 2013 places schizophrenia in 11th place when comparing the leading causes of YLD (Years Living with Disability) (Vos 2015). Much of this burden is carried in the developing world where access to proven antipsychotic treatments and basic psycho-education is still lacking (de Jesus 2009).

The symptoms of schizophrenia can be divided into three broad categories; positive symptoms such as delusions, hallucinations and disturbance of thought and speech; negative symptoms where emotions are dulled, pleasure, motivation and the ability to sustain planned activities are lost; and thirdly cognitive symptoms which affect executive functioning, concentration and working memory. Gender differences in the onset and course of schizophrenia have been observed to favour women (da Silva 2015; Ochoa 2012). The onset in women is several years later than men and they have a second peak of illness after their mid-1940's (Aleman 2003; McGrath 2008) coinciding with the menopause. In terms of symptoms and severity, the evidence suggests that men suffer with more negative and cognitive symptoms whilst women suffer with more affective symptoms (Ochoa 2012). The premorbid functioning in females is better than males, and women have better remission and lower relapse rates than men (Ochoa 2012).

Why these gender differences are found is not understood; neurodevelopmental, psycho-social factors (Jablensky 1997), substance abuse (Ochoa 2012), poorer compliance with medication in men (Aleman 2003), and greater efficacy of typical antipsychotic medication in pre-menopausal women (Goldstein 2002) have been cited as possible reasons.

One explanation, 'the oestrogen hypothesis' proposes that these differences are due to the neuroprotective effects of oestrogen (Hafner 2003). Thus, pre-menopausal women who are relatively protected compared to men, become vulnerable to psychosis when there is a fall in oestrogen levels, for example at the menopause (Seeman 2012) or following childbirth (Kendell 1987). Markham argues that women develop schizophrenia in some part due to being hypo-oestrogenic (Markham 2012).

Description of the intervention

Antipsychotics are the mainstay for the treatment and prevention of relapse in schizophrenia (Kishimoto 2013). Antipsychotics are effective in treating positive symptoms, but less so in treating negative symptoms and cognitive symptoms. (Citrome 2014). Negative symptoms and cognitive symptoms are correlated with poor social and occupational outcomes (Fervaha 2015; Green 2006). There also remain a sizable minority of 30% who do not achieve remission of symptoms with antipsychotic treatment (Meltzer 1997). In some treatment-resistant patients adjunctive treatments, such as oestrogens, may be considered.

Oestrogens are produced by the ovaries and regulated by the gonado-pituitary axis. The term oestrogen includes 30 hormones, the most widely known are 17 -beta - estradiol (E2) and estrone (E3); 17 - beta- estradiol is the most potent form, naturally occurring. The actions of oestrogen are mediated by two receptors, ER - alpha and ER - beta, found in the reproductive organs and the brain (Hughes 2009). Oestrogens are in hormone replacement therapy (HRT), for symptoms of the menopause, and in oral contraceptives. There are many preparations of oestrogens, conjugated and synthetic, these have different potency. Oestrogens can be administered as a tablet, transdermal patch, gel, cream, subcutaneous implant or nasal spray (Panay 2013)

Oestrogens are currently, not used routinely in clinical practice for the treatment of schizophrenia (Craig 2013).

Any possible benefits of prescribing oestrogen in schizophrenia, needs to be balanced against the long-term risks of cancers, venous thromboembolism, stroke, coronary heart disease (Panay 2013, Seeman 2012). Oestrogens are prescribed with progesterone in all women with an intact womb to counter the additional risks of endometrial cancer of oestrogen prescribed unopposed (BNF 2015). Transdermal administration is not associated with venous thromboembolism (Canonico 2015). Other adverse effects include altered lipid profile, depression, reduced libido, sodium and fluid retention (BNF 2015).

How the intervention might work

The actions of oestrogens in the brain are highly complex and are not well-understood (Hayes 2012). Oestrogen receptors are widely distributed in the brain, in the cerebral cortex, hypothalamus, pituitary and limbic system (Hughes 2009). Oestrogens are important in brain development, differentiation and maturation during adolescence (Markham 2012). It is thought that the neuroprotective actions of oestrogens reducing neuronal cell death, and by promoting neuronal cell growth. have contributed to the better illness outcomes and functioning observed in females, particularly in the cognitive domains (da Silva 2015).

Oestrogens are thought to modulate dopamine, noradrenaline, glutamate, serotonin and acetylcholine pathways. These same pathways are implicated in schizophrenia (Cyr 2002; Hughes 2009). It is hypothesised that oestrogen could exert an antipsychotic effect by reducing dopamine activity, or acting on any number of neurotransmitter pathways believed to be relevant to schizophrenia and related psychosis (Riecher-Rossler 2011). The future treatments of schizophrenia look to exploit these other neurotransmitters, one being glutamate. It is proposed that glutaminergic dysfunction may be relevant in those where negative symptoms, cognitive symptoms and deterioration are prominent (Citrome 2014).

Despite the promising rationale of oestrogen in the treatment of schizophrenia, the clinical findings are controversial. Observational studies examining the improvement or otherwise of symptoms of schizophrenia over the course of the menstrual cycle have provided no consensus regarding psychotic symptoms, depressive symptoms and cognitive symptoms (Bergemann 2007a; Harris 1997; Ko 2006b; Riecher-Rossler 1993; Rubin 2015). Oestrogen as a therapeutic intervention alone for women with schizophrenia is limited to case reports (Bergemann 2007b). Small open-label studies of oestrogen as an adjunctive treatment for schizophrenia have reported mixed results (Kulkarni 1999; Liao 2002; Lindamer 1997).

Randomised controlled trials have been carried out to investigate the potential role for oestrogens as an adjunctive treatment for schizophrenia in post and pre-menopausal women (Ghafari 2013; Kulkarni 2015; Kulkarnia 2010). These studies looked at patients in the acute phase and chronic phase of their illness. The outcomes of interest included positive symptoms, negative symptoms, neurocognitive functioning, extra-pyramidal side effects and mood.

Why it is important to do this review

This is a split title from the Cochrane systematic review of randomised trials entitled *Estrogen for schizophrenia* (Chua 2005) (Other published versions of this review). The original review identified 19 trials but only five fulfilled the methodological criteria, including just 122 patients. It concluded that adjunctive oestrogen with or without progesterone did not appear to offer convincing advantages over placebo. Since then more trials have been carried out and two recent reviews of trials in this area concluded that oestrogens could be an effective augmentation strategy in schizophrenia warranting further investigation (Begemann 2012; Heringa 2015), necessitating the need to split the original

title into more specific titles involving the effects of oestrogen for schizophrenia (Table 1.)

Experts in the field hold different views of what potential role of oestrogen as an adjunctive treatment has, if at all, in the clinical setting. Some argue that oestrogen therapy should be considered only for certain groups of patients as part of a holistic approach, weighing the risk of harm and benefits (such as women around the menopause experiencing a worsening of symptoms, or pre-menopausal women who are hypo-oestrogenic (Mortimer 2007; Seeman 2012)). Others argue that is there a role for adjunctive oestrogen in the treatment of schizophrenia more broadly, in both pre-menopausal and post menopausal women, as well as men (Kulkarni 2012).

This review will not include studies of Selective Estrogen Receptor Modulators (SERMs) (e.g. raloxifene). Any such studies found will be evaluated in a separate review to be titled '*Raloxifene or bazedoxifene (selective oestrogen receptor modulator*) for schizophrenia in men and women' (Table 1). SERMS act specifically on the brain and bone are believed to offer a better long-term safety and tolerability profile (Kulkarni 2012).

This review will not include male participants who will have different safety and tolerability issues. Any such studies found will be evaluated in a separate review to be titled '*Oestrogens for schizophrenia*'

This review will not include studies where oestrogen was used as sole treatment for schizophrenia. This is because antipsychotics treatments with proven efficacy exist, and it is unlikely that clinically this would be either acceptable or ethical.

OBJECTIVES

To evaluate the clinical efficacy and safety of oestrogen as an adjunctive treatment versus placebo, in women with schizophrenia or schizophrenia-like illnesses.

METHODS

Criteria for considering studies for this review

Types of studies

We will include all relevant randomised controlled trials. If a trial is described as 'double-blind' but implies randomisation, we will include such trials in a sensitivity analysis (see Sensitivity analysis). We will exclude quasi-randomised studies, in which allocation was not concealed, such as those allocating by alternate days of the week

Types of participants

Women with schizophrenia or schizophrenia-like illnesses, including schizophreniform disorder, schizo-affective disorder and delusional disorder. If a trial included women with less severe mental illness, it will be accepted for inclusion if the majority (> 50%) of the participants suffered from severe functional psychotic illnesses such as schizophrenia. The diagnostic criteria are revised from time to time, the relevant version of International Classification of Disease (ICD-10 1992), Diagnostic and Statistical Manual (DSM-V 2013) or other validated diagnostic criteria will be considered.

To help make this review relevant, we propose, if possible, to highlight the participants current clinical state and stage of illness. For example, the current clinical state may be described as acute, early post-acute, partial remission or remission. The stage of illness may be first episode, early or chronic. Where studies focused on participants with a particular problem for example, we will highlight treatment-resistant illnesses or negative symptoms.

Types of interventions

1. Oestrogen as an adjunct to anti-psychotic medication: any preparation, dose and dosing schedule and any mode of administration (e.g. oral, subdermal, transdermal or nasal).
2. Oestrogen with progesterone as an adjunct to anti-psychotic medication: any preparation, dose and dosing schedule and any mode of administration (e.g. oral, subdermal, transdermal or nasal).
3. Placebo or nothing: as an adjunct to anti-psychotic medication.

Types of outcome measures

As schizophrenia is a long-term condition, we aim to report outcomes for the short term (up to 12 weeks), medium term (13 to 26 weeks), and long term (more than 26 weeks).

Primary outcomes

1. Global state: clinically important improvement: as defined by individual study

For example, global impression of much improved, or more than 50% improvement on a rating scale (Leucht 2005).

2. Leaving the study early for any reason

Secondary outcomes

1. Global state

1.1 Relapse - as defined by the study
1.2 Any change in global state
1.3 Average endpoint/change scores global state scale

2. Mental state

2.1 Overall mental sate

2.1.1 Clinically important change in overall mental state
2.1.2 Any change in overall mental state
2.1.3 Average endpoint/change scores (total) mental state scale

2.2 Specific mental state (positive/negative symptoms)

2.2.1 Clinically important change in specific mental state
2.2.2 Any change in specific aspects of mental state
2.2.3 Average endpoint/change scores specific mental state scale

3. Cognitive function

3.1 General cognitive function

3.1.1 Clinically important change in overall cognitive function
3.1.2 Any change in overall cognitive function
3.1.3 Average endpoint score cognitive function scale
3.1.4 Average change scores cognitive function scale

3.2 Specific cognitive function

3.2.1 Clinically important change in specific aspects of cognitive function
3.2.2 Any change in specific aspects of cognitive function
3.2.3 Average endpoint/change scores specific cognitive function scale

4. Death - any cause suicide, natural causes, homicide

5. Adverse effects (antipsychotic related)

General adverse effects

5.1 Clinically important general adverse effects
5.2 Any general adverse effects
5.3 Average endpoint/change scores adverse-effect scales

Specific adverse effects

5.4 Anticholinergic.
5.3 Cardiovascular.
5.4 Central nervous system.
5.5 Gastrointestinal.
5.6 Endocrine (e.g. amenorrhoea, galactorrhoea, hyperlipidaemia, hyperglycaemia, hyperinsulinaemia).
5.7 Haematology (e.g. haemogram, leukopenia, agranulocytosis/ neutropenia).
5.8 Hepatitic (e.g. abnormal transaminase, abnormal liver function).
5.9 Metabolic.
5.10 Movement disorders.
5.11 Various other.

6. Adverse effects (oestrogen-related)

6.1 Life-threatening (breast cancer or endometrial cancer cerebrovascular disease, cholestatic jaundice, myocardial infarction, thromboembolic disease)
6.2 Non life-threatening (altered blood lipids, depression, hypersensitivity reaction, nausea and vomiting)
6.3 Physiological effects of the compound (changes in libido, feminisation, pregnancy, pre-menstrual type syndrome, sodium and fluid retention)

7. Service utilisation

7.1 Hospital admission
7.2 Days in hospital
7.3 Change in hospital status i.e. transfer from intensive care ward to general open ward

8. Social function

8.1 Clinically important change social function
8.2 Any change social function
8.3 Average endpoint/change scores social function scales
8.4 Employment status during trial (employed / unemployed)

9. Behaviour

9.1 Clinically important change in general or specific behaviours - as defined of the studies
9.2 Average endpoint/change score behaviour scales
9.3 Violence against others
9.4 Reduction in significant risks (as defined by the authors e.g. reduction in rates of suicide, homicide, violence)

10. Economic outcomes

10.1 Direct costs
10.2 Indirect costs

Summary of findings

We will use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to interpret findings (Schünemann 2008), and use the GRADEPRO software to import data from the Cochrane Collaboration's statistical software, Review Manager, to create a 'Summary of Findings Outcomes' table. These tables provide outcome-specific information concerning the overall quality 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 for inclusion in the 'Summary of Findings table'.

1. Global State
2. Leaving the study early
3. Mental State
4. Cognitive function
5. Adverse effects (antipsychotic specific)
6. Adverse effects (oestrogen specific)
7. Economic costs

Search methods for identification of studies

Electronic searches

1. Cochrane Schizophrenia Group's Trials Register

The Information Specialist will search the Cochrane Schizophrenia Group's Registry of Trials using the following search strategy which has been developed based on literature review and consulting with the authors of the review:

((*estradiol* OR *estrogen* OR *hormone* OR *progesterone*) AND Placebo) in Intervention Field of STUDY

The Cochrane Schizophrenia Group's Registry of Trials is compiled by systematic searches of major resources (including AMED, BIOSIS, CINAHL, Embase, MEDLINE, PsycINFO, PubMed, and registries of clinical trials) and their monthly updates, handsearches, grey literature, and conference proceedings (see Group Module). There are no language, date, document type, or publication status limitations for inclusion of records into the register.

Searching other resources

1. Cited reference searching

We will inspect the references of all identified trials for any additional relevant studies.

2. Personal contact

We will contact the primary authors of all studies initially selected for inclusion in order to identify further relevant trials. We will also attempt to contact companies producing relevant compounds for copies of published, unpublished and archived trials. If we receive replies we will note these in the Characteristics of included studies table, and in the text.

3. Handsearching

We aim to identify high-yield journals and, if available and not already handsearched, we will chose one for a complete page-by-page inspection.

Data collection and analysis

Selection of studies

Review authors WLC and HG will independently inspect citations from the searches and identify relevant abstracts. Where disputes arise, we will acquire the full report for more detailed scrutiny. We will obtain reports of the abstracts meeting the review criteria; WLC and HG will inspect these. Where it is not possible to resolve disagreement by discussion, we will attempt to contact the authors of the study for clarification.

Data extraction and management

1. Extraction

Review authors WLC and HG will extract data from all included studies. In addition, to ensure reliability, review author JH will independently extract data from a random sample of these studies, comprising 10% of the total. We will discuss any disagreement and document decisions. If necessary, we will contact authors of studies for clarification. With any remaining disagreements, JH will help clarify issues and we will document these final decisions. We will attempt to extract data presented only in graphs and figures whenever possible, but include only if two review authors independently have the same result. We will attempt to contact authors through an open-ended request in order to obtain missing information or for clarification whenever necessary. If studies are multi-centre, where possible, we will extract data relevant to each component centre separately. Study tags will attempt to describe type of oestrogen preparation and doses if appropriate to allow for clear sorting and presentation in the graphs.

2. Management

2.1 Forms

We will extract data onto standard, 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); and
b) the measuring instrument has not been written or modified by one of the trialists for that particular trial.

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. On the other hand, calculation of change needs two assessments (baseline and endpoint), which can be difficult 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. We will present endpoint and change data separately and analyse each using standard mean differences (MD). If combining the endpoint and change data alter the direction of effect of the primary outcome, we will present the data using mean differences (Higgins 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 aim to apply the following standards to all data before inclusion.
Endpoint data N > 200
We will enter data from studies of at least 200 participants, in analyses irrespective of the following rules, because skewed data pose less of a problem in large studies.
Change data
We will also enter 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 data are skewed or not. We will present and enter change data into statistical analyses
Endpoint data N < 200
(a) when a scale starts from the nite number zero, we will subtract the lowest possible value from the mean, and divided this by the standard deviation (SD). If this value is lower than 1, it strongly suggests a skew and we will exclude these data. If this ratio is higher than 1 but below 2, there is suggestion of skew. We will enter these data and test whether their inclusion or exclusion would change the results substantially. Finally, if the ratio is larger than 2, we can include such data because skew is less likely (Altman 1996; Higgins 2011).
b) if a scale starts from a positive value (such as the Positive and Negative Syndrome Scale (PANSS), (Kay 1986)), which can have values from 30 to 210), we will modify the calculation described to take the scale starting point into account. In these cases skew is present if 2 SD > (S-S min), where S is the mean score and 'S min' is the minimum score.

2.5 Common measure

To facilitate comparison between trials, we intend 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, efforts will be made 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 Positive and Negative Syndrome Scale (PANSS, Kay 1986), this could be considered as a clinically significant response (Leucht 2005; Leucht 2005). 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 oestrogen. 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. This will be noted in the relevant graphs.

Assessment of risk of bias in included studies

Again, review authors WLC and HG will work independently to assess risk of bias by using criteria described in the *Cochrane Handbook for Systematic reviews of Interventions* (Higgins 2011) to assess trial quality. This set of criteria is based on evidence of associations between overestimate of effect and high risk of bias of the article such as sequence generation, allocation concealment, blinding, incomplete outcome data and selective reporting.

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 contact authors of the studies in order to obtain further information. We will report non-concurrence in quality assessment, but if disputes arise as to which category a trial is to be allocated, again, we will resolve by discussion. We will note the level of risk of bias in both the text of the review and in the 'Summary of findings' table.

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). It has been shown that RR is more intuitive (Boissel 1999) than odds ratios, and that odds ratios tend to be interpreted as RR by clinicians (Deeks 2000). The Number Needed to Treat/Harm (NNT/H) statistic with its confidence intervals is intuitively attractive to clinicians but is problematic both in its accurate calculation in meta-analyses and interpretation (Hutton 2009). For binary data presented in the 'Summary of findings' table/s, where possible, we will calculate illustrative comparative risks.

2. Continuous data

For continuous outcomes will estimate mean difference (MD) between groups. We prefer not to calculate effect size measures (standardised mean difference (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. Firstly, authors often fail to account for intra-class correlation in clustered studies, leading to a 'unit of analysis' error (Divine 1992) whereby P values are spuriously low, confidence intervals unduly narrow and statistical significance overestimated. This causes type I errors (Bland 1997; Gulliford 1999).

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). 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.

We have sought statistical advice and have been advised that the binary data as 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 [Design effect = 1+(m-1)*ICC] (Donner 2002). If the ICC is not reported it will be assumed to be 0.1 (Ukoumunne 1999).

If cluster studies have been appropriately analysed taking into account ICCs and relevant data documented in the report, 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, on entry to the second phase the participants can differ systematically from their initial state 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 effects are very likely in severe mental illness, we will only use data of 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 combined within the two-by-two table. If data are continuous we will combine data following the formula in section 7.7.3.8 (Combining groups) of the *Cochrane Handbook for Systematic reviews of Interventions* (Higgins 2011). Where the additional treatment arms are not relevant, we will not use 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 loss be 30% 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, with the exception of the outcome of death and adverse effects. For these outcomes, the rate of those who stay in the study - in that particular arm of the trial - will be used for 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

In the case 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, we will reproduce these.

3.2 Standard deviations

If standard deviations (SDs) are not reported, we will first try to obtain the missing values from the authors. If not available, where there are missing measures of variance for continuous data, but an exact standard error (SE) and confidence intervals available for group means, and either 'P' value or 't' value available for differences in mean, we can calculate them according to the rules described in the *Cochrane Handbook for Systematic reviews of Interventions* (Higgins 2011): When only the SE is reported, SDs are calculated by the formula SD = SE * square root (n). Chapters 7.7.3 and 16.1.3 of the *Cochrane Handbook for Systematic reviews of Interventions* (Higgins 2011) present detailed formulae for estimating SDs from P values, t or F values, confidence intervals, ranges or other statistics. 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. We nevertheless will examine the validity of the imputations in a sensitivity analysis excluding 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 in the reasons for leaving the studies early between groups is often the core problem in randomised schizophrenia trials. We will therefore not exclude studies based on the statistical approach used. However, we will preferably use the more sophisticated approaches. e.g. we prefer to use MMRM or multiple-imputation to LOCF and 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 clearly outlying people or situations which we had not predicted would arise and discuss any issues.

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 issues.

3. Statistical heterogeneity

3.1 Visual inspection

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

3.2 Employing the I^2 statistic

We will investigate heterogeneity between studies by considering the I^2 method alongside the Chi^2 P value. The I^2 provides an estimate of the percentage of inconsistency thought to be due to chance (Higgins 2003). The importance of the observed value of I^2 depends on i. magnitude and direction of effects and ii. strength of evidence for heterogeneity (e.g. P value from Chi^2 test, or a confidence interval for I^2). We will interpret an I^2 estimate greater than or equal to around 50% accompanied by a statistically significant Chi^2 statistic, as evidence of substantial levels of heterogeneity (Section 9.5.2 *Cochrane Handbook for Systematic reviews of Interventions* - Higgins 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

1. Protocol versus full study

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

Reporting biases arise when the dissemination of research findings is influenced by the nature and direction of results (Egger 1997). These are again described in Section 10 of the *Cochrane Handbook for Systematic reviews of Interventions* (Higgins 2011). 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 the random-effects model for all analyses.

Subgroup analysis and investigation of heterogeneity

1. Subgroup analyses

We propose to undertake this review to provide an overview of oestrogens in their various preparations for women with schizophrenia in general. In addition, however, we will try to report data on subgroups of people in the same clinical state, stage and with similar problems. If the data allow, we will look to report subgroups of hypo-oestrogenic pre-menopausal women, women with chronic treatment-resistant schizophrenia, women with predominantly negative symptoms and cognitive symptoms of schizophrenia. We will limit subgroup analyses to primary outcomes only.
We propose to undertake a sensitivity analysis of post-menopausal women and pre-menopausal women. If this does not significantly alter the direction of effect, we will not carry out a subgroup analysis. If it does, we will limit subgroup analysis to primary outcomes only.

2. Investigation of heterogeneity

We will report if inconsistency is high. First, we will investigate whether data have been entered correctly. Second, if data are correct, we will visually inspect the graph and successively remove outlying studies to see if homogeneity is restored. For this review we decided that should this occur with data contributing to the summary finding of no more than around 10% of the total weighting, we will present these data. If not, we will not pool data and discuss 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 are 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

1. Risk of bias

We will analyse the effects of excluding trials that are judged to be at high risk of bias across one or more of the domains of randomisation (implied as randomised with no further details available, allocation concealment, blinding and outcome reporting). If the exclusion of trials at high risk of bias does not substantially alter the direction of effect or the precision of the effect estimates, then we will include data from these trials in the analysis.

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 of the primary outcomes when we use our assumption/s and when we use data only from people who complete the study to that point. If there is a substantial difference, we will report results and discuss them, but will continue to employ our assumption.
Where assumptions have to be made regarding missing SDs data (see Dealing with missing data), we will compare the findings of the primary outcomes when we use our assumption/s and when we

use data only from people who complete the study to that point. We will undertake a sensitivity analysis to test how prone results are to change when completer-only data only are compared to the imputed data using the above assumption. If there is a substantial difference, we will report results and discuss them but will continue to employ our assumption.

4. 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.
If substantial differences are noted in the direction or precision of effect estimates in any of the sensitivity analyses listed above, we will not pool data from the excluded trials with the other trials contributing to the outcome, but will present them separately.

5. Fixed-effect and random-effects

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

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The Cochrane Schizophrenia Group Editorial Base in Nottingham produces and maintains standard text for use in the 'Methods' section of their reviews. We have used this text as the basis of what appears here and adapted it as required.

The search term was developed by the Trial Search Co-ordinator of the Cochrane Schizophrenia Group and the contact author of this protocol.

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* *Indicates the major publication for the study*

ADDITIONAL TABLES

Table 1. Other related titles

Title	Reference
Raloxifene or bazedoxifene (selective oestrogen receptor modulator) for schizophrenia in men and women	Unpublished.
Oestrogens for schizophrenia	Will be updated version of Chua 2005.
Oestrogen (adjunct) versus placebo for women with schizophrenia	This review.

CONTRIBUTIONS OF AUTHORS

Lian Chua - thought of the review title, instigated the work, wrote the protocol, analysed results.

Hristo Grigov - helped write the protocol.

John Hiley - helped write the protocol.

DECLARATIONS OF INTEREST

Lian Chua - None known.

Hristo Grigov - None known.

John Hiley - None known.

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