

Systematic review of interventions for treating or preventing antipsychotic-induced tardive dyskinesia

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Scientific summary

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Scientific summary

Background

Since the 1950s, antipsychotic medication has been used extensively to control psychotic symptoms and to reduce the harm caused by the symptoms of chronic mental illness, including schizophrenia, bipolar disorder and dementia. Antipsychotic drugs are associated with a wide range of adverse effects, including tardive dyskinesia (TD), the late onset of involuntary, repetitive body movements, often involving the face and tongue. Critical problems associated with severe TD include difficulty swallowing, locomotion difficulties, involvement of respiratory muscles, and speech being rendered unintelligible. TD can be extremely disfiguring, compounds stigma and is associated with poor compliance with treatment.

Tardive dyskinesia occurs in > 20% of people who use first-generation antipsychotic drugs continually for > 3 months, and every year about 5% of those who continually use these drugs begin to show signs of TD. When second-generation antipsychotic (SGA) drugs were introduced in the 1990s, many hoped that they would not cause TD. Risks of developing TD with SGA drugs seem to be reduced but not eliminated. There is, however, some evidence to indicate that rates of TD do not differ at all between first- and second-generation antipsychotic drugs. Increasingly the distinction between first and second generation has become redundant.

The need for prevention or treatment is clear. Unfortunately, there has been sparse evidence to guide clinicians and, although many treatments have been tested, no one intervention has been shown to be clearly effective. Although antipsychotic reduction and/or cessation would seem to be a logical first step in the management of TD, this is not always possible because of the over-riding need to manage current psychotic symptoms and/or reduce the risk of relapse. Many other approaches have been proposed, including changing medication, anticholinergic drugs, use of benzodiazepines, vitamin E (tocopherol), bupirone and non-pharmacological treatments such as relaxation techniques and hypnosis.

High-quality Cochrane reviews assessing treatments for TD were first published in 1995–6, and an overview was published in 1999. They found no compelling evidence for the effect of any approach. This project has been funded to update relevant reviews fully with new evidence, using more sophisticated techniques of synthesis while also undertaking a public consultation process and making all data from reports fully accessible to future reviewers.

Objectives (list of research questions)

1. To identify all relevant evaluative studies.
2. To produce an overview of evaluative research in this area and prioritise the top 10 candidate treatments for head-to-head comparisons.
3. To extract and make accessible all relevant useful data from reports of evaluations of treatments and to ensure that the source of these data is entirely transparent.
4. To update existing relevant Cochrane reviews on antipsychotic-induced TD in people with schizophrenia and, if possible, to create comparisons relevant to people with dementia while ranking identified interventions according to their relevance for the NHS, and performing a network meta-analysis (NMA).
5. To consult people with/at risk of TD on the degree to which they believe these research questions to be important.

Methods

Data sources

1. We sought to consult with the public in order to access voices of people with personal experience of TD. The consultation process was held at the McPin Foundation offices in London. All discussions were audio-recorded for transcription while the attendees were asked to write down their ideas throughout the day on paper tablecloths and Post-it® (3M, Bracknell, UK) notes to help keep an accurate record of discussion, and to encourage everyone to participate.
2. For the reviews, we attempted to identify all relevant studies regardless of language or publication status (published, unpublished, in press and in progress). We searched Cochrane Schizophrenia Group's Study-Based Register of Trials (on 16 July 2015) as well as Cochrane Dementia and Cognitive Improvement Group's Register of Trials via the Cochrane Register of Studies Online (CRSO; www.crsco.cochrane.org) (on 21 July 2015). We also searched electronic databases for observational studies (on 9 January 2017). We inspected references of all identified studies for further relevant studies.

Study selection (inclusion criteria)

Methods

Randomised controlled trials (RCTs).

Participants

Adults who had used antipsychotic drugs for ≥ 3 months and in whom the antipsychotic doses had been stable for at least 1 month.

Interventions

Any intervention, but with a particular focus on those relevant to the NHS.

Outcomes

Any clinical outcomes, however measured – but with a particular focus on those chosen in the public consultation process as being of particular importance:

- TD
 - improved to a clinically important extent
 - deteriorated
- adverse effect
 - any adverse event
 - adverse effects: no clinically significant extrapyramidal adverse effects
- acceptability of treatment
 - leaving the study early
- social confidence, social inclusion, social networks or personalised quality-of-life measures
 - no important change in social confidence, social inclusion, social networks or personalised quality-of-life measures for either recipients of care or caregivers.

We excluded data from studies that were over 10 years old and reported no useable data, but which otherwise qualified for inclusion. In those cases, we contacted study authors to request data and excluded studies for which we received no reply, no new information or for which we were unable to contact study authors.

Data extraction (and assessment of validity)

Search results were uploaded into a web-based system and two reviewers independently screened all citations and abstracts. Two reviewers inspected all studies from the nine Cochrane reviews on TD. We obtained full reports for potentially eligible studies and these were independently screened by two review authors. One reviewer extracted data from all included studies, which were then cross-checked by another researcher. We attempted to contact authors in order to obtain missing information or for clarification whenever necessary.

Two reviewers worked independently and rated studies as having a low, unclear or high risk of bias based on domain-specific assessments of risk of bias, done using Cochrane's existing risk-of-bias tools for randomised and non-randomised studies. When inadequate details of randomisation and other characteristics of trials were provided, authors of studies were contacted for clarification. These judgements were incorporated into the process of assessing limitations in study design for outcomes in the summary-of-findings tables.

Data, quantitative and qualitative, were extracted into tabular format, but each original document was fully 'marked up' to allow tracing back from extracted data to origin. All data extracted in this way are fully available.

Data synthesis

Study level

For each study, for binary outcomes the risk ratio (RR) and 95% confidence interval (CI) were derived for people receiving the intervention compared with those in the control group. For continuous data, we included data from valid rating scales and calculated the mean difference (MD) between groups and 95% CIs.

Meta-analyses

Where studies were considered substantively similar enough for meta-analysis to be appropriate, fixed-effect analyses were carried out using RevMan software version 5.3.5 (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark).

Visual inspection of the forest plots was used to evaluate the potential statistical heterogeneity (differences between the true intervention effects in the different studies). Heterogeneity was quantified by estimating the between-study variance χ^2 and the I^2 -statistics, which measure the percentage of observed variation that can be attributed to true differences between the studies.

Quality assessment

We used the Grading of Recommendations, Assessment Development and Evaluation (GRADE) approach to assess the quality of the evidence for the various interventions. We have presented a 'summary of findings' table based on GRADE results for all NHS-prioritised interventions and outcomes.

Network meta-analysis

Odds ratios were employed for dichotomous outcomes. When continuous outcomes were measured, we analysed them using the MD if all studies used the same measure to assess the same outcome. Standardised mean difference Hedges' adjusted g was used when a different measure was used across studies to assess a common continuous outcome. We estimated P-scores, which are frequent analogues of surface under the cumulative ranking curve, to obtain a hierarchy of the competing interventions. We assessed the presence of clinical and methodological heterogeneity within each pairwise comparison by comparing trial and study

population characteristics across all eligible trials. We were unable to compare the distribution of effect modifiers across comparisons as a result of limited data, but we compared particular study characteristics qualitatively. Moreover, we assessed whether or not the indication of the included interventions varied according to the alternative it is compared against. Initially, standard pairwise meta-analyses were performed for all pairwise comparisons with at least two studies using the random-effects inverse variance model in Stata® 2015 (StataCorp LP, College Station, TX, USA). We intended to perform the NMA using the methodology of multivariate meta-analysis, in which different treatment comparisons are handled as different outcomes using the 'network' package (which includes the 'mvmeta' command) in Stata. As a result of the substantial number of treatment nodes, we used the 'netmeta' package in R 3.2.3 (The R Foundation for Statistical Computing, Vienna, Austria). We used available Stata routines to present the evidence base and illustrate the results. We produced a plot to present jointly the relative ranking of treatments for 'no clinical improvement' and 'total discontinuation rates', and we used a hierarchical cluster analysis to group interventions in meaningful subsets.

In pairwise meta-analysis we assumed different heterogeneity variances for each comparison. In NMA, we assumed a common heterogeneity variance across all treatment comparisons in the network. Between-study variance τ^2 was estimated in both pairwise meta-analysis and NMA using the DerSimonian and Laird estimator. We assessed statistical heterogeneity based on the magnitude of the estimated parameter. We also compared the magnitude of τ^2 with empirical distributions.

Results

We included 112 randomised trials (nine Cochrane reviews) and eight prospective cohort studies. Overall, risk of individual study biases was rated as being high and this showed little sign of improvement across decades of research. Cochrane reviews were indeed outdated, both in content and in methods; however, their findings have not substantively changed by the inclusion of new data and novel methods.

Studies reported thousands of outcomes measured in many ways over different periods of time. The public consultation process of this project, however, helped focus the reviewing process on targeted outcomes of importance to people with/at risk of TD (see *Outcomes*). The key outcome was binary – TD symptoms improved to a clinically important extent.

Seventy-nine separate interventions were the focus of the trials, whereas prospective cohort studies focused on comparing different strategies for antipsychotics. We categorised these and then invested most effort into those thought to be of practical importance within the NHS. These were grouped into three broad categories:

1. reducing antipsychotic dose
2. switching antipsychotic drug
3. adjunctive treatments in addition to antipsychotic drugs.

No intervention outside those thought to be relevant to NHS practice shows convincing promise.

Reducing antipsychotic dose

For this important and practical intervention we identified only two trials ($n = 17$). The combined result of these extremely small trials found no clear effect for the outcome of TD symptoms improved to a clinically important extent (RR 0.42, 95% CI 0.17 to 1.04). These data were judged to be of very low quality.

In addition, six observational studies ($n = 160$) found that psychiatric patients with TD whose antipsychotic medication was reduced or discontinued showed greater improvement in TD symptoms after 1–10 years of follow-up. These data were unreliable, varied from 19% to 75% improvement and were judged to be of very low quality.

Switching antipsychotic drug

There are many possibilities for how, when and what to switch to, but we identified only two relevant trials reporting on 'TD symptoms improved to a clinically important extent'. The first switched people off their antipsychotic drug altogether or to risperidone ($n = 42$; RR 0.45, 95% CI 0.23 to 0.89), and the second ($n = 45$) switched from older drugs to either quetiapine or haloperidol (RR 0.80, 95% CI 0.52 to 1.22). Both studies were judged to report data of low quality.

Adjunctive treatments in addition to antipsychotic drugs

We found no trials reporting relevant outcomes of anticholinergic continuation versus withdrawal. Two small trials ($n = 32$) reported on the effects of adding benzodiazepine drugs compared with placebo (TD symptoms improved to a clinically important extent; RR 1.12, 95% CI 0.60 to 2.09; very low-quality evidence). For the same outcome, vitamin E was found to have no clear effect when compared with placebo (six RCTs, $n = 264$; RR 0.95, 95% CI 0.89 to 1.01; low-quality evidence). Adding buspirone in the one trial that compared this with placebo caused a clear effect favouring the experimental treatment ($n = 42$, TD symptoms improved to a clinically important extent RR 0.53, 95% CI 0.33 to 0.84), but these data were felt to be of low quality. Finally, adding hypnosis and relaxation to treatment as usual did help (TD symptoms improved to a clinically important extent; RR 0.45, 95% CI 0.21 to 0.94) in one very small study ($n = 15$). Data were judged to be of very low quality.

The NMA model found that, for data such as those reported in TD trials, indirect estimates were imprecise and failed to produce useful summaries on relative effects of interventions or interpretable results for decision-making.

Consultation with people with/at risk of TD highlighted that management of TD remains a concern and found that people are deeply disappointed by the amount of time researchers have taken to investigate the issue. They supported the outcomes used in the TD Cochrane reviews, but would recommend the field is broadened to address issues such as social stigma, as public reactions to people living with TD can be as hard to cope with as the symptoms of underlying mental health problems themselves, like schizophrenia.

Conclusions

Implications for health care

Clinicians, policy-makers and people with/at risk of TD are little better informed than they were decades ago. Underpowered trials of limited quality repeatedly fail to provide answers.

Although it seems prudent to use the lowest effective dosage of antipsychotic drug possible (within the licensed range) for individual patients, there is no evidence that antipsychotic discontinuation will improve TD symptoms.

Current treatments for TD are prescribed in the hope that they will have an impact on TD, but do not have a strong evidence base. It could be argued that these treatments are only ethical within well-designed pragmatic trials aimed at informing clinical practice with people with this disfiguring problem.

Recommendations for research (in order of priority)

Tardive dyskinesia reviews have data from current trials extracted, tabulated and traceable to source. TD reviews, whether or not those within Cochrane, should use this resource to save time and money.

The NMA highlights one context in which support for this technique is ill advised. When studies are short, small, have similar results and are of poor quality, NMA is not indicated.

All relevant trials, even if not primarily addressing the issue of TD, should report appropriate binary outcomes on groups of people with this problem.

Randomised trials of treatments for people with established TD are indicated, with the most obvious intervention being dose reduction. These trials should be large (> 800), necessitating accrual through accurate local/national registers, intervention with acceptable treatments, and recording outcomes used in clinical practice.

Public consultation findings may be best summarised by a quotation from a person concerned with this problem. This person wrote 'It's about time TD was addressed. It [has] only been 30 years coming!!!'. This review summarises > 30 years of pioneering work, but also of systemic failure to properly address the ongoing issue of TD. Public consultation has provided a list of simple, universally relevant and practical outcomes for the large trials that should happen before another three decades or more lapses.

Study registration

This study is registered as PROSPERO CRD4201502045.

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