UNIVERSITY OF BIRMINGHAM
University of Birmingham Research at Birmingham

Celecoxib plus standard care for people with schizophrenia

Kotecha, Ayesha; Upthegrove, Rachel

DOI:
10.1002/14651858.CD009205.pub2

License:
None: All rights reserved

Document Version
Publisher's PDF, also known as Version of record

Citation for published version (Harvard):
Kotecha, A & Upthegrove, R 2018, 'Celecoxib plus standard care for people with schizophrenia', *Cochrane Database of Systematic Reviews*, vol. 2018, no. 12, CD009205. https://doi.org/10.1002/14651858.CD009205.pub2

Link to publication on Research at Birmingham portal

Publisher Rights Statement:
Checked for eligibility: 30/07/2019

This Protocol of a Cochrane Review was published in the Cochrane Database of Systematic Reviews 2018, Issue 12. Cochrane Protocols and Reviews are regularly updated as new evidence emerges and in response to feedback, and the Cochrane Database of Systematic Reviews should be consulted for the most recent version of the Protocol.

Kotecha A, Upthegrove R. Celecoxib plus standard care for people with schizophrenia (Protocol). Cochrane Database of Systematic Reviews 2018, Issue 12. Art. No.: CD009205. DOI: 10.1002/14651858.CD009205.pub2.

General rights
Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

•Users may freely distribute the URL that is used to identify this publication.
•Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
•User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
•Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

Take down policy
While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.

Download date: 10. May. 2024

Cochrane Library

Cochrane Database of Systematic Reviews

Celecoxib plus standard care for people with schizophrenia (Protocol)

Kotecha A, Upthegrove R

Kotecha A, Upthegrove R.
Celecoxib plus standard care for people with schizophrenia.
Cochrane Database of Systematic Reviews 2018, Issue 12. Art. No.: CD009205.
DOI: 10.1002/14651858.CD009205.pub2.

www.cochranelibrary.com

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

WILEY

TABLE OF CONTENTS

HEADER 1
ABSTRACT 1
BACKGROUND 1
OBJECTIVES 2
METHODS 2
ACKNOWLEDGEMENTS 9
REFERENCES 9
APPENDICES 12
WHAT'S NEW 12
CONTRIBUTIONS OF AUTHORS 12
DECLARATIONS OF INTEREST 12
SOURCES OF SUPPORT 12

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

[Intervention Protocol]

Celecoxib plus standard care for people with schizophrenia

Ayesha Kotecha[1], Rachel Upthegrove[2]

[1]Department of Medicine, The University of Birmingham, Birmingham, UK. [2]Institute of Clinical Science and School of Psychology, Institute for Mental Health, University of Birmingham and Forward Thinking Birmingham, Birmingham, UK

Contact address: Ayesha Kotecha, Department of Medicine, The University of Birmingham, Edgbaston, Birmingham, B15 2TT, UK. ANK342@student.bham.ac.uk.

Editorial group: Cochrane Schizophrenia Group.
Publication status and date: Edited (no change to conclusions), published in Issue 12, 2018.

Citation: Kotecha A, Upthegrove R. Celecoxib plus standard care for people with schizophrenia. *Cochrane Database of Systematic Reviews* 2018, Issue 12. Art. No.: CD009205. DOI: 10.1002/14651858.CD009205.pub2.

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ABSTRACT

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

To evaluate the efficacy and safety of celecoxib as an add-on treatment to standard care for people with schizophrenia.

BACKGROUND

Description of the condition

Schizophrenia is a serious mental illness characterised by distortions of thinking and perception (positive symptoms) and cognition (cognitive symptoms), as well as inappropriate or blunted affect (negative symptoms) (WHO 2016). Affecting around 0.3% to 0.7% of people worldwide at some point in their life, schizophrenia typically has an onset in early adulthood; it may have a continuous course, or it may be episodic with either a progressive or a stable deficit (WHO 2016; van Os 2009). Schizophrenia has high human and financial costs; people diagnosed with schizophrenia tend to live 12 to 15 years less than the general population (van Os 2009). This raised mortality is mainly linked to poor physical health, which results from increased exposure to risk factors such as poor diet, low levels of exercise, smoking and obesity, together with suicide (van Os 2009).

Current treatments for schizophrenia are only partially effective, with up to 30% of people having treatment-resistant positive symptoms, and the majority having poor long-term social and occupational functioning (Gaughran 2018). Antipsychotic medications, traditionally categorised into typical (or first generation) and atypical (or second generation), are the mainstay treatment for schizophrenia (Tandon 2011). They are effective for treating the positive symptoms of schizophrenia, but are not as effective for cognitive and negative symptoms (El-Sayed El-Sisi 2016; Sangani 2017). Antipsychotics can cause debilitating, sometimes irreversible side effects (Girgis 2014). First-generation antipsychotics are primarily associated with movement disorders and hyperprolactinaemia, as well as muscarinic side effects such as dry mouth and urinary retention, while second-generation antipsychotics are associated with adverse events that include Type 2 diabetes mellitus, weight gain, dizziness and somnolence (Sangani 2017). Therefore additional treatments are often given alongside antipsychotics to help improve clinical efficacy or alleviate side effects, or both.

The aetiology of schizophrenia is unclear but there are several risk factors associated with the development of the illness that include both genetic and environmental factors. Recent research also suggests that schizophrenia could be linked to immune system activation in the brain (Schwieler 2015; Upthegrove 2014a). This

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

has led to the consideration of anti-inflammatory agents as a new avenue for much needed therapies.

Description of the intervention

Celecoxib is a non-steroidal anti-inflammatory medication (NSAID) that is relatively safe and inexpensive (Riedel 2005). Celecoxib is a specific cyclo-oxygenase-2 (COX-2) inhibitor and may be safer than other NSAIDs in terms of its side-effect profile, particularly on the gastrointestinal tract (Davies 2000), although some research suggests there may be a cardiovascular risk (Solomon 2008; De Vecchis 2014). Celecoxib is taken orally at doses between 50 mg and 400 mg daily, divided.

How the intervention might work

Within the immune system, T helper Type 1 (Th1) lymphocytes stimulate Type 1 immunity, whilst T helper Type 2 (Th2) lymphocytes stimulate Th2 immunity (Spellberg 2001). A 2013 study, as well as others, have observed a clear Th2 shift in schizophrenia (Chiang 2013), therefore we can infer that the Th1 and Th2 immune responses become imbalanced in schizophrenia. Cyclo-oxygenase-2 inhibitors, such as celecoxib, reduce the synthesis of pro-inflammatory cytokines, such as Th1-like cytokines. Therefore, COX-2 inhibitors bring the Th1 and Th2 immune responses back into balance (Akhondzadeh 2007).

Secondly, COX-2 inhibitors, such as celecoxib, have also been found to prevent neuronal death induced by kainic acid (Akhondzadeh 2007). Kainic acid is an excito-toxin, which is a potent agonist of ionotrophic glutamate receptors (Yoon 2008). The glutametergic system has been proposed to be key in both positive and negative symptoms in schizophrenia, making this mechanism of action potentially relevant (Akhondzadeh 2007).

However, Yokota and colleagues examined neuronal COX-2 expression in the hippocampus of patients with schizophrenia, and suggested that celecoxib's mechanism of action in schizophrenia may involve COX-2 independent actions, such as regulation of the transcription factor nuclear factor-kappa B (NF-κB)'s activity, rather than inhibiting COX-2 (Yokota 2004).

Why it is important to do this review

Currently available antipsychotic medications used in the treatment of schizophrenia only have partial effectiveness, and can cause significant, often unpleasant, side effects; additional treatments are often needed (Girgis 2014). Research indicates that adding celecoxib to antipsychotic treatment may be a safe and efficacious for schizophrenia, particularly in first-episode schizophrenia (Baheti 2013; Girgis 2014; Marini 2016; Müller 2005; Müller 2013; Müller 2016; Riedel 2005; Torrey 2012; Zheng 2017). However, there is also published literature which does not support this hypothesis (Andrade 2016; Nitta 2013; Rapaport 2005; Sommer 2014). Additionally, concerns have been raised over celecoxib increasing cardiovascular risk (De Vecchis 2014; Solomon 2008), which contradicts previous research that concluded that celecoxib did not carry an increased cardiovascular risk compared to placebo or NSAIDs (White 2007).

Although a meta-analysis investigating the effects of celecoxib as an add-on treatment for people with schizophrenia was published very recently in 2017, that review had a number of limitations, including the investigation only of randomised, placebo-controlled trials, and literature searches restricted to English and Chinese databases only (Zheng 2017). Additionally, five out of the eight included trials used risperidone as the baseline antipsychotic; the authors stated that this may result in their findings not being generalisable to other antipsychotics (Zheng 2017).

Therefore it is important to systematically collate and analyse all available data from randomised controlled trials to create a high-quality evidence base for the effects of adding celecoxib to standard care. We propose to conduct a Cochrane systematic review which includes a greater variety of studies than previous papers have done. We will include studies which compare celecoxib administered as an add-on treatment with either: antipsychotics, interventions other than antipsychotics, placebo in combination with antipsychotics, placebo, or no treatment. We will also search Cochrane Schizophrenia's Study-Based Register of Trials, with the aim of searching a broader range of databases than previous papers have done. Using these methods we will endeavour to include a wider range of studies into our review, and thus gain a greater, higher quality evidence base on the effects and safety of celecoxib as an add-on treatment for people with schizophrenia.

OBJECTIVES

To evaluate the efficacy and safety of celecoxib as an add-on treatment to standard care for people with schizophrenia.

METHODS

Criteria for considering studies for this review

Types of studies

We will consider all relevant randomised controlled trials (RCTs). We will include RCTs which meet our inclusion criteria and report useable data. We will consider trials that are described as 'double blind' - in which randomisation is implied - and include or exclude once we have carried out a sensitivity analysis (see Sensitivity

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

analysis). We will exclude quasi-randomised studies, such as those that allocate the intervention by alternate days of the week. Where people are given additional treatments as well as celecoxib we will only include data if the adjunct treatment is evenly distributed between groups and it is only the celecoxib that is randomised.

Types of participants

Adults, however defined, with a diagnosis (by any means) of schizophrenia.

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

Types of interventions

1. Experimental interventions

1.1 Celecoxib (alone or in combination with other medication) plus standard care: any dose, frequency or route of administration.

2. Comparator interventions

2.1 Antipsychotics (alone or combination): any dose, frequency or route of administration.

2.2 Placebo (active or inactive), or no treatment.

2.3 Other interventions (alone or in combination with antipsychotics, or placebo): any dose, frequency or route of administration.

We define standard care as the care a participant in the trial would normally receive.

Types of outcome measures

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

We will endeavour to report binary outcomes recording clear and clinically meaningful degrees of change (e.g. global impression of much improved, or more than 50% improvement on a rating scale, as defined within the trials) before any others. Thereafter we will list other binary outcomes and then those that are continuous.

Primary outcomes

1. Global state

1.1 Clinically important change in global state, as defined by individual studies

1.2 Relapse, as defined by individual studies

2. Mental state

2.1 Clinically important change in specific symptoms: positive, negative, depression

2.2 Clinically important change in overall mental state, as defined by individual studies

3. Adverse effects

3.1 Cardiovascular: clinically important change or incidence of cardiovascular adverse effects, as defined by individual studies

Secondary outcomes

1. Global state

1.1 Any change in global state

1.2 Average endpoint/change score on global state scale

2. Mental state

2.1 Any change in mental state

2.2 Average endpoint/change score on mental state scale

3. Quality of life

3.1 Clinically important change in quality of life, as defined by individual studies

3.2 Clinically important change in specific aspects of quality of life, as defined by individual studies

3.3 Any change in quality of life

3.4 Average endpoint/change score on quality of life scale

4. Leaving the study early

4.1 For any reason

4.2 Due to inefficacy

4.3 Due to adverse effect

5. Other adverse effects

5.1 At least one event

5.2 Clinically important change in other adverse effects (e.g. anticholinergic; central nervous system; gastrointestinal; endocrine; haematological; hepatic; metabolic; movement disorders), as defined by individual studies

5.3 Any change in other adverse effects (e.g. anticholinergic; central nervous system; gastrointestinal; endocrine; haematological; hepatic; metabolic; movement disorders)

5.4. Average endpoint/change score on adverse effect scale

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

'Summary of findings' table

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

- Global state: clinically important change in global state, as defined by individual studies.
- Mental state: clinically important change in positive symptoms, as defined by individual studies.
- Mental state: clinically important change in negative symptoms, as defined by individual studies.
- Mental state: clinically important change in depressive symptoms, as defined by individual studies.
- Quality of life: clinically important change in quality of life, as defined by individual studies.
- Adverse effects: clinically important change in cardiovascular adverse effects, as defined by individual studies.
- Leaving the study early.

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

Search methods for identification of studies

Electronic searches

Cochrane Schizophrenia Group's Study-Based Register of Trials

The information specialist will search their register using the following search strategy:
Celecoxib in the intervention field of STUDY
In such a study-based register, searching the major concept retrieves all the synonyms and relevant studies because all the studies have already been organised based on their interventions, and linked to the relevant topics (Shokraneh 2017).
This register is compiled by systematic searches of major resources (AMED, BIOSIS, CENTRAL, CINAHL, ClinicalTrials.gov, Embase, MEDLINE, PsycINFO, PubMed, WHO ICTRP) and their monthly updates, ProQuest Dissertations and Theses A&I and its quarterly update, Chinese databases (CBM, CNKI, and Wanfang) and their annual updates, handsearches, grey literature, and conference proceedings (see Group's Module). There are no language, date, document type, or publication status limitations for inclusion of records into the register.
For previous searches, please see Appendix 1.

Searching other resources

1. Reference searching

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

2. Personal contact

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

Data collection and analysis

Selection of studies

Review author (AK) will independently inspect citations from the searches and identify relevant abstracts; review author (RU) will independently re-inspect a random sample of 20% of these abstracts to ensure reliability of selection. Where disputes arise, we will acquire the full report for more detailed scrutiny. AK will then obtain and inspect full reports of the abstracts or reports meeting the review criteria; RU will re-inspect a random 20% of these full reports in order to ensure reliability of selection. Where it is not possible to resolve disagreement by discussion, we will attempt to contact the authors of the study. We will summarise the study selection process using PRISMA 2015.

Data extraction and management

1. Extraction

Review author (AK) will extract data from all included studies. In addition, to ensure reliability, review author (RU) will independently extract data from a random sample of these studies, comprising 10% of the total. We will attempt to extract data presented only in graphs and figures whenever possible, but will include these only if two reviewers independently obtain the same result. If studies are multi-centre, then where possible we will extract data relevant to each centre. We will discuss any disagreement and document our decisions. If necessary, we will attempt to contact study authors through an open-ended request in order to

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

obtain missing information or for clarification. CIaire Irving (see Acknowledgements) will help clarify issues regarding any remaining problems and we will document these final decisions.

2. Management

2.1 Forms

We will extract data onto standard, pre-designed, simple forms (Cochrane 2014).

2.2 Scale-derived data

We will include continuous data from rating scales only if:

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

Ideally the measuring instrument should either be 1) a self-report or 2) completed by an independent rater or relative (not the therapist). We realise that this is not often reported clearly; we will note if this is the case or not in the 'Description of studies' section of the review.

2.3 Endpoint versus change data

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

2.4 Skewed data

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

- When a scale starts from the nite number zero, we will subtract the lowest possible value from the mean, and divide this by the standard deviation (SD). If this value is lower than one, it strongly suggests that the data are skewed and we will exclude these data. If this ratio is higher than one but less than two, there is suggestion that the data are skewed: we will enter these data and test whether their inclusion or exclusion would change the results substantially. If such data change the results we will enter them as 'other data'. Finally, if the ratio is larger than two we will include these data, because it is less likely that they are skewed (Altman 1996; Higgins 2011).
- If a scale starts from a positive value - such as the Positive and Negative Syndrome Scale (PANSS), which can have values from 30 to 210 (Kay 1986) - we will modify the calculation described above to take the scale starting point into account. In these cases, skewed data are present if $2\ SD > (S - S\ min)$, where S is the mean score and 'S min' is the minimum score.

Please note: we will enter all relevant data from studies of more than 200 participants in the analysis, irrespective of the above rules, because skewed data pose less of a problem in large studies. We will also enter all relevant change data, as when continuous data are presented on a scale that includes a possibility of negative values (such as change data), it is difficult to tell whether or not data are skewed.

2.5 Common measurement

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

2.6 Conversion of continuous to binary

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

2.7 Direction of graphs

Where possible, we will enter data in such a way that the area to the left of the line of no effect indicates a favourable outcome for celecoxib. In situations where this method makes it impossible to avoid outcome titles with clumsy double-negatives (e.g. 'not un-

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

improved') we will report data where the left of the line indicates an unfavourable outcome, and note this in the relevant graphs.

Assessment of risk of bias in included studies

Review authors AK and RU will work independently to assess risk of bias by using criteria described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). This set of criteria is based on evidence of associations between potential overestimation of effect and the level of risk of bias of the article that may be due to aspects of sequence generation, allocation concealment, blinding, incomplete outcome data and selective reporting, or the way in which these 'domains' are reported.
If the raters disagree, we will make the final rating by consensus. Where inadequate details of randomisation and other characteristics of trials are provided, we will attempt to contact the authors of the studies in order to obtain further information. We will report non-concurrence in quality assessment, but if disputes arise regarding the category to which a trial is to be allocated, we will resolve this by discussion.
We will note the level of risk of bias in both the text of the review, summary 'Risk of bias' figures, and the 'Summary of findings' table/s.

Measures of treatment effect

1. Binary data

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

2. Continuous data

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

Unit of analysis issues

1. Cluster-randomised trials

Studies increasingly employ 'cluster randomisation' (such as randomisation by clinician or practice), but analysis and pooling of clustered data poses problems. Authors often fail to account for intra-class correlation in clustered studies, leading to a unit of analysis error whereby P values are spuriously low, CIs unduly narrow and statistical significance overestimated (Divine 1992). This causes type I errors (Bland 1997; Gulliford 1999).
Where clustering has been incorporated into the analysis of primary studies, we will present these data as if from a non-cluster-randomised study, but adjust for the clustering effect.
Where clustering is not accounted for in primary studies, we will present data in a table, with a (*) symbol to indicate the presence of a probable unit of analysis error. We will seek to contact first authors of studies to obtain intra-class correlation coefficients for their clustered data, and to adjust for this by using accepted methods (Gulliford 1999).
We have sought statistical advice and have been advised that the binary data from cluster-randomised trials presented in a report should be divided by a 'design effect'. This is calculated using the mean number of participants per cluster (m) and the intra-class correlation coefficient (ICC): thus design effect = 1 + (m − 1) * ICC (Donner 2002). If the ICC is not reported we will assume it to be 0.1 (Ukoumunne 1999).
If cluster-randomised studies have been appropriately analysed and have taken intra-class correlation coefficients and relevant data documented in the report into account, synthesis with other studies will be possible using the generic inverse variance technique.

2. Cross-over trials

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

3. Studies with multiple treatment groups

Where a study involves more than two treatment arms, if relevant, we will present the additional treatment arms in comparisons. If data are binary we will simply add these and combine within the two-by-two table. If data are continuous we will combine data

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

following the formula in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Where additional treatment arms are not relevant, we will not reproduce these data.

Dealing with missing data

1. Overall loss of credibility

At some degree of loss of follow-up, data must lose credibility (Xia 2009). We choose that, for any particular outcome, should more than 50% of data be unaccounted for we will not reproduce these data or use them within analyses. If, however, more than 40% of those in one arm of a study are lost, but the total loss is less than 60%, we will address this within the 'Summary of findings' table/s by down-rating our assessments of the quality of the evidence. Finally, we will also downgrade our quality assessments within the 'Summary of findings' table/s should the loss be 25% to 60% in total.

2. Binary data

In the case where attrition for a binary outcome is between 0% and 40% and where these data are not clearly described, we will present data on a 'once-randomised-always-analyse' basis (an intention-to-treat analysis (ITT)). In this approach, those leaving the study early are all assumed to have the same rates of negative outcome as those who completed. We will use the rate of those who stay in the study - in that particular arm of the trial - and apply this also to those who did not. We will undertake a sensitivity analysis to test how prone the primary outcomes are to change when data only from people who completed the study to that point are compared to the ITT analysis using the above assumptions.

3. Continuous data

3.1 Attrition

We will use data where attrition for a continuous outcome is between 0% and 40%, and data only from people who complete the study to that point are reported.

3.2 Standard deviations

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

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

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

Assessment of heterogeneity

1. Clinical heterogeneity

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

2. Methodological heterogeneity

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

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

3. Statistical heterogeneity

3.1 Visual inspection

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

3.2 Employing the I^2 statistic

We will investigate heterogeneity between studies by considering the I^2 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 the magnitude and direction of effects as well as the strength of evidence for heterogeneity (e.g. P value from Chi^2 test, or a confidence interval for I^2). We will interpret an I^2 estimate greater than or equal to 50% and accompanied by a statistically significant Chi^2 statistic as evidence of substantial heterogeneity (in accordance with Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions,* Deeks 2011). When substantial levels of heterogeneity are found in the primary outcome, we will explore reasons for heterogeneity (Subgroup analysis and investigation of heterogeneity).

Assessment of reporting biases

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

1. Protocol versus full study

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

2. Funnel plot

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

Data synthesis

We understand that there is no closed argument for preference for use of fixed-effect or random-effects models. The random-effects method incorporates an assumption that the different studies are estimating different, yet related, intervention effects. This often seems to be true to us and the random-effects model takes into account differences between studies, even if there is no statistically significant heterogeneity. There is, however, a disadvantage to the random-effects model: it puts added weight onto small studies, which often are the most biased ones. Depending on the direction of effect, these studies can either inflate or deflate the effect size. We choose that if I^2 is less than 50%, and so there is enough homogeneity amongst included studies, then we will use a fixed-effect model for analyses. However, if I^2 is greater than or equal to 50%, and so there is substantial heterogeneity amongst included studies, and if this heterogeneity cannot be explained, we will use a random-effects model for analyses.

Subgroup analysis and investigation of heterogeneity

We will investigate factors which may be associated with heterogeneity by using subgroup analyses as studies allow, for example in those with a first episode of psychosis and chronic schizophrenia. If any of these post-hoc factors show promising links to the observed heterogeneity, then we will discuss these in this review.

Sensitivity analysis

If there are substantial differences in the direction or precision of effect estimates in any of the sensitivity analyses listed below, we will not add data from the lower-quality studies to the results of the higher-quality trials, but will present these data within a subcategory. If their inclusion does not result in a substantive difference, we will retain them in the analyses.

1. Implication of randomisation

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

2. Assumptions for lost binary data

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

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

using completer data only. We will undertake a sensitivity analysis testing how prone results are to change when completer 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 continue to employ our assumption.

3. Risk of bias

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

4. Imputed values

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

5. Fixed-effect and random-effects

If a random-effects model is used in this review, we will conduct a sensitivity analysis to assess whether there is a substantial difference between the results of primary outcomes where a random-effects model is used for meta-analysis, and where a fixed-effect model is used.

ACKNOWLEDGEMENTS

The editorial base of Cochrane Schizophrenia produce and maintain a methods template for use in their reviews. We have used and adapted this template for this protocol.

A protocol for this Cochrane Review was previously published (Akhondzadeh 2011), and the current team of review authors have taken over the title to complete this research. Elements from the previous author team's protocol have been used as the basis of this protocol and we would like to acknowledge the previous team (Akhondzadeh S, Modabbernia A, Taslimi S, Daneshmand A, Ostovaneh MR) for their contributions.

Ayesha Kotecha would like to acknowledge their project supervisor, Dr Rachel Upthegrove, for her continual assistance and support, as well as Claire Irving for her help with protocol development.

We acknowledge and thank peer review comments from Fang Dong, Zhen Mao, Cynthia Zavala Gaete, Paulina Maravilla Herrera and Noelia Álvarez.

REFERENCES

Additional references

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

Andrade 2016
Andrade C. Anti-inflammatory strategies in the treatment of schizophrenia. *Expert Review of Clinical Pharmacology* 2016;**9**(2):161–3.

Baheti 2013
Baheti T, Nischal A, Nischal A, Khattri S, Arya A, Tripathi A, et al. A study to evaluate the effect of celecoxib as add-on to olanzapine therapy in schizophrenia. *Schizophrenia Research* 2013;**147**(1):201–2.

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

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

Cochrane 2014
Cochrane. Data collection forms for intervention reviews. http://training.cochrane.org/resource/data-collection-forms-intervention-reviews (accessed 23 November 2017).

Davies 2000
Davies NM, McLachlan AJ, Day RO, Williams KM. Clinical Pharmacokinetics and Pharmacodynamics of Celecoxib. *Clinical Pharmacokinetics* 2000;**38**(3):225–42.

De Vecchis 2014
De Vecchis R, Baldi C, Di Biase G, Ariano C, Cioppa C, Giasi A, et al. Cardiovascular risk associated with celecoxib or etoricoxib: a meta-analysis of randomized controlled trials which adopted comparison with placebo or naproxen. *Minerva Cardioangiology* 2014;**62**(6):437–48.

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

Deeks 2011
Deeks JJ, Higgins JP, Altman DG. Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins JP, Green S editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

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

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

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

El-Sayed El-Sisi 2016
El-Sayed El-Sisi A, Sokkar SS, El-Sayed El-Sayad M, Sayed Ramadan E, Osman EY. Celecoxib and omega-3 fatty acids alone and in combination with risperidone affect the behavior and brain biochemistry in amphetamine-induced model of schizophrenia. *Biomedical Pharmacotherapy* 2016; **82**:425–31.

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

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

Gaughran 2018
Gaughran F, Lally J, Beck K, McCormack R, Gardner-Sood P, Coutinho E, et al. Brain-relevant antibodies in first-episode psychosis: a matched case-control study. *Psychological Medicine* 2018;**48**(8):1257–63.

Girgis 2014
Girgis RR, Kumar SS, Brown AS. The cytokine model of schizophrenia: emerging therapeutic strategies. *Biological Psychiatry* 2014;**75**(4):292–9.

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

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

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

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

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

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

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

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

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

Marini 2016
Marini S, De Berardis D, Vellante F, Santacroce R, Orsolini L, Valchera A, et al. Celecoxib adjunctive treatment to antipsychotics in schizophrenia: a review of randomized clinical add-on trials. *Mediators of Inflammation* 2016: Article ID 3476240.

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

Müller 2005
Müller N, Riedel M, Schwarz MJ, Engel RR. Clinical effects of COX-2 inhibitors on cognition in schizophrenia. *European Archives of Psychiatry and Clinical Neuroscience* 2005;**255**(2):149–51.

Müller 2013
Müller N. The role of anti-inflammatory treatment in psychiatric disorders. *Psychiatria Danubina* 2013;**25**(3): 292–8.

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Müller 2016
Müller N. What role does inflammation play in schizophrenia?. *Expert Review of Neurotherapeutics* 2016;**16** (12):1337–40.

Nitta 2013
Nitta M, Kishimoto T, Müller N, Weiser M, Davidson M, Kane JM, et al. Adjunctive use of nonsteroidal anti-inflammatory drugs for schizophrenia: a meta-analytic investigation of randomized controlled trials. *Schizophrenia Bulletin* 2013;**39**(6):1230–41.

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

PRISMA 2015
PRISMA. PRISMA Flow Diagram. http://www.prisma-statement.org/PRISMAStatement/FlowDiagram.aspx (accessed 23 November 2017).

Rapaport 2005
Rapaport MH, Delrahim KK, Bresee CJ, Maddux RE, Ahmadpour O, Dolnak D. Celecoxib augmentation of continuously ill patients with schizophrenia. *Biological Psychiatry* 2005;**57**(12):1594–6.

Riedel 2005
Riedel M, Strassnig M, Schwarz MJ, Müller N. COX-2 inhibitors as adjunctive therapy in schizophrenia: rationale for use and evidence to date. *CNS Drugs* 2005;**19**(10): 805–19.

Sangani 2017
Sangani A, Saadabadi A. Neuroleptic Medications. *StatPearls Treasure Island (FL)*. StatPearls Publishing, 2017.

Schwieler 2015
Schwieler L, Larsson MK, Skogh E, Kegel ME, Orhan F, Abdelmoaty S, et al. Increased levels of IL-6 in the cerebrospinal fluid of patients with chronic schizophrenia--significance for activation of the kynurenine pathway. *Journal of Psychiatry & Neuroscience* 2015;**40**(2):126–33.

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

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

Solomon 2008
Solomon SD, Wittes J, Finn PV, Fowler R, Viner J, Bertagnolli MM, et al. Cardiovascular risk of celecoxib in 6 randomized placebo-controlled trials: the cross trial safety analysis. *Circulation* 2008;**117**(16):2104–13.

Sommer 2014
Sommer IE, van Westrhenen R, Begemann MJ, de Witte LD, Leucht S, Kahn RS. Efficacy of anti-inflammatory agents to improve symptoms in patients with schizophrenia: an update. *Schizophrenia Bulletin* 2014;**40**(1):181–91.

Sterne 2011
Sterne JAC, Egger M, Moher D. Chapter 10: Addressing reporting biases. In: Higgins JPT, Green S editor (s). Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Tandon 2011
Tandon R. Antipsychotics in the treatment of schizophrenia: an overview. *Journal of Clinical Psychiatry* 2011;**72**(S1):4–8.

Torrey 2012
Torrey EF, Davis JM. Adjunct treatments for schizophrenia and bipolar disorder: what to try when you are out of ideas. *Clinical Schizophrenia & Related Psychoses* 2012;**5**(4): 208–16.

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

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

White 2007
White WB, West CR, Borer JS, Gorelick PB, Lavange L, Pan SX, et al. Risk of cardiovascular events in patients receiving celecoxib: a meta-analysis of randomized clinical trials. *American Journal of Cardiology* 2007;**99**(1):91–8.

WHO 2016
Schizophrenia, schizotypal and delusional disorders (F20-F29). http://apps.who.int/classifications/icd10/browse/2016/en#/F20 (accessed 15 November 2017).

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

Zheng 2017
Zheng W, Cai D, Yang X, Ungvari GS, Ng CH, Müller N, et al. Adjunctive celecoxib for schizophrenia: A meta-analysis of randomized, double-blind, placebo-controlled trials. *Journal of Psychiatric Research* 2017;**92**:139–46.

References to other published versions of this review

Akhondzadeh 2011
Akhondzadeh S, Modabbernia A, Taslimi S, Daneshmand A, Ostovaneh MR. Celecoxib for schizophrenia. *Cochrane Database of Systematic Reviews* 2011, Issue 7. DOI: 10.1002/14651858.CD009205

* *Indicates the major publication for the study*

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

APPENDICES

Appendix 1. Previous searches

Search methods in protocol (2011)

Cochrane Schizophrenia Group Trials Register (October 2010)

We will search the register using the phrase:
[*Celecoxib* OR *Celebrex* OR *SC 58635* OR *SC-58635* in title, abstract and index terms of REFERENCE and intervention of STUDY]

WHAT'S NEW

Date	Event	Description
30 November 2018	New citation required and minor changes	A new author team from The University of Birmingham has undertaken the completion of this review and have completed a new protocol

CONTRIBUTIONS OF AUTHORS

Ayesha Kotecha developed and drafted the protocol.

Rachel Upthegrove supervised the development of the protocol, and provided feedback on protocol drafts.

DECLARATIONS OF INTEREST

Ayesha Kotecha: none.

Rachel Upthegrove: none.

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

SOURCES OF SUPPORT

Internal sources

- The University of Birmingham, UK.

Ayesha Kotecha is a medical student and Rachel Upthegrove is a Clinical Senior Lecturer and Consultant Psychiatrist plus Psychological Medicine Program Lead at the University of Birmingham.

External sources

- None, Other.

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.