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Pharmacological interventions for clozapine-induced sinus tachycardia

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ABSTRACT

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

To assess the clinical effects and efficacy of pharmacological interventions for clozapine-induced sinus tachycardia.

To systematically review adverse events associated with pharmacological interventions for clozapine-induced sinus tachycardia.

BACKGROUND

Schizophrenia is a severe and chronic mental illness. Treatment-resistant schizophrenia occurs in a minority of patients in which their response to antipsychotic medication is sub optimal. Clozapine is the only drug with established efficacy in treatment-resistant schizophrenia (Chakos 2001; Kane 1988; McEvoy 2006; Meltzer 2005; Siris 2001; Wahlbeck 1999). Further, it has been demonstrated to reduce mortality rates, both in comparison with past users of clozapine (Walker 1997), and when compared to other antipsychotics (Tiihonen 2009). This exceptional position which clozapine holds in the pharmacopeia for treatment-resistant schizophrenia necessitates that adverse events secondary to its usage are minimised and aggressively treated when they occur. This is in order to reduce morbidity and maximise adherence with clozapine, particularly since adverse effects are a frequent reason for clozapine discontinuation (Pat 2012; Taylor 2009).

Description of the condition

Sinus tachycardia is one of the more common adverse events, which is reported to occur in 25% of patients treated with clozapine (Lieberman 1998; Safferman 1991). The development of tachycardia is considered generally to be a transient, benign occurrence (Young 1998), which may be related to the rapid dose titration of clozapine (Marinkovic 1994; Merrill 2005). Rapid clozapine titration rates (to 300 mg over one week) have been associated with increased pulse rates of 20 to 25 beats/minute (Sandoz 1987). In medication-free healthy volunteers, clozapine, at a relatively low dose of 50 mg, has been shown to cause a significant mean increase in heart rate of 14.3 beats/minute greater than that caused by placebo (Pretorius 2001). Patients with schizophrenia, taking clozapine at daily doses of 300-700 mg, have been shown to have significantly higher heart rates (mean 107 beats/minute) than patients treated with haloperidol (86 beats/minute) or olanzapine (89 beats/minute) or in unmedicated healthy controls (mean 62 beats/minute) (Pai 2012; Taylor 2009).
beats/minute) (Cohen 2001). For some patients, the clozapine-induced sinus tachycardia persists and is symptomatic, necessitating further investigation and consideration of interventions to control the sinus tachycardia.

**Description of the intervention**

Various effective treatments may exist to control heart rate increase due to clozapine use and we plan to evaluate studies to discover if evidence of effective proven pharmacological treatments exist.

**How the intervention might work**

The intervention would work to reduce the heart rate and any symptoms, such as palpitations, which may occur with an increased heart rate. Interventions to manage sinus tachycardia associated with clozapine include dose reduction, a decreased rate of clozapine titration (Safferman 1991), a switch to a different antipsychotic (Cohen 2001), or treatment with negative chronotropic drugs. Traditionally, beta-blockers are the most commonly used agents that are used to reduce the heart rate by blocking peripheral beta receptors, dampening sympathetic hyperactivity and increasing parasympathetic activity (Stryjer 2009). In patients with coronary heart disease, reducing the heart rate is a generally accepted treatment modality; it directly minimises the myocardial oxygen demand and enhances its supply by improving subendocardial blood flow (Cook 2007; Diaz 2005).

**Why it is important to do this review**

Clozapine-induced sinus tachycardia seems to be problematic in the early stages of treatment and is probably dose-related (Lieberman 1998; Merrill 2008). It is important that adverse events due to clozapine use are managed appropriately, in order to minimise unnecessary clozapine discontinuation. Sinus tachycardia is an identified reason for clozapine discontinuation, but the frequency of clozapine discontinuation secondary to tachycardia has not been widely described. In a 15-year naturalistic retrospective study of clozapine use, tachycardia was identified as the cause of discontinuation in 4% of clozapine users (Davis 2014). While cardiovascular events have been identified as the most common cause of deaths during treatment with clozapine (Davis 2014), and the occurrence of myocarditis or cardiomyopathy should prompt the immediate discontinuation of clozapine, the emergence of an isolated sinus tachycardia (provided that myocarditis is ruled out) should not be a cause for clozapine discontinuation (Nielsen 2013) and should be appropriately managed.

Substantial epidemiological evidence shows resting sinus tachycardia to be a risk factor for coronary artery disease and cardiovascular morbidity and mortality (Borer 2008; Diaz 2005; Kannel 1987), comparable to that of hypertension and dyslipidaemia. Sinus tachycardia is associated with both greater myocardial oxygen consumption and decreased myocardial perfusion, the latter by shortening the duration of diastole, which can induce or exacerbate myocardial ischaemia (Diaz 2005). An elevated heart rate is also strongly associated with mortality in the general population (Cook 2007). Individuals with established psychosis have increased mortality rates compared to the general population due to cardiovascular disease, necessitating that cardiovascular risk factors, such as sinus tachycardia, be minimised in this population. An ongoing resting sinus tachycardia is also recognised as a risk factor for cardiomyopathy (Shinbane 1997), a serious adverse event associated with clozapine treatment. The need to minimise the risk of cardiac adverse events secondary to clozapine use and to reduce the risk of cardiovascular morbidity are pertinent reasons for the symptomatic treatment of sinus tachycardia in clozapine-treated patients.

Various pharmacological approaches have been used to try to alleviate this problem, however, to the best of our knowledge there are no drug treatments licensed for this indication. Effective treatments may exist to control the heart rate increase due to clozapine use and we intend to evaluate studies to discover if evidence of effective proven treatments exist. A systematic review of pharmacological interventions for clozapine-induced sinus tachycardia has yet to be carried out. A systematic review on this subject would bring together completed studies in this area, to aid in making clinical decisions and guiding future research.

**OBJECTIVES**

To assess the clinical effects and efficacy of pharmacological interventions for clozapine-induced sinus tachycardia.

To systematically review adverse events associated with pharmacological interventions for clozapine-induced sinus tachycardia.

**METHODS**

**Criteria for considering studies for this review**

**Types of studies**

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 (Sensitivity analysis). If their inclusion does not result in a substantive difference, they will remain in the analyses. If their inclusion does result in important clinically significant, but not necessarily statistically significant differences,
we will not add the data from these lower quality studies to the results of the better trials, but will present such data within a subcategory. We will exclude quasi-randomised studies, such as those allocating by alternate days of the week. Where people are given additional treatments within the treatment intervention, we will only include data if the adjunct treatment is evenly distributed between groups and it is only the treatment intervention that is randomised.

Types of participants
Adults, however defined, with schizophrenia or related disorders, including schizophreniform disorder, schizoaffective disorder and delusional disorder, again, by any means of diagnosis who have been treated with clozapine irrespective of gender, age or diagnosis. There is no specific duration of clozapine treatment required. All participants need to have evidence of a heart rate > 100 beats/minute with a documented sinus tachycardia, judged to be clozapine-induced.

We are interested in making sure that information is as relevant to the current care of people with schizophrenia as possible so propose to clearly highlight the current clinical state (acute, early post-acute, partial remission, remission). Individuals will be largely classified as meeting the criteria for treatment-resistant schizophrenia or psychosis, as it is only for this treatment-resistant group of patients for whom clozapine is used as a licensed treatment.

Types of interventions
1. Any pharmacological intervention at any dose or route of administration whose primary aim is to treat the clozapine-induced tachycardia compared with:
2. another pharmacological agent, placebo or no treatment.

Types of outcome measures
All outcomes will be divided into short term - short term (up to 12 weeks), medium term (13 to 26 weeks) and long term (more than 26 weeks).

Primary outcomes
The primary measure of efficacy will be clinical improvement in pulse rate, measured either as a dichotomous outcome (proportions of patients with treatment response as defined by each of the studies), or as a continuous outcome (reported either as endpoint score or change in pulse rate from baseline to endpoint).

1. Measurement of pulse rate
1.1 Normalisation of pulse rate (as defined by a pulse rate < 100 beats/minute or by the individual studies)
1.2 Clinically important change in pulse rate (as defined by individual studies)
1.3 Mean change in pulse rate documented by electrocardiogram (ECG) or from case record
1.4 Mean endpoint pulse rate documented by ECG or from case record

Secondary outcomes
1. ECG measurement
1.1 Heart rate and rhythm
1.2 QTc interval
1.3 T-wave morphology
1.4 Other ECG markers

2. Service outcomes
2.1 Hospitalisation
2.2 Duration of hospitalisation
2.3 Time to hospitalisation

3. Global state
3.1 Relapse (as defined in trial)
3.2 Clinically important change in global state (as defined by individual studies)
3.3 Average endpoint global state score
3.4 Average change in global state scores

4. Mental state (with particular reference to the positive and negative symptoms of schizophrenia)
4.1 Clinically important change in general mental state
4.2 Average endpoint general mental state score
4.3 Average change in general mental state scores
4.4 Clinically important change in specific symptoms (positive symptoms of schizophrenia, negative symptoms of schizophrenia, depression, mania)
4.5 Average endpoint specific symptom score
4.6 Average change in specific symptom scores

5. General functioning
5.1 Clinically important change in general functioning
5.2 Average endpoint general functioning score
5.3 Average change in general functioning scores
5.4 Clinically important change in specific aspects of functioning, such as social or life skills
5.5 Average endpoint specific aspects of functioning, such as social or life skills
5.6 Average change in specific aspects of functioning, such as social or life skills

6. Adverse effects - general and specific
6.1 Clinically important general adverse effects
6.2 Average endpoint general adverse effect score
6.3 Average change in general adverse effect scores
6.4 Clinically important specific adverse effects
6.5 Average endpoint specific adverse effects (including endpoint blood pressure (BP))
6.6 Average change in specific adverse effects (including change in BP)
6.7 Sudden and unexpected death

7. Satisfaction with treatment
7.1 Leaving the studies early
7.2 Recipient of care not satisfied with treatment
7.3 Recipient of care average satisfaction score
7.4 Recipient of care average change in satisfaction scores
7.5 Carer not satisfied with treatment
7.6 Carer average satisfaction score
7.7 Carer average change in satisfaction scores

8. Quality of life (recipient or informal carers or professional carers)
8.1 Clinically important change in overall quality of life
8.2 Average endpoint quality of life score
8.3 Average change in quality of life scores
8.4 Clinically important change in specific aspects of quality of life
8.5 Average endpoint specific aspects of quality of life
8.6 Average change in specific aspects of quality of life

9. 'Summary of findings' table
We will use the GRADE approach to interpret findings (Schünemann 2008) and will use GRADE profiler (GRADEPRO) to import data from RevMan 5 (Review Manager) to create 'Summary of findings' tables. 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 will 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. Measurement of pulse rate
   2. ECG measurement

3. Service outcomes
4. Global state
5. Mental state (with particular reference to the positive symptoms of schizophrenia)
6. Adverse effects-specific, such as hypotension and bradycardia
7. Satisfaction with treatment

Search methods for identification of studies

Electronic searches

1. Cochrane Schizophrenia Group's Trials Register
The Trials Search Co-ordinator (TSC) will search the Cochrane Schizophrenia Group's Register of Trials using the following phrase:
   ((clozapin* or clozaril* or denzapin* or zaponex* or alemoxan or azaleptin or clopime or clopsine or dorval or dozapine or elicrt or fazaclo or "hf 1854" or hf1854 or lapen*x or lozapin* or sizopin or versacloz or zapan) and (tachycardia*)):ti,ab,kw of REFERENCE or ((clozapin* or clozaril* or denzapin* or zaponex* or alemoxan or azaleptin or clopime or clopsine or dorval or dozapine or elicrt or fazaclo or "hf 1854" or hf1854 or lapen*x or lozapin* or sizopin or versacloz or zapan) and tachycardia*):sin and (tachycardia*):sco,spr of STUDY
The Cochrane Schizophrenia Group's Register 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, hand-searches, grey literature, and conference proceedings (see Group Module). There is no language, date, document type, or publication status limitations for inclusion of records in 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 or awaiting assessment studies tables.
Data collection and analysis

Selection of studies
The principal review author JL and review author MJD will independently inspect all citations from the searches and identify relevant abstracts. The sample will be independently re-inspected by review author JM to ensure reliability. Where disputes arise, the full report will be acquired for more detailed scrutiny. Full reports of the abstracts meeting the review criteria will be obtained and inspected by each of review authors JL, MJD and JM in order to ensure reliable selection. 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 JL and MJD will independently extract data from all included studies. In addition, to ensure reliability, JM will independently extract data from a random sample of these studies, comprising 50% of the total. Again, any disagreement will be discussed, decisions documented and, if necessary, authors of studies will be contacted for clarification. With remaining problems, JM will help clarify issues and these final decisions will be documented. Data presented only in graphs and figures will be extracted whenever possible, but included 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.

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. Endpoint and change data will be combined in the analysis as we will use mean differences (MD) rather than standardised mean differences (SMD) throughout (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: We will enter data from studies of at least 200 participants, for example, in the analysis irrespective of the following rules, because skewed data pose less of a problem in large studies. 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 For endpoint data:
(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. If this value is lower than 1, it strongly suggests a skew and the study will be excluded. If this ratio is higher than one but below 2, there is suggestion of skew. We will enter the study and test whether its inclusion or exclusion would change the results substantially. Finally, if the ratio is larger than 2, the study will be included, 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), the calculation described above will be modified 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 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 interventions for clozapine-induced tachycardia. 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 JL and MJD 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, the final rating will be made by consensus, with the involvement of another member of the review group.
Where adequate details of randomisation and other characteristics of trials are provided, we will contact authors of the studies in order to obtain further information. Non-concurrence in quality assessment will be reported, but if disputes arise as to which category a trial is to be allocated, again, we will resolve by discussion. The level of risk of bias will be noted 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, we 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 SMD 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. In subsequent versions of this review, 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. It 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, the additional treatment arms will be presented in comparisons. If data are binary, these will be simply added 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 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 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 intention-to-treat analysis using the above assumptions.

3. Continuous

3.1 Attribition
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 Systemic reviews of Interventions (Higgins 2011). Where 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 Systemic 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 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 preferentially use the more sophisticated approaches. For example,. MMRM or multiple-imputation will be preferred to LOCF and completer analyses will only be presented if some kind of intention-to-treat 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

Pharmacological interventions for clozapine-induced sinus tachycardia (Protocol)
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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. When such situations or participant groups arise, these will be fully discussed.

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. When such methodological outliers arise these will be fully discussed.

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
Heterogeneity between studies will be investigated 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 $I^2$). An $I^2$ estimate greater than or equal to around 50% accompanied by a statistically significant $\chi^2$ statistic, will be interpreted as evidence of substantial levels of heterogeneity (Section 9.5.2 - 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, outcomes in the protocol and in the published report will be compared. If the protocol is not available, outcomes listed in the methods section of the trial report will be compared 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 sizes. 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 the fixed-effect model for all analyses. The reader is, however, able to choose to inspect the data using the random-effects model.

Subgroup analysis and investigation of heterogeneity

1. Subgroup analyses

1.1 Primary outcomes
Subgroup analyses will, if possible, be performed to analyse for different components of the intervention for clozapine-associated tachycardia, including: different types of medication used; different doses of medication used; and mode of medication administration.

1.2 Clinical state, stage or problem
We propose to undertake this review and provide an overview of the effects of pharmacological intervention for clozapine-induced tachycardia for people with schizophrenia and psychotic disorders 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.
2. Investigation of heterogeneity

If inconsistency is high, this will be reported. First, we will investigate whether data have been entered correctly. Second, if data are correct, we will visually inspect the graph and outlying studies will be successively removed 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 around 10% of the total weighting, data will be presented. If not, data will not be pooled and issues will be discussed. 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. Implication of randomisation

We aim to include trials in a sensitivity analysis if they are described in some way as to imply randomisation. For the primary outcomes, we will include these studies and if there is no substantive difference when the implied randomised studies are added to those with better description of randomisation, then all data will be employed from these studies.

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 SD 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. A sensitivity analysis will be undertaken 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.

3. 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 for the meta-analysis of the primary outcome. 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 data from these trials will be included in the analysis.

4. Imputed values

We will also undertake a sensitivity analysis to assess the effects of including data from trials where we used 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 fixed-effect model, however, we will also synthesise data for the primary outcome using a random-effects model to evaluate whether this alters the significance of the results.

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* Indicates the major publication for the study

**CONTRIBUTIONS OF AUTHORS**

John Lally: conceived and designed the review, will co-ordinate the review, collect data, design search strategies and contribute to study selection. He will provide a methodological and clinical perspective to the review and wrote the protocol.

Mary J Docherty: will aid in the design of the review and data collection for the review, will contribute to the design of search strategies and study selection, assisted in writing the protocol and provided methodological and general advice on the protocol.

James H MacCabe: reviewed the draft protocol and assisted in writing the protocol, will contribute to designing the review, study selection and writing the review. Provided methodological and general advice, as well as a clinical perspective on the protocol.

**DECLARATIONS OF INTEREST**

John Lally: None known

Mary J Docherty: None known

James H MacCabe: None known

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