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Pharmacological interventions for clozapine-induced sinus tachycardia (Review)

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Pharmacological interventions for clozapine-induced sinus tachycardia

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A B S T R A C T

Background

Clozapine is an efficacious treatment for treatment-resistant schizophrenia; however its use can be limited by side effect intolerability. Sinus tachycardia is a common adverse event associated with clozapine treatment. Various pharmacological treatments are used to control heart rate increase due to clozapine use and can include a decreased rate of clozapine titration, a switch to a different antipsychotic, or treatment with negative chronotropic drugs.

Objectives

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

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

Search methods

On 23 March 2015, we searched the Cochrane Schizophrenia Group's Study-Based Register of Trials, which is based on regular searches of CINAHL, BIOSIS, AMED, EMBASE, PubMed, MEDLINE, PsycINFO and registries of clinical trials. There are no language, date, document type or publication status limitations for inclusion of records in the register.

Selection criteria

Randomised controlled trials comparing pharmacological interventions, at any dose and by any route of administration, for clozapine-induced tachycardia.

Data collection and analysis

We independently screened and assessed studies for inclusion using pre-specified inclusion criteria.

Main results

The electronic searches located three references. However, we did not identify any studies that met our inclusion criteria.

Authors' conclusions

With no studies meeting the inclusion criteria, it is not possible to arrive at definitive conclusions. There are currently insufficient data to confidently inform clinical practice. We cannot, therefore, conclude whether specific interventions, such as beta-blockers, are less effective or more effective than standard courses of alternative treatments for tachycardia. This lack of evidence for the treatment of clozapine-induced tachycardia has implications for research and practice. Well-planned, conducted and reported randomised trials are indicated. One trial is currently underway. Current practice outside of well-designed randomised trials should be clearly justified.

PLAIN LANGUAGE SUMMARY

Pharmacological interventions for clozapine-induced sinus tachycardia

Clozapine is an antipsychotic medication used in the treatment of schizophrenia. Clozapine is the only treatment proven to be effective for those people who do not respond to other antipsychotic medications. A fast pulse rate (tachycardia) is one of the more common side effects associated with clozapine use. It is reported to occur in 25 out of every 100 people treated with clozapine. The occurrence of a fast pulse rate may lead to palpitations in the person treated with clozapine, which can be unpleasant and worrying. A fast pulse rate by itself is not necessarily dangerous to the person and can be treated. There are medications available to treat a fast pulse rate and slow it down to a normal rate. Examples of such medications include beta-blockers and calcium channel blockers. However, a fast pulse rate can lead to clozapine being stopped by doctors.

This review is about ways to reduce this problem, to find out if any treatment for a fast heart rate with clozapine use is better than another. This review investigated the best available evidence for interventions aimed at treating a fast heart rate associated with clozapine treatment. Unfortunately, we found no studies that could be included. Nevertheless, this review raises many unanswered questions and strongly suggests that future research on the treatment is much needed. Finding answers to this question will aid people treated with clozapine, and their doctors, in ensuring that a fast heart rate with clozapine can be treated and that clozapine can be safely continued.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [*Explanation*]

Pharmacological interventions for clozapine-induced sinus tachycardia

Patient or population: adults with schizophrenia or related disorders treated for clozapine-induced tachycardia
Setting: any
Intervention: one pharmacological treatment for tachycardia
Comparison: another pharmacological treatment for tachycardia or placebo or no treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with another pharmacological treatment for tachycardia or placebo or no treatment	Risk with one pharmacological treatment for tachycardia				
Clinical improvement in pulse rate Assessed with: pulse rate	Study population		Not estimable	-	-	We found no trial data for this series of important outcomes
	0 per 1000	0 per 1000 (0 to 0)				
Improvement in heart rate assessed with ECG measurement	-	The mean improvement in heart rate assessed with ECG measurement in the intervention group was 0 (0 to 0)	-	-	-	No trial data
Duration of hospitalisation	Study population		Not estimable	-	-	No trial data
	0 per 1000	0 per 1000 (0 to 0)				
Clinically important adverse events	Study population		Not estimable	-	-	No trial data

	0 per 1000	0 per 1000 (0 to 0)				
Patient satisfaction	Study population		Not estimable	-	-	No trial data
	0 per 1000	0 per 1000 (0 to 0)				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

__CI:__ confidence interval; __ECG:__ electrocardiogram

__GRADE Working Group grades of evidence__
__High quality:__ We are very confident that the true effect lies close to that of the estimate of the effect
__Moderate quality:__ We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
__Low quality:__ Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
__Very low quality:__ We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

BACKGROUND

Schizophrenia is a severe and chronic mental illness. Treatment-resistant schizophrenia occurs in a minority of people whose response to antipsychotic medication is suboptimal. 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). The exceptional position held by clozapine in the pharmacopoeia for treatment-resistant schizophrenia means that adverse events secondary to its usage must be 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 (Pai 2012; Taylor 2009).

Description of the condition

Sinus tachycardia is one of the more common adverse events and is reported to occur in 25% of patients treated with clozapine (Lieberman 1998; Safferman 1991). The development of tachycardia is generally considered 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 mg to 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 unmedicated healthy controls (mean 62 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 it.

Description of the intervention

Various effective treatments may exist to control heart rate increase due to clozapine use and can include decreased rate of clozapine titration (Safferman 1991), a switch to a different antipsychotic (Cohen 2001), or treatment with negative chronotropic drugs.

How the intervention might work

The intervention would work by reducing 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 and work 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 2005). 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 the minimisation of cardiovascular risk factors, such as sinus tachycardia, 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 increase in heart rate due to clozapine use and we intended to evaluate studies to discover whether evidence of effective proven treatments exists. 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 the 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 was described as 'double-blind' but implied randomisation, we planned to include such trials in a sensitivity analysis (Sensitivity analysis). If their inclusion did not result in a substantive difference, they were to remain in the analyses. If their inclusion did result in important, clinically significant but not necessarily statistically significant differences, we planned not to add the data from these lower quality studies to the results of the better trials, but would have presented such data within a subcategory. We also decided to exclude quasi-randomised studies, such as those allocating by alternate days of the week. Where people were given additional treatments within the treatment intervention, we planned to only include data if the adjunct treatment was evenly distributed between groups and it was only the treatment intervention that was 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. No specific duration of clozapine treatment was required. All participants needed to have evidence of a heart rate greater than 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 we proposed to clearly highlight the current clinical state (acute, early post-acute, partial remission, remission). In future searches for trials, we will largely classify individuals as meeting the criteria for treatment-resistant schizophrenia or psychosis, as it is only for this treatment-resistant group of patients that clozapine is used as a licensed treatment.

Types of interventions

1. Pharmacological intervention

Any pharmacological intervention at any dose or route of administration the primary aim of which is to treat clozapine-induced tachycardia.
Compared with:

2. Control

Another pharmacological agent, placebo or no treatment.

Types of outcome measures

All outcomes were to be divided into 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 is 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 an 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 of less than 100 beats/minute or by the individual studies)
1.2 Clinically important change in pulse rate (as defined by the 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 planned to use the GRADE approach to interpret findings (Schünemann 2008), and to 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 rate as important to patient care and decision-making. We aimed 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

On 23 March 2015, the Trials Search Co-ordinator (TSC) searched the Cochrane Schizophrenia Group's Register of Trials using the following phrase:

((clozapin* or clozaril* or denzapin* or zaponex* or alemoxan or azaleptin or clopine or clopsine or dorval or dozapine or elcrit or fazaclo or "hf 1854" or hf1854 or lapen?x or lozapin* or sizopin or versacloz or zapen) and (tachycardia*)):ti,ab,kw of REFERENCE or ((clozapin* or clozaril* or denzapin* or zaponex* or alemoxan or azaleptin or clopine or clopsine or dorval or dozapine or elcrit or fazaclo or "hf 1854" or hf1854 or lapen?x or lozapin* or sizopin or versacloz or zapen) and tachycardia*):sin and (tachycardia*): sco,spo 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 are no language, date, document type or publication status limitations for inclusion of records in the register.

Searching other resources

1. Other trials registers

On 28 February 2015, we searched the ClinicalTrials.gov register of clinical trials (https://clinicaltrials.gov). Clinical trials entries are delivered from the US National Institutes of Health. Please see the attached link above to retrieve further details from the government database.

2. Reference searching

We inspected the references of all included studies for further relevant studies.

3. Personal contact

We also planned to contact the first author of each included study for information regarding unpublished trials.

Data collection and analysis

Selection of studies

The principal review author JL, and review author MJD, independently inspected all citations from the searches and identified relevant abstracts. JM independently re-inspected these to ensure reliability. JL and MJD obtained and inspected full reports of the abstracts that met the review criteria. JM re-inspected these in order to ensure reliable selection. We were not blinded to the name(s) of the study author(s), their institution(s) or publication sources at any stage of the review.

Data extraction and management

1. Extraction

Review authors JL and MJD independently extracted data from all included studies. In addition, to ensure reliability, we planned for JM to independently extract data from a random sample of these studies, comprising 50% of the total. Again, any disagreement would have been discussed, decisions documented and, if necessary, we planned to contact the authors of the study for clarification. However, this did not happen.

With remaining problems, we planned that JM would help clarify issues and these final decisions would be documented. Data presented only in graphs and figures would be extracted whenever possible, but included only if two review authors independently had the same result. We planned to contact authors through an open-ended request in order to obtain missing information or for clarification whenever necessary. If studies were multi-centre, where possible, we had planned to extract data relevant to each component centre separately. However, we did not undertake these steps as none of the studies fulfilled the review's inclusion criteria.

2. Management

2.1 Forms

We extracted data onto standard, simple forms.

2.2 Scale-derived data

We planned to include continuous data from rating scales only if:
a) the psychometric properties of the measuring instrument had been described in a peer-reviewed journal (Marshall 2000); and
b) the measuring instrument had 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 planned to note if this was 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 decided to primarily use endpoint data, and only use change

data if the former were not available. Endpoint and change data were to be combined in the analysis as we were going to use mean differences (MD) rather than standardised mean differences (SMDs) 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 aimed to apply the following standards to data before inclusion:

We planned to 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 also planned to 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 planned to present and enter change data into statistical analyses

For endpoint data:

(a) When a scale starts from the finite number zero, we planned to 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 would have been excluded. If this ratio is higher than one but below 2, there is suggestion of skew. We decided to primarily use endpoint data, and only use change data if the former were not available. Endpoint and change data were to be combined in the analysis as we were going to use mean differences (MD) rather than standardised mean differences (SMDs) throughout (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 would have been 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 intended 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 planned to make efforts to convert outcome measures to dichotomous data. This would 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 were not available, we planned to use the primary cut-off presented by the original authors.

2.7 Direction of graphs

Where possible, we planned to 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 planned to report data where the left of the line indicates an unfavourable outcome. This was to be noted in the relevant graphs.

Assessment of risk of bias in included studies

We included no trials. If trials had been included, review authors JL and MJD planned to work independently to assess risk of bias by using the criteria described in the *Cochrane Handbook for Systematic Reviews of Interventions* to assess trial quality (Higgins 2011). 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 trials had been included JM would have independently assessed a random sample of included trials for risk of bias, to ensure reliability. Again, if the raters had included trials, where there was disagreement, the final rating was to be made by consensus, with the involvement of JM. Where inadequate details of randomisation and other characteristics of trials were provided, we planned to contact authors of the studies in order to obtain further information. Non-concurrence in 'Risk of bias' assessment was to be reported, but if disputes arose as to which rating a domain was to be allocated, resolution was to be made by discussion. The level of risk of bias was to be noted in both the text of the review and in the 'Summary of findings' table, and reported in 'Risk of bias' tables.

Measures of treatment effect

1. Binary data

For binary outcomes, we planned to calculate a standard estimation of the risk ratio (RR) and its 95% confidence interval (CI). It has been shown that RR is more intuitive than the odds ratio (Boissel 1999), and that odds ratios tend to be interpreted as RR by clinicians (Deeks 2000). The number needed to treat/harm (NNTB/NNTH) 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 planned to calculate illustrative comparative risks.

2. Continuous data

For continuous outcomes, we planned to estimate the mean difference (MD) between groups. We preferred not to calculate effect size measures (standardised mean difference (SMD)). However, if scales of considerable similarity were used, we were going to presume there was a small difference in measurement, and we were going to calculate the 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 was not accounted for in primary studies, we planned to 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 had been incorporated into the analysis of primary studies, we planned to present these data as if from a non-cluster randomised study, but adjust for the clustering effect. Statistical advice suggested 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 was not reported, we would have assumed it to be 0.1 (Ukoumunne 1999).

If cluster studies had been appropriately analysed by taking into account ICCs and relevant data documented in the report, synthesis with other studies would 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 would only have used data from the first phase of cross-over studies.

3. Studies with multiple treatment groups

Where a study involved more than two treatment arms, if relevant, the additional treatment arms were to be presented in comparisons. If data were binary these were to be simply added and combined within the two-by-two table. If data were continuous we planned to combine data following the formula in section 7.7.3.8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Where the additional treatment arms were not relevant, we would not have used 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). If, for any particular outcome, more than 50% of data were unaccounted for, we planned not to reproduce these data or use them within analyses. If, however, more than 50% of those in one arm of a study were lost, but the total loss was less than 50%, we were going to address this within the 'Summary of findings' table/s by downgrading quality. We also planned to 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 was between 0% and 50% and where these data were not clearly described, we planned to present data on an intention-to-treat (ITT) basis. Those leaving the study early would all be 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 stayed in the study - in that particular arm of the trial - was to be used for those who did not. We planned to undertake a sensitivity analysis to test how prone the primary outcomes were to change when data only from people who completed the study to that point were compared to the ITT analysis using the above assumptions.

3. Continuous

3.1 Attrition

In the case where attrition for a continuous outcome was between 0% and 50%, and data only from people who completed the study to that point were reported, we planned to reproduce these.

3.2 Standard deviations

If standard deviations (SDs) were not reported, we planned to first try to obtain the missing values from the authors. If not available, where there were missing measures of variance for continuous data, but an exact standard error (SE) and confidence intervals were available for group means, and either P value or t value were available for differences in mean, we planned to calculate them according to the rules described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). When only the SE was 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* present detailed formulae for estimating SDs from P values, t or F values, confidence intervals, ranges or other statistics (Higgins 2011). If these formula did not apply, we were going to 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 planned to 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 therefore planned not to exclude studies based on the statistical approach used. However, we preferred to use the more sophisticated approaches. For example, where MMRM or multiple-imputation data were reported, we planned to use these in preference to LOCF, and completer analyses would have only been presented if some kind of intention-to-treat data were not available at all. Moreover, we planned to address this issue in the 'incomplete outcome data domain of the 'Risk of bias' tool.

Assessment of heterogeneity

1. Clinical heterogeneity

We planned to consider all included studies initially, without seeing comparison data, to judge clinical heterogeneity. We were to simply inspect all studies for clearly outlying people or situations that we had not predicted would arise. When such situations or participant groups arose, these were to be fully discussed.

2. Methodological heterogeneity

We planned to consider all included studies initially, without seeing comparison data, to judge methodological heterogeneity. We planned to inspect all studies for clearly outlying methods that we had not predicted would arise. When such methodological outliers arose, these were to be fully discussed.

3. Statistical heterogeneity

3.1 Visual inspection

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

3.2 Employing the I^2 statistic

We planned to investigate heterogeneity between studies by considering the I^2 statistic alongside the Chi^2 P value. The I^2 statistic 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 (1) the magnitude and direction of effects, and (2) the 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 result, was to be interpreted as evidence of substantial levels of heterogeneity (Section 9.5.2 - Higgins 2011). When substantial levels of heterogeneity were found in the primary outcome, we planned to explore the 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 (Egger 1997). These are described in section 10.1 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We planned to locate protocols for included randomised trials. If the protocol was available, outcomes in the protocol and in the published report were to be compared. If the protocol was not available, the outcomes listed in the methods section of the trial report were to be compared with the 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 planned not to use funnel plots for outcomes where there were 10 or fewer studies, or where all studies were of similar sizes. In other cases, where funnel plots were possible, we planned to 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 planned to apply 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 would have been performed, if possible, 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 proposed 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, we had sought to try to report data on subgroups of people in the same clinical state, stage and with similar problems.

2. Investigation of heterogeneity

If inconsistency was high, this would have been reported. First, we planned to investigate whether data had been entered correctly. Second, if data were correct, then we would have visually inspected the graph and outlying studies would have been successively removed to see if homogeneity was restored. For this review, we had

planned that should this occur with data contributing to the summary finding of no more than around 10% of the total weighting, we would present the data. If not, then we planned that data would not be pooled and the issues would 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 was obvious, we planned to simply state hypotheses regarding these for future reviews or versions of this review. We did not anticipate undertaking analyses relating to these.

Sensitivity analysis

1. Implication of randomisation

We aimed to include trials in a sensitivity analysis if they were described in some way as to imply randomisation. For the primary outcomes, we would have included these studies and if there was no substantive difference when the implied randomised studies were added to those with better description of randomisation, then all data would have been employed from these studies.

2. Assumptions for lost binary data

Where assumptions had to be made regarding people lost to follow-up, or missing SDs (see Dealing with missing data), we planned to compare the findings of the primary outcomes when we used our assumption compared with completer data only. If there was a substantial difference, we planned to report the results and discuss them but continue to employ our assumption.

3. Risk of bias

We planned to analyse the effects of excluding trials that were 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 did not substantially alter the direction of effect or the precision of the effect estimates, then data from these trials were to be included in the analysis.

4. Imputed values

We planned to undertake a sensitivity analysis to assess the effects of including data from trials for which we used imputed values for ICC in calculating the design effect in cluster-randomised trials. If we had noted substantial differences in the direction or precision of effect estimates in any of the sensitivity analyses listed above, we would not pool data from these excluded trials with those of other trials contributing to the outcome but would have presented them separately.

5. Fixed-effect and random-effects

We planned to synthesise all data using a fixed-effect model, however, we would have also synthesised data for the primary outcome using a random-effects model to evaluate whether this would have altered the significance of the results.

R E S U L T S

Description of studies

We did not find any studies that fulfilled the inclusion criteria.

Results of the search

We found three records through electronic searching of the Cochrane Schizophrenia Register up to March 2015; none of these were duplicates leaving three records for screening (Figure 1). After screening, we obtained the three full-text articles for further assessment. These were closely assessed for inclusion, but none could eventually be included in the review. These three studies, Liang 2001, Wang 1995 and Wei 1995, are in the excluded studies table (Characteristics of excluded studies).

Figure 1. Study flow diagram.
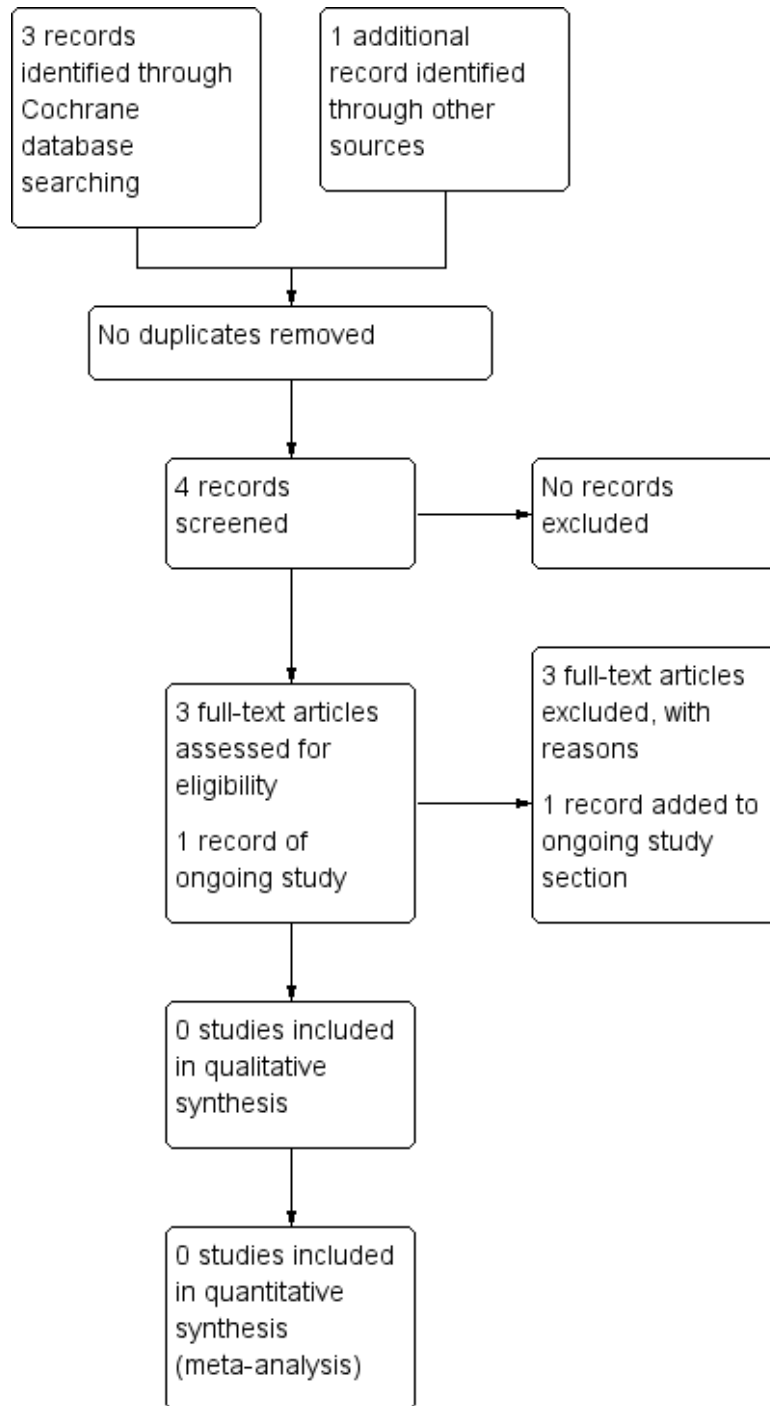
Searches of trial registries identified one ongoing and eligible trial in this area (NCT00882856) (https://clinicaltrials.gov/show/NCT00882856).

Awaiting assessment studies

There are no studies awaiting assessment.

Ongoing studies

We know of one ongoing trial (NCT00882856).

Included studies

There are no included studies in this review.

Excluded studies

We assessed three studies carefully for inclusion, but excluded all of them as none specified treatment for clozapine-induced tachycardia. The three excluded trials used interventions for antipsychotic-induced tachycardia, without specifically identifying treatment for clozapine-induced tachycardia (Liang 2001; Wang 1995; Wei 1995).

Risk of bias in included studies

No studies could be included in this review, hence we were unable to assess risk of bias.

Effects of interventions

See: **Summary of findings for the main comparison** Pharmacological interventions for clozapine-induced tachycardia No study met the inclusion criteria. The excluded studies demonstrate that trials of pharmacotherapeutic interventions for antipsychotic-induced tachycardia are possible, however no trials comparing interventions specifically for clozapine-induced tachycardia have been conducted. We had hoped to gather information on global and mental state, issues around use of services, quality of life, satisfaction with treatment and costs. Such data are not available from randomised trials.

DISCUSSION

Summary of main results

We did not find any study that compared treatments for clozapine-induced tachycardia. Three randomised studies used some

form of pharmacotherapeutic intervention for antipsychotic-induced tachycardia, but did not specify response for those on clozapine or did not include patients treated with clozapine (Liang 2001; Wang 1995; Wei 1995). We further identified one retrospective chart review (Stryjer 2009), and four case reports (Das 2014; Lally 2014; van Dam 2012) , which reported on the use of beta-blockers (Stryjer 2009; van Dam 2012), ivabradine (Lally 2014), and verapamil (Das 2014) in the treatment of clozapine-induced tachycardia. These studies could be relevant in guiding the management of clozapine-induced tachycardia, but none met the review's inclusion criteria.

Overall completeness and applicability of evidence

There is currently no randomised trial-based evidence.

Quality of the evidence

There is currently no randomised trial-based evidence.

Potential biases in the review process

We limited potential biases in the review process by following the Cochrane methodology. The search for trials was thorough with no language, date, document type or publication status limitations. We strictly followed the review protocol in the process of study selection, data extraction and analysis.

Agreements and disagreements with other studies or reviews

We know of no other reviews focusing on this intervention.

AUTHORS' CONCLUSIONS

Implications for practice

1. For people with clozapine-induced tachycardia

Despite the fact that clozapine-induced tachycardia is a common adverse effect, in this review we were unable to identify studies that compared interventions for its treatment. However, this review does indicate that trials in this area are possible. Pharmacological interventions for this troublesome adverse effect have not

been adequately investigated within the context of a trial and this needs to be addressed. People with clozapine-induced tachycardia could encourage this investigation or support it by agreeing to be randomised to well-designed and reported studies.

2. Clinicians

Despite growing interest in the management of the adverse events associated with clozapine use, the literature in the area of treatment for clozapine-induced tachycardia is still very limited. Researchers and clinicians have undertaken studies, but these studies fall well short of rigorous trials. A retrospective chart review demonstrated that atenolol had increased effectiveness and better tolerability than propranolol in controlling tachycardia associated with clozapine therapy (Stryjer 2009). Two case reports described the use of ivabradine to effectively treat clozapine-induced tachycardia and reported that it was well tolerated (Lally 2014). A further case report described the use of verapamil to effectively treat clozapine-induced tachycardia (Das 2014). However, this evidence is fully open to biases with the potential harm that these can bring.

It seems that clinicians have no choice but to continue with their current practice, based on clinical judgement, because of the lack of randomised evidence to help guide their choice of intervention. Clinicians have a responsibility to lobby for and help good research in this area.

3. For policymakers

Clinical practice guidelines should include the best available evidence. Currently, however, there is insufficient evidence from trials on which to base guidelines for the treatment of clozapine-induced tachycardia. It could be suggested as policy that in such cases clinical practice should take place within well-designed trials.

Implications for research

1. General

Clinically meaningful randomised studies are needed to help guide clinicians in their management of clozapine-induced tachycardia. Available publications indicate that such studies are possible. There is a need for randomised trials to compare pharmacotherapeutic interventions for clozapine-induced tachycardia. These trials

should focus on the treatment of tachycardia with a focus on patient tolerability and satisfaction with the intervention, along with consideration of clinical state outcome measures. Validated measures regarding the primary outcome and adverse effects should be used.

2. Specific

Pragmatic, real world randomised controlled trials should be carried out to determine the value of possible treatments for clozapine-induced tachycardia in standard clinical practice. Studies need to have a duration longer than one month and involve people whose problems are clearly documented, whether by clinical measurement of pulse rate, electrocardiogram (ECG) recordings or from case records. The methods should be very clearly described and tested and the interventions should probably involve the use of a placebo, however the best chosen experimental treatment may be one that is used or accepted locally. From this review a beta-blocker may be indicated as a first-line intervention for investigation; based on practice in the UK, this could be bisoprolol. Studies need to include a validated method of measuring clozapine-induced tachycardia and some medium- and long-term outcomes including adverse events (specifically hypotension and bradycardia), discontinuation of treatment and satisfaction with treatment. We have suggested a design for a study in Table 1.

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NCT00882856 *{unpublished data only}*
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* Indicates the major publication for the study

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Liang 2001	Allocation: randomised (no further detail) Participants: diagnosis not stated; only stated that participants were taking antipsychotics Intervention: Tian-wang-bu-xin-dan (Chinese traditional medicine) versus propranolol; clozapine not specified as a treatment used
Wang 1995	Allocation: randomised (no further detail) Participants: schizophrenia inpatients with tachycardia; n = 100; male and female; 18 to 60 years of age Intervention: propranolol versus verapamil; clozapine use not specified
Wei 1995	Allocation: randomised (no further detail) Participants: 100 people diagnosed with schizophrenia; all had sinus tachycardia induced by antipsychotic drugs Intervention: propranolol 10 mg 3 times a day versus verapamil 20 mg 3 times a day, each for 2 weeks; investigated the effects of propranolol and verapamil for antipsychotic-induced tachycardia and did not investigate clozapine-induced tachycardia specifically

Characteristics of ongoing studies *[ordered by study ID]*

NCT00882856

Trial name or title	'Treating clozapine-induced sinus tachycardia with bisoprolol - a double blinded placebo controlled cross over study'
Methods	Allocation: randomised Endpoint classification: safety/efficacy study Intervention model: cross-over assignment Masking: double-blind (subject, caregiver, investigator, outcomes assessor) Primary purpose: treatment

Participants	36 individuals with a diagnosis of schizophrenia or schizoaffective disorder on clozapine
	Age: over 18 to 65
	Sex: both male and female
	All with clozapine-induced sinus tachycardia
	Inclusion criteria:
	    • Treated with clozapine > 3 months and minimum 100 mg/day
	    • Fixed dose 14 days before inclusion
	    • Heart rate > 100 (ECG)
	    • Pregnancy test negative
	    • Clozapine-induced sinus tachycardia documented by ECG or case record
	    • Sexual abstinence or contraception
	    • Informed consent
	Exclusion criteria:

	• Substance abuse • Physical diseases, contraindications for clozapine or bisoprolol • Asthma or chronic obstructive lung disease • Blood pressure < 100/60 or recent history of syncope • QTc > 500 ms, SA-block, AV- block II or III • Restrictions by Danish mental act • Allergic to clozapine or bisoprolol
Interventions	Bisoprolol 10 mg daily compared with placebo for the treatment of clozapine-induced sinus tachycardia
Outcomes	Primary outcome measures: • Heart rate variability (time frame: baseline, visit 1 + 2 + 3) (designated as safety issue: no) Secondary outcome measures: • QTc, T-wave morphology and other ECG markers (time frame: baseline, visit 1 + 2 + 3) (designated as safety issue: yes) • Hamilton Anxiety Scale (time frame: baseline, visit 1 + 2 + 3) (designated as safety issue: no) • Salivation rate (time frame: baseline, visit 1 + 2 + 3) (designated as safety issue: no) • Orthostatic blood pressure (time frame: baseline, visit 1 + 2 + 3) (designated as safety issue: yes) • WHO QoL (time frame: baseline, visit 1 + 2 + 3) (designated as safety issue: no) • Nocturnal Hypersalivation Rating Scale (NHRS) (time frame: baseline, visit 1 + 2 + 3) (designated as safety issue: no)
Starting date	16 April 2009
Contact information	Contact: Jimmi Nielsen, MD; Contact: Sonja Snel, MD
Notes	Principal Investigator: Dr Jimmi Nielsen, PhD, Aalborg Psychiatric Hospital Sponsor: University of Aarhus

ECG: electrocardiogram
QoL: quality of life
WHO: World Health Organization

DATA AND ANALYSES

This review has no analyses.

ADDITIONAL TABLES

Table 1. Suggested design for trials

Methods	Participants	Interventions	Outcomes	Notes
Allocation: centralised sequence generation with table of random numbers or computer generated code Sequence concealed until interventions assigned	Diagnosis: treatment-resistant schizophrenia, schizoaffective disorder or other psychotic disorders for which longer-term clozapine treatment is indicated and who have developed sustained clozapine-induced tachycardia	1. Bisoprolol 5 mg to 10 mg 3 times a day 2. Placebo: flexible dose or 1. Ivabradine 5 mg to 7.5 mg twice a day 2. Placebo: flexible dose	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: 2. ECG measurement 2.1 Heart rate and rhythm 2.2 QTc interval 2.3 T-wave morphology 2.4 Other ECG markers	Size of study to detect a 10% difference in improvement with 80% certainty
Blinding: participants, those recruiting and assigning participants, those assessing outcomes will be blind to treatment allocation Blinding can be tested by asking participants and raters to guess the treatment they were exposed to	All with clozapine-induced sinus tachycardia Age: adults. 18 to 65 years Sex: men and women Setting: hospital and community	-	1. Adverse effects-specific, such as hypotension and bradycardia 2. Discontinuation of treatment 3. Satisfaction with treatment 4. Service outcomes 5. Global state 6. Mental state (with particular reference to the positive symptoms of	-

Table 1. Suggested design for trials *(Continued)*

			schizophrenia) 7. Cost	
Duration: minimum of 1 year	Inclusion criteria: • Treated with clozapine > 3 weeks and minimum 100 mg/day • Heart rate > 100 (ECG) • Pregnancy test negative • Clozapine-induced sinus tachycardia documented by ECG or case record Exclusion criteria: • Substance abuse • Physical illnesses, contraindications for bisoprolol or ivabradine • Asthma or chronic obstructive lung disease (if beta-blocker used) • Blood pressure < 100/60 or recent history of syncope • QTc > 500 ms, SA-block, AV- block II • Allergic to bisoprolol or ivabradine	-	-	-

CONTRIBUTIONS OF AUTHORS

John Lally: conceived and designed the review, co-ordinated the review, collected data, assisted in the design of the search strategies, contributed to study selection, trial selection, data extraction from excluded studies and the write-up of the report. Provided a methodological and clinical perspective to the review.

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

James H MacCabe: reviewed the protocol. Contributed to the design of the review, study selection and advice with completion of the report. Provided methodological and general advice, as well as a clinical perspective on the review.

DECLARATIONS OF INTEREST

John Lally: none known

Mary J Docherty: none known

James H MacCabe: none known

SOURCES OF SUPPORT

Internal sources

- Institute of Psychiatry,Psychology and Neuroscience, King's College London, UK.

Salary support provided by the Institute of Psychiatry, Psychology and Neuroscience for all authors

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None