NHS
National Institute for Health Research

UNIVERSITY *of York*
Centre for Reviews and Dissemination

Systematic review

1. * Review title.

Give the working title of the review, for example the one used for obtaining funding. Ideally the title should state succinctly the interventions or exposures being reviewed and the associated health or social problems. Where appropriate, the title should use the PI(E)COS structure to contain information on the Participants, Intervention (or Exposure) and Comparison groups, the Outcomes to be measured and Study designs to be included.

Safety of Risperidone and Paliperdone in schizophrenia and bipolar disorder diagnosed patients - a

systematic review and meta-analysis

2. Original language title.

For reviews in languages other than English, this field should be used to enter the title in the language of the review. This will be displayed together with the English language title.

Safety of Risperidone and Paliperdone in schizophrenia and bipolar disorder diagnosed patients - a

systematic review and meta-analysis

3. * Anticipated or actual start date.

Give the date when the systematic review commenced, or is expected to commence.

28/06/2019

4. * Anticipated completion date.

Give the date by which the review is expected to be completed.

31/12/2020

5. * Stage of review at time of this submission.

Indicate the stage of progress of the review by ticking the relevant Started and Completed boxes. Additional information may be added in the free text box provided.
Please note: Reviews that have progressed beyond the point of completing data extraction at the time of initial registration are not eligible for inclusion in PROSPERO. Should evidence of incorrect status and/or completion date being supplied at the time of submission come to light, the content of the PROSPERO record will be removed leaving only the title and named contact details and a statement that inaccuracies in the stage of the review date had been identified.
This field should be updated when any amendments are made to a published record and on completion and publication of the review. If this field was pre-populated from the initial screening questions then you are not able to edit it until the record is published.

The review has not yet started: No

Review stage	Started	Completed
Preliminary searches	Yes	No
Piloting of the study selection process	Yes	No
Formal screening of search results against eligibility criteria	Yes	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Provide any other relevant information about the stage of the review here (e.g. Funded proposal, protocol not yet finalised).

6. * Named contact.

The named contact acts as the guarantor for the accuracy of the information presented in the register record.

Alexander Hodkinson

Email salutation (e.g. "Dr Smith" or "Joanne") for correspondence:

Dr Hodkinson

7. * Named contact email.

Give the electronic mail address of the named contact.

alexander.hodkinson@manchester.ac.uk

8. Named contact address

Give the full postal address for the named contact.

Centre for Primary Care, Division of Population Health, Health Services Research & Primary Care, Floor 6,

Williamson Building, Oxford Road, Manchester, M13 9PL

9. Named contact phone number.

Give the telephone number for the named contact, including international dialling code.

+44 (0)161 2753535

10. * Organisational affiliation of the review.

Full title of the organisational affiliations for this review and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.

University of Manchester

Organisation web address:

11. * Review team members and their organisational affiliations.

Give the title, first name, last name and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong.

Dr Alexander Hodkinson. University of Manchester

12. * Funding sources/sponsors.

Give details of the individuals, organizations, groups or other legal entities who take responsibility for initiating, managing, sponsoring and/or financing the review. Include any unique identification numbers assigned to the review by the individuals or bodies listed.

Fellowship

13. * Conflicts of interest.

List any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic investigated in the review.

None

14. Collaborators.

Give the name and affiliation of any individuals or organisations who are working on the review but who are not listed as review team members.

Dr Maria Panagioti. University of Manchester
Professor Evangelos Kontopantelis. University of Manchester
Professor Carl Heneghan. University of Oxford
Dr Kamal Mahtani. University of Oxford

15. * Review question.

State the question(s) to be addressed by the review, clearly and precisely. Review questions may be specific or broad. It may be appropriate to break very broad questions down into a series of related more specific questions. Questions may be framed or refined using PI(E)COS where relevant.

Does 'Risperidone' and 'Paliperdone' use increase the risk of 'gynecomastia' and other serious adverse

events (SAEs) for patients suffering from schizophrenia and other mental health problems such as bipolar

disorder?

16. * Searches.

State the sources that will be searched. Give the search dates, and any restrictions (e.g. language or publication period). Do NOT enter the full search strategy (it may be provided as a link or attachment.)

We searched the electronic databases Cochrane Schizophrenia Groups Trials Register and Cochrane

Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, BIOSIS, CINAHL, LILACS and

PsycINFO dating from inception to March 2019 using phrases "risperidone", "paliperdone" and

"schizophrenia" and "bipolar". Additionally, we contacted all risperidone and paliperdone-marketing pharma companies for missing relevant

data. The 'ClinicalTrials.gov' and 'OpenTrials.net' was searched to identify any potential unpublished trials.

Medical Reviews at the Drugs@FDA and European Public Assessment Reports were checked="checked"

value="1" for any further missing data. For trials that were not accessible via Yale Open Data Acess (YODA)

project, the CSRs were requested via the EMA.

17. URL to search strategy.

Give a link to a published pdf/word document detailing either the search strategy or an example of a search strategy for a specific database if available (including the keywords that will be used in the search strategies), or upload your search strategy.Do NOT provide links to your search results.

Alternatively, upload your search strategy to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Yes I give permission for this file to be made publicly available

18. * Condition or domain being studied.

Give a short description of the disease, condition or healthcare domain being studied. This could include health and wellbeing outcomes.

We include patients diagnosed with schizophrenia and other types of schizophrenia-like psychosis and

bipolar disorder, irrespective of the diagnosis criteria used. There is no clear evidence that the schizophrenia

like psychoses is caused by fundamentally different disease processes or requires different treatment

approaches. Bipolar disorder is a very difficult condition to diagnose, with patients usually indicated as mania

and mixed states, depression, or maintenance and prevention of relapse.

19. * Participants/population.

Give summary criteria for the participants or populations being studied by the review. The preferred format includes details of both inclusion and exclusion criteria.

Any participant in use of the antipsychotic drug risperidone or paliperdone irrespective of age, gender or

ethnicity.

20. * Intervention(s), exposure(s).

Give full and clear descriptions or definitions of the nature of the interventions or the exposures to be reviewed.

Risperidone or Paliperdone - any oral form of application and any dose.

21. * Comparator(s)/control.

Where relevant, give details of the alternatives against which the main subject/topic of the review will be compared (e.g. another intervention or a non-exposed control group). The preferred format includes details of both inclusion and exclusion criteria.

Placebo as the control intervention.

22. * Types of study to be included.

Give details of the types of study (study designs) eligible for inclusion in the review. If there are no restrictions on the types of study design eligible for inclusion, or certain study types are excluded, this should be stated. The preferred format includes details of both inclusion and exclusion criteria.

Randomised placebo-controlled trials of the anti-psychotic drugs Risperidone or Paliperdone. No further

restrictions.

23. Context.

Give summary details of the setting and other relevant characteristics which help define the inclusion or exclusion criteria.

24. * Main outcome(s).

Give the pre-specified main (most important) outcomes of the review, including details of how the outcome is defined and measured and when these measurement are made, if these are part of the review inclusion criteria.

Numbers of serious adverse events in the risperidone or paliperdone treatment group and placebo group.

Timing and effect measures

Timing onset of events will be assessed based on outcome.

25. * Additional outcome(s).

List the pre-specified additional outcomes of the review, with a similar level of detail to that required for main outcomes. Where there are no additional outcomes please state 'None' or 'Not applicable' as appropriate to the review

1. Any other serious adverse event of interest2. Patient safety listings3. Dropouts for any reason4. Deaths

Timing and effect measures

Time of dropout.

26. * Data extraction (selection and coding).

Describe how studies will be selected for inclusion. State what data will be extracted or obtained. State how this will be done and recorded.

Because of the novelty and size of clinical study reports we subdivided the extraction, appraisal, and analysis of the data into a two stage exercise. We included trials meeting our inclusion criteria (that is, had an appropriate study design) in stage 1. Trials not meeting our inclusion criteria (for example, open label studies) were not included in stage 1. In stage 1 we assessed the reliability and completeness of the identified trial data. This allowed us to identify missing important text or data. To aid us in determining completeness of the relevant parts of clinical study reports we constructed an extraction form based on the CONSORT-harms statement checklist and expert opinion from the research team.

We decided to only include data in stage 2 of the review (full analysis following standard Cochrane methods) if they satisfied the following three criteria:

1. Completeness: clinical study reports include identifiable CONSORT harms statement specified methods to enable replication of the study. Identifiable CONSORT harms statement specified results (safety results in the core report, tables of adverse and serious adverse events, appendices with patient safety narratives and safety listing data with CRFs) should be available. A comparison table checklist will be used to support this decision.

2. Internal consistency: all parts (for example, denominators) of the same clinical study reports or

unpublished reports are consistent.

3. External consistency: consistency of data as reported in regulatory documents, other versions of the same clinical study reports or unpublished reports, and other references, established by cross-checking.

27. * Risk of bias (quality) assessment.

Describe the method of assessing risk of bias or quality assessment. State which characteristics of the studies will be assessed and any formal risk of bias tools that will be used.

We assessed the methodological quality of included trials in this review using the Cochrane risk of bias and GRADE assessment tools. For the purposes of this review trials were included if they demonstrated low or moderate risk of bias as part of a sensitivity analysis. Publication bias will be examined with funnel-plots (using trim-and-fill method)

28. * Strategy for data synthesis.

Provide details of the planned synthesis including a rationale for the methods selected. This **must not be generic text** but should be **specific to your review** and describe how the proposed analysis will be applied to your data.

The analysis will become clearer after we have access to the reports. However an initial plan is detailed below:

Adverse events and Serious adverse events will be assessed by pooling the relative risk (RR) across trials. Effect estimates will be pooled across trials using Mantel-Haenszel fixed or random-effect meta-analysis dependent upon the number of studies reporting the outcome of interest. If there are less than five trials reporting the outcome, then we will use the fixed-effect approach as recommended in the Cochrane handbook. Initial sensitivity analysis was also performed pooling the relative difference instead of RR for rare events (Bradburn et al 2007, Sweating et al 2002). However, because adverse events are likely to be sparse, we will include the peto-odds ratio approach as this has been found to be more effective method for analysing rare event outcomes. We will also calculate the number needed to treat to provide benefit/to induce harm, and its 95% CIs.

Heterogeneity was assessed visually in the forest plots and the I² statistics will be compared between the CSR-based and the journal publication-based analyses to determine the magnitude of heterogeneity. I² values greater than 50% we interpreted as considerable levels of heterogeneity.

29. * Analysis of subgroups or subsets.

State any planned investigation of 'subgroups'. Be clear and specific about which type of study or participant will be included in each group or covariate investigated. State the planned analytic approach.

If possible, other potential predictors that will be addressed in the subgroup analysis include diagnostic subgroup (schizophrenia/bipolar), age (children or adolescents), gender, combination of drugs and dosage.

30. * Type and method of review.

Select the type of review and the review method from the lists below. Select the health area(s) of interest for your review.

Type of review

Cost effectiveness
No

Diagnostic
No

Epidemiologic
No

Individual patient data (IPD) meta-analysis
No

Intervention
No

Meta-analysis
Yes

Methodology
Yes

Narrative synthesis
No

Network meta-analysis
No

Pre-clinical
No

Prevention
No

Prognostic
No

Prospective meta-analysis (PMA)
No

Review of reviews
No

Service delivery
No

Synthesis of qualitative studies
No

Systematic review
Yes

Other
No

Health area of the review

Alcohol/substance misuse/abuse
No

Blood and immune system
No

Cancer
No

Cardiovascular
No

Care of the elderly
No

Child health
Yes

Complementary therapies
No

Crime and justice
No

Dental
No

Digestive system
No

Ear, nose and throat
No

Education
No

Endocrine and metabolic disorders
No

Eye disorders
No

General interest
No

Genetics
No

Health inequalities/health equity
No

Infections and infestations
No

International development
No

Mental health and behavioural conditions
Yes

Musculoskeletal
No

Neurological
No

Nursing
No

Obstetrics and gynaecology
No

Oral health
No

Palliative care
No

Perioperative care
No

Physiotherapy
No

Pregnancy and childbirth
No

Public health (including social determinants of health)
No

Rehabilitation
No

Respiratory disorders
No

Service delivery
No

Skin disorders
No

Social care
No

Surgery
No

Tropical Medicine
No

Urological
No

Wounds, injuries and accidents
No

Violence and abuse
No

31. Language.

Select each language individually to add it to the list below, use the bin icon to remove any added in error.
English

There is an English language summary.

32. Country.

Select the country in which the review is being carried out from the drop down list. For multi-national collaborations select all the countries involved.

England

33. Other registration details.

Give the name of any organisation where the systematic review title or protocol is registered (such as with The Campbell Collaboration, or The Joanna Briggs Institute) together with any unique identification number assigned. (N.B. Registration details for Cochrane protocols will be automatically entered). If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.

34. Reference and/or URL for published protocol.

Give the citation and link for the published protocol, if there is one

Give the link to the published protocol.

Alternatively, upload your published protocol to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Yes I give permission for this file to be made publicly available

Please note that the information required in the PROSPERO registration form must be completed in full even if access to a protocol is given.

35. Dissemination plans.

Give brief details of plans for communicating essential messages from the review to the appropriate audiences.

NIHRs evidence synthesis working group (workstream 3)

Cochrane Methods Innovation Fund working group (TBC)

Publication in a prestigious scientific medical journal

University of Manchester's press release and social media etc.

Do you intend to publish the review on completion?

Yes

36. Keywords.

Give words or phrases that best describe the review. Separate keywords with a semicolon or new line. Keywords will help users find the review in the Register (the words do not appear in the public record but are included in searches). Be as specific and precise as possible. Avoid acronyms and abbreviations unless these are in wide use.

Risperidone

Paliperidone

Placebo

schizophreniabipolar disorder

adverse events

safety

randomised

clinical study reports

37. Details of any existing review of the same topic by the same authors.

Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible.

38. * Current review status.

Review status should be updated when the review is completed and when it is published. For newregistrations the review must be Ongoing.
Please provide anticipated publication date

Review_Ongoing

39. Any additional information.

Provide any other information the review team feel is relevant to the registration of the review.

40. Details of final report/publication(s).

This field should be left empty until details of the completed review are available.

Give the link to the published review.

This field should be left empty until details of the completed review are available.

Give the link to the published review.