Research Protocol

Title: A systematic review and network meta-analysis of the safety and clinical effectiveness of interventions for treating or preventing deterioration of symptoms of antipsychotic-induced tardive dyskinesia (TD)

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Interventions being assessed

We aim to evaluate any intervention used for treating or preventing deterioration of symptoms of antipsychotic-induced TD. There are a vast array of strategies to deal with TD - one review identified over 100 (7). Based on our experience with Cochrane reviews in this research area, the interventions are likely to be grouped as follows:

1. Vitamins, antioxidants and other food supplements;
2. GABA agonists including benzodiazepines;
3. Anticholinergics;
4. Cholinergics;
5. Calcium-channel blockers;
6. Noradrenergics;
7. Non-antipsychotic dopaminergics;
8. Specific antipsychotic drugs;
9. Antipsychotic reduction or cessation including intermittent therapy;
10. Other interventions, including botulin toxin, insulin or lithium, among others.

We will compare interventions to:

- Other interventions used to treat or prevent deterioration of symptoms of antipsychotic induced TD of relevance to people in the NHS;
- Placebo, or no intervention.

Measurement of outcomes

No established Core Outcomes exist for antipsychotic-induced TD, although clearly, as TD is an adverse event of the prolonged use of antipsychotics (39), outcomes relevant to the latter will be evaluated. The following outcomes will be measured:

- Clinical improvement or any improvement of TD symptoms.
- Deterioration of TD symptoms,
- Compliance with antipsychotic medication
- Health-related quality of life
- Adverse events leading to treatment discontinuation
- Total discontinuation rates

Design and theoretical/conceptual framework

Randomised or quasi-randomised controlled trials and observational studies containing data related to antipsychotic-induced TD, irrespective of language or place of publication will be included. We will consider observational studies for inclusion with the following designs: (i) non-randomised controlled trials; (ii) prospective cohort studies with a control group; and (iii) case-control studies. The systematic reviews and the overview of reviews will follow Cochrane Collaboration design and methodology (10).

Network meta-analyses (NMA) are typically restricted to evidence based on randomised controlled trials (RCTs). The randomised participant assignment to parallel treatment arms keeps study groups as similar as possible with known and unknown confounding factors balanced. Well-conducted RCTs are the gold standard of clinical information. However, by including only RCTs in NMA a great deal of information from studies with other designs is ignored. Observational studies are considered to reflect data from real life better than RCTs, but they are prone to biases and meta-analysis is often avoided. Combining both randomised and observational evidence in NMA, while adjusting for potential biases due to study design, allows for informed decision regarding the efficacy of potential interventions. If different study designs are available we will apply NMA combining all sources of evidence using a three-level hierarchical model (50).

Target population

We will include studies of adults with a diagnosis of antipsychotic-induced TD (according to any criteria), regardless of the primary condition and measured at baseline and at least one other occasion. Participant groups with a primary diagnosis of schizophrenia or dementia (all forms) will be targeted for Cochrane reviews, but the main report will include participants with any condition with antipsychotic-induced TD.

Inclusion/Exclusion Criteria

We will exclude studies in which participants had used antipsychotic drugs for less than three months or in which the antipsychotic doses have not been stable for at least one month (43). In addition, we will exclude studies evaluating children and adolescents, or studies evaluating interventions that are not relevant to the National Health Services (NHS).

Setting/Context

Participants may be receiving treatment in any setting, any country or health care system.

Search strategy

We will attempt to identify all relevant studies regardless of language or publication status (published, unpublished, in press and in progress).

Search strategies will be developed specifically for each database similar the ones described in Appendix 1. We will search the *Cochrane Schizophrenia* and *Dementia* Group Registers and the Cochrane Library (continuous update); MEDLINE (January 1946 to current date); EMBASE (January 1980 to current date); and PsycINFO (January 1960 to current date). We will also search the metaRegister of Controlled Trials (mRCT) (http://www.controlled-trials.com/mrct/), and the reference lists of all included articles.

In addition, we will work with the Cochrane Schizophrenia and Dementia Groups to undertake in-house searches of their registers. Out of necessity, only a proportion of citations identified by the Cochrane Groups are made fully accessible on the Cochrane Library's Central Register of Studies (CRS). For example, because of copyright issues with the records, only 25% of the Cochrane Schizophrenia Group's register can be made fully available in the John Wiley Cochrane Library. Working with the in-house search will identify many more reports than searching on the public interfaces. These Cochrane registers also contain extensive holdings of the 'grey' literature.

Selection of studies

Search results will be uploaded into a web-based system (DistillerSR®, www.systematic-review.ca). Two review authors will independently screen all citations and abstracts identified by the search. We will obtain full reports for potentially eligible studies and these will be independently screened by two review authors. We will resolve any disagreements through discussion. Justifications for excluding studies from the review will be documented.

Data Extraction and management

We will develop the forms in an electronic format using a web-based systematic review system (DistillerSR®). We will pilot the data extraction forms to ensure ease of use and ability to capture all relevant data. The pilot will include 10% randomly selected potentially eligible articles, and it will be conducted independently by two reviewers.

Data extraction will be done by one review author, and 100% of the extracted data will be cross-checked by a senior review author. Any disagreements about data extraction will be documented and resolved by consensus. Any potential differences or data entry problems will be discussed and decisions documented.

If more than one publication is identified reporting data from the same participants, the main publication will be considered as the one with more information or with longer-term outcomes; all others will be considered companion publications and data will only be collected from these if they have not been provided in the main publication.

Data will be extracted into tabular format, but each original document will be fully 'marked up' to allow tracing back from extracted data to origin. Electronic techniques for mark-up have been piloted (http://szg.cochrane.org/jacobs-pet) and these allow future researchers to verify extraction and avoid duplication of effort. All data extracted in this way will be made fully available to researchers in the future by storage of the dataset online with links through the Cochrane CRS to this repository.

Assessment of risk of bias of the included studies

Controlled trials: In randomised trials and quasi-randomised trials, for each outcome, we will classify results as low, moderate, serious or critical risk of bias, based on domain-specific assessments of risk of bias done using the Cochrane Collaboration's existing "Risk of Bias" tool (10). If such assessments cannot be made due to lack of information, we will classify the study accordingly. Any disagreements will be resolved through discussion or by consulting a senior expert in the team.

Observational studies: We will use a risk of bias assessment tool for observational studies, which is currently being tested by the Cochrane Collaboration (11). This will include separate assessments for cohort studies and case-control studies. In assessing the risk of bias of the observational studies we will consider: (i) confounding and selection bias (including confounders measured and addressed, use of matching, and methods of adjustment); (ii) performance bias (including any considerations of co-intervention); (iii) missing data; (iv) detection bias (for cohort studies) or recall bias (for case-control studies); and (v) selective reporting bias. Two reviewers will independently evaluate study quality and differences will be resolved by discussions with a third reviewer. For each observational study, we will categorize the judgments as 'yes' (low risk of bias), 'no' (high risk of bias), or 'unclear', and resolve disagreements through discussion and by consulting a senior expert in the team.

Data Analysis

Broad overview

From the included studies we will calculate simple totals of studies and participants with antipsychotic-induced TD, regardless of the primary condition, in order to map research activity. From this mapping we will take the top ten interventions that seem to have demonstrated some efficacy and that are relevant for clinical practice and the NHS to target for head-to-head comparisons.

Analyses of single studies

Dichotomous data

For each study, the rate ratio (RR) and 95% confidence interval (CI) will be derived for people receiving intervention compared to controls. For case-control studies we will derive the odds ratios: we will assume

that these approximate to RRs in the general population. Where possible, we will compare published estimates with those directly calculated from raw data. If only the 2×2 tables (rather than person-years) are available we will estimate risk ratios. We will assume that these approximate to rate ratios provided that the overall risk of events is low. Where data are available for two or more time periods we will plot RRs and 95% CIs over time.

Continuous data

We will include continuous data from rating scales only if:

a) The psychometric properties of the measuring instrument has been described in a peer-reviewed journal (51); and
b) The measuring instrument was not written or modified by only one of the authors of the particular study where the data is taken from, but has also received independent validation.

For each study, the mean difference (MD) between groups and 95% CIs will be estimated.

We will also produce descriptive tables summarising information about study design, risk of bias, and results of all included studies. Data will be presented by each specific intervention according to the main diagnosis (schizophrenia or dementia).

Meta-analyses

Where studies are considered substantively similar enough for meta-analysis to be appropriate, both fixed- and random-effects analyses will be carried out using the RevMan software (52), and the **metan** command for Stata (53).

Random-effects meta-analyses are based on the assumption that the intervention effects have a normal distribution across studies. All meta-analyses will be stratified according to study design (RCTs or quasi-RCTs, or cohort studies, or case-control studies) and by type of underlying disease. Meta-analyses of crude and adjusted effect sizes will be derived separately for each observational study design.

For dichotomous outcome data, analyses will be on the logRR scale, while results will be displayed both as RR and as intervention's efficacy (=1-RR), if this is appropriate. For continuous outcome data, the standardised mean difference (SMD) will be calculated as we expect that different scales will be used to assess the same outcome data. All effect sizes will be displayed along with their 95% CIs.

Fixed- and random-effects summary estimates will be displayed with estimates from the individual studies in forest plots. Differences between fixed- and random-effects estimates suggest that there are differences between RRs estimated from smaller and larger studies. If relevant, such differences will be examined using funnel plots and Harbord's test for funnel plot asymmetry. Funnel plots will be drawn when ten or more studies are available in the meta-analysis. In case of asymmetry we will look at the individual studies to determine possible reasons for it.

Studies assessed as being at *critical risk of bias* will be excluded from analyses and described only narratively.

Variation in efficacy according to characteristics of individuals and studies

Visual inspection of the forest plots will be used to evaluate the potential statistical heterogeneity (differences between the true intervention effects in the different studies). Heterogeneity will be quantified by estimating the between-study variance τ^2 and the I^2 statistics (54, 55), which measures the percentage of observed variation that can be attributed to true differences between the studies (54).In forest plots and meta-analyses, τ^2 will be estimated using the restricted maximum likelihood estimator (56), whereas its 95% CIs will be estimated by the Q-profile method (57).

Detailed examination of effect modification

We will explore effect modification by type of antipsychotic (first or second generation) based on contrasts of subgroups. From each study we will, where available, extract or compute an estimate of interaction between effect modifier and the severity of the TD symptoms. We will then follow the strategies described for the main analysis, focusing on this interaction term (representing a difference in (log) relative risks) rather than the main effect (which represents a (log) relative risk). For studies on which more than 50% of participants are not accounted for, data will be described, but not added to any meta-analyses.

Summarising and interpreting results

We will use the GRADE approach (58-60), to assess the evidence of the various interventions according to:

1. Underlying disease;
2. Length of treatment [where available]; and
3. Type of antipsychotic used (first or second-generation).

For all outcomes, we will present 'Summary of Findings' tables based on GRADE results.

Overview of reviews

We will use the same methodology used in performing individual systematic reviews and include in the overview all relevant Cochrane reviews. We will present data from the included reviews in summary tables.

Data in the overview will be organised according to: i. underlying disease (schizophrenia, bipolar disease, dementia or other); ii. type of intervention used (grouped into appropriate categories); and iii. length of exposure to antipsychotic drugs.

All available outcomes will be used in the overview of reviews (clinical improvement or any improvement of TD symptoms, deterioration of symptoms, antipsychotic medication compliance, health related quality of life and serious adverse events).

If missing data are not above 50% of included participants and heterogeneity in outcome measures are not above 75%, we will conduct meta-analysis of the included reviews; otherwise we will present narrative review summaries of the results. In the latter, analyses will be reported as the number of outcomes favouring the intervention out of the total number of outcomes reported, based on the direction of effect and not statistical significance (10).

We will classify the reviews according to the decision rules suggested by Weir et al (61):

- 0% of studies (outcomes) favour intervention = no effect;
- 1% to 33% of studies (outcomes) favour intervention = generally ineffective;
- 34% to 66% studies (outcomes) favour intervention = mixed effects;
- 67%+ studies (outcomes) favour intervention = generally effective

Network meta-analysis

As we expect that few, if any, studies will report trials with head-to-head comparisons of different interventions, we plan to conduct a network meta-analysis (NMA), in order to facilitate clinical decision-making and plan of future research (62, 63). Our purpose with the NMA analysis is to summarise the clinical evidence regarding the efficacy of the most promising treatments for antipsychotic-induced TD (or to prevent further deterioration of symptoms), therefore, we will create a matrix with a 'network of the evidence between the treatments' identified in the Cochrane reviews (overview of reviews). NMA synthesizes information from a connected network of trials that address the same question and involve different treatments. To ensure that a network is connected, we will construct network plots.

It is common that an active treatment is compared to a placebo or a non-active control, rather than another active treatment. Decision-makers often have to deal with such lack of data and subsequently cannot make judgements. When direct comparative data are not available, but the treatments of interest are compared to a common intervention, e.g. placebo, an indirect comparison can provide important information. For example, , there could be a network of placebo, oxypertine and tiapride treatments with placebo vs. oxypertine and placebo vs. tiapride available head-to-head comparisons.. To infer in the efficacy of oxypertine and tiapride treatments, the indirect comparison can be employed by analysing placebo vs. oxypertine and placebo vs. tiapride studies jointly (64). NMA synthesises both direct and indirect estimates to make inference on all treatments included in the network of trials. The method provides more precise estimates than pairwise meta-analysis and indirect comparisons, as it 'borrows strength' from all the available evidence in the network (55), while randomisation is respected. We will perform random-effects NMA assuming common within-network heterogeneity and restricting initially to RCTs, which will be the primary analysis of interest. Then we will include data from quasi-RCTs and finally data from observational trials. For each NMA we will present the RR or SMD for each pair of treatments along with their 95% confidence interval regarding the efficacy of treatments used for antipsychotic-induced TD. We will also estimate the ranking probabilities for each treatment of being the best, second best etc., and we will use rankograms and the surface under the cumulative ranking curve (SUCRA) to present them (38). The NMA analyses will be conducted in Stata using the **mvmeta** routine (65).

The NMA results should be interpreted with caution and the required assumptions of the analysis should be carefully examined. A key assumption is the similarity of the distribution of the effect modifiers across comparisons, known as transitivity assumption (13, 66). In order to verify this assumption, we will visually inspect the similarity of potential effect modifiers of the treatment effect using boxplots or percentages. Lack of transitivity in network meta-analysis can question the consistency of the underlying estimates and the validity of the results. It is therefore important to statistically evaluate the consistency between direct and indirect evidence, as the joint analysis of treatments can be misleading if the network is inconsistent. Inconsistency is a property of closed loops of evidence (treatment pairs that form 'evidence cycles'). Prior to conducting NMA we will therefore evaluate the assumption of consistency, which can be violated in either the entire network (global inconsistency) or in certain parts (local inconsistency) of the network. We will use two different approaches for the evaluation of the consistency assumption. First, we will examine for any material differences within each closed loop of the network separately using the loop-specific method (19, 64), and then we will evaluate the whole network using the design-by-treatment interaction model (67). To measure the percentage of variability due to inconsistency beyond what is expected by random error and heterogeneity we will calculate the I^2 suggested by Jackson et al (68).

The strength of NMA is that it allows consideration of a more complete evidence base and facilitates a valid comparison of a range of treatment strategies. Although concerns are often raised regarding the use of indirect approaches in establishing the efficacy of particular interventions, given the lack of head-to-head trials evaluating the efficacy of treatments used for antipsychotic-induced TD, this approach might help us to assess a full range of potential intervention being compared, and avoid the potential inaccuracies that could be introduced by a series of separate comparisons.

Investigation of heterogeneity and inconsistency

We consider a degree of heterogeneity inevitable, and hence we will explore only important heterogeneity ($I^2 \geq 75\%$) using meta-regression or subgroup analyses for the effect modifiers: (a) risk of bias in the different study designs, (b) length of antipsychotics use, (c) underlying disease (dementia or schizophrenia); (d) gender/age; (e) type of treatment use, specifically first or second generation antipsychotics; (f) whether other concomitant drug interventions were used. The prevalence of inconsistency will be also explored on the same factors.

Sensitivity analyses

To ensure that our imputations do not bias our results, we will conduct a sensitivity analysis. We also plan to restrict the analyses to studies considered to be at low, and low or unclear, risk of selection and detection bias.

Dissemination and projected outputs

The dissemination and outputs will take six forms:

- **Cochrane reviews**: Currently there are nine Cochrane reviews relevant to the management of TD (20-29). It is difficult to tell at this point how many should be fully updated and how many additional new reviews will be indicated by the selection of the top ten relevant interventions. What can be confidently predicted is that the nine existing reviews are likely to be fully updated and expanded upon. New methods will be employed and *Summary of Findings* tables included. In addition, they will be interlinked by an overview of reviews, which will be possible because of the parallel updating of all these reviews. These reviews will be produced, edited, peer-reviewed to reach full publication within the timeframe of the grant, and be fully available to everyone in the NHS.
- **Paper publication**: A paper for publication in standard peer-reviewed journal will be produced, including participants regardless of the primary condition, randomised and observational study designs and including the network meta-analysis.
- **Cochrane Corner:** Because of the relationship between the Cochrane Schizophrenia Group and the specialist journal 'Schizophrenia Bulletin' (highest impact specialist mental health journal), further dissemination will happen through the *Cochrane Corner* within that quarterly journal – and in this way, if not by any other, reach the US readership.
- **Social Media**: Dissemination will also occur through the now standard social media systems. We plan to disseminate findings to our current 6,000 followers on Twitter/WiBo Currently we are actively evaluating the effectiveness of dissemination through Twitter (ISRCTN 84658943 – please follow us @CochraneSzGroup).
- **Plain Language Summaries**: Through our work with McPin Foundation and Ben Gray we will produce plain language summaries of each review for dissemination through the Cochrane website (free to all) but also through Ben's blog which gets heavy use by service users.
- **Marked up dataset**: Each paper which has been fully data extracted will be paired with its tabulated extracted data and a new document constructed. Each piece of tabulated data will have an 'address' back to the original PDF/HTML to make the knowledge entirely traceable. These new documents will be stored online and their records in the publically available Cochrane Register of Studies (CRS) annotated to alert future users of the existence of a fully extracted set of data

Appendix 1: Proposed search strategies

EMBASE via Ovid SP

1. exp cohort analysis/
2. exp longitudinal study/
3. exp prospective study/
4. exp case control study/
5. exp follow up/
6. exp case study/
7. case report/
16. (case$ adj2 report$).tw.
17. (case$ adj2 stud$).tw.
18. random$.tw.
19. factorial$.tw.
20. cross?over$.tw.
21. placebo$.tw.
22. ((doubl$ or singl$) adj blind$).tw.

8. epidemiology/
9. crossover-procedure/
10. double-blind procedure/
11. randomized controlled trial/
12. single-blind procedure/
13. cohort$.tw.
14. (case$ and control$).tw.
15. (case$ and series).tw.
23. assign$.tw.
24. allocat$.tw.
25. volunteer$.tw.
26. or/1-25
27. tardive dyskinesia/
28. "tardive dyskinesia?".mp.
29. or/27-28
30. 26 and 29
31. limit 30 to human

MEDLINE via Ovid SP

1. exp cohort studies/
2. epidemiologic methods/
3. exp case-control studies/
4. exp epidemiologic studies/
5. case reports.pt.
6. randomized controlled trial.pt.
7. controlled clinical trial.pt.
8. (case$ and control$).tw.
9. (case$ and series).tw.
10. (case$ adj2 report$).tw.
11. (case$ adj2 stud$).tw.
12. cohort$.tw.
13. randomized.ab.
14. placebo.ab.
15. randomly.ab.
16. trial.ab.
17. groups.ab.
18. drug therapy.fs.
19. or/1-18
20. "tardive dyskinesia?".mp.
21. 19 and 20
22. limit 21 to humans

PsycINFO via Ovid SP

1. epidemiology/
2. case report/
3. cohort analysis/
4. followup studies/
5. exp longitudinal studies/
6. exp treatment outcomes/
7. exp placebo/
8. exp treatment effectiveness evaluation/
9. exp mental health program evaluation/
10. (case$ adj2 report$).tw.
11. (case$ adj2 stud$).tw.
12. (case$ and control$).tw.
13. (case$ and series).tw.
14. cohort$.tw.
15. randomi$.mp.
16. ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).mp.
17. placebo$.mp.
18. crossover.mp.
19. (random$ adj (assign$ or allocate$)).mp.
20. or/1-19
21. tardive dyskinesia/
22. "tardive dyskinesia?".mp.
23. or/21-22
24. limit 23 to ("0200 clinical case study" or "0430 followup study" or "0450 longitudinal study" or "0451 prospective study" or "2000 treatment outcome/clinical trial")
25. 20 and 23
26. 24 or 25

27. limit 26 to human

Cochrane Schizophrenia Group's Register

"tardive dyskinesia*":ti,ab

The Cochrane Library via Wiley Online Library

"tardive dyskinesia*":ti,ab