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[Intervention Review]

Anticholinergic medication for antipsychotic-induced tardive dyskinesia

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ABSTRACT

Background

Antipsychotic (neuroleptic) medication is used extensively to treat people with serious mental illnesses. However, it is associated with a wide range of adverse effects, including movement disorders. Because of this, many people treated with antipsychotic medication also receive anticholinergic drugs in order to reduce some of the associated movement side-effects. However, there is also a suggestion from animal experiments that the chronic administration of anticholinergics could cause tardive dyskinesia.

Objectives

To determine whether the use or the withdrawal of anticholinergic drugs (benzhexol, bengtropine, biperiden, orphenadrine, procyclidine, scopolamine, or trihexylphenidyl) are clinically effective for the treatment of people with both antipsychotic-induced tardive dyskinesia and schizophrenia or other chronic mental illnesses.

Search methods

We retrieved 712 references from searching the Cochrane Schizophrenia Group's Study-Based Register of Trials including the registries of clinical trials (16 July 2015 and 26 April 2017). We also inspected references of all identified studies for further trials and contacted authors of trials for additional information.

Selection criteria

We included reports identified in the search if they were controlled trials dealing with people with antipsychotic-induced tardive dyskinesia and schizophrenia or other chronic mental illness who had been randomly allocated to (a) anticholinergic medication versus placebo (or no intervention), (b) anticholinergic medication versus any other intervention for the treatment of tardive dyskinesia, or (c) withdrawal of anticholinergic medication versus continuation of anticholinergic medication.

Data collection and analysis

We independently extracted data from included trials and we estimated risk ratios (RR) with 95% confidence intervals (CIs). We assumed that people who left early had no improvement. We assessed risk of bias and created a 'Summary of findings' table using GRADE.

Main results

The previous version of this review included no trials. We identified two trials that could be included from the 2015 and 2017 searches. They randomised 30 in- and outpatients with schizophrenia in the USA and Germany. Overall, the risk of bias was unclear, mainly due to poor reporting: allocation concealment was not described; generation of the sequence was not explicit; studies were not clearly blinded; and outcome data were not fully reported.

Findings were sparse. One study reported on the primary outcomes and found that significantly more participants allocated to procyclidine (anticholinergic) had not improved to a clinically important extent compared with those allocated to isocarboxazid (MAO-inhibitor) after 40 weeks' treatment (1 RCT, $n = 20$; RR 4.20, 95% CI 1.40 to 12.58; *very low quality evidence*); that there was no evidence of a difference in the incidence of any adverse effects (1 RCT, $n = 20$; RR 0.33, 95% CI 0.02 to 7.32; *very low quality evidence*); or acceptability of treatment (measured by participants leaving the study early) (1 RCT, $n = 20$; RR 0.33, 95% CI 0.02 to 7.32; *very low quality evidence*). The other trial compared anticholinergic withdrawal with anticholinergic continuation and found no evidence of a difference in the incidence of acceptability of treatment (measured by participants leaving the study early) (1 RCT, $n = 10$; RR 2.14, 95% CI 0.11 to 42.52; *very low quality evidence*).

No trials reported on social confidence, social inclusion, social networks, or personalised quality of life — outcomes designated important to patients. No studies comparing either i. anticholinergics with placebo or no treatment, or ii. studies of anticholinergic withdrawal, were found that reported on the primary outcome 'no clinically important improvement in TD symptoms and adverse events'.

Authors' conclusions

Based on currently available evidence, no confident statement can be made about the effectiveness of anticholinergics to treat people with antipsychotic-induced tardive dyskinesia. The same applies for the withdrawal of such medications. Whether the withdrawal of anticholinergics may benefit people with antipsychotic-induced TD should be evaluated in a parallel-group, placebo-controlled randomised trial, with adequate sample size and at least 6 weeks of follow-up.

PLAIN LANGUAGE SUMMARY

Anticholinergic medication for people who have tardive dyskinesia after taking antipsychotic medication

Review question.

Are anticholinergic drugs or withdrawal of anticholinergic drugs effective in the treatment of tardive dyskinesia in people with schizophrenia or other similar mental health problems.

Background.

People with schizophrenia often hear voices and see things (hallucinations) and have beliefs which are at odds with those held by people without schizophrenia (delusions). The main treatment of these symptoms are antipsychotic drugs. However, these drugs can have debilitating side-effects. Tardive dyskinesia is an involuntary movement that causes the face, mouth, tongue and jaw to convulse, spasm and grimace. It is caused by long-term use, or high doses, of antipsychotic drugs, is difficult to treat and can be incurable. Many people being treated with antipsychotic medication also receive anticholinergic drugs to try to reduce some of these movement side-effects. There is, however, evidence from animal experiments that anticholinergic drugs could cause tardive dyskinesia.

Study characteristics.

The review includes two small randomised studies with a total of 30 people with schizophrenia who had also developed antipsychotic-induced tardive dyskinesia. Participants in one study received either the anticholinergic drug procyclidine or isocarboxazid, an antidepressant drug. One participant group in the other study was withdrawn from the anticholinergic drug biperiden whereas the other group of participants continued taking biperiden.

Key results.

There were sparse findings from two small and poorly reported trials. It is uncertain whether giving anticholinergic drugs is helpful in the treatment of tardive dyskinesia for people who are taking antipsychotic medication. It is also uncertain whether the withdrawal of anticholinergic medication improves the symptoms of tardive dyskinesia.

Quality of the evidence.

Available evidence is very low or low quality, limited, and small scale. It is not possible to recommend these drugs or the withdrawal of these drugs as a treatment for tardive dyskinesia. To fully investigate whether the withdrawal of anticholinergic drugs has any positive effects for people with tardive dyskinesia, we need more high quality research data.

This plain language summary was adapted by the review authors from a summary originally written by Ben Gray, Senior Peer Researcher, McPin Foundation (mcpin.org).

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Anticholinergic medication compared with placebo for antipsychotic-induced tardive dyskinesia

Anticholinergic medication compared with other treatments for antipsychotic-induced tardive dyskinesia

Patient or population: patients with antipsychotic-induced tardive dyskinesia

Settings: anywhere.

Intervention: any anticholinergic

Comparison: placebo

Outcomes	Illustrative comparative risks* (CI)		Relative effect (CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	risk with placebo	risk with anticholinergic drugs				
Tardive dyskinesia: not improved to a clinically important extent	see comment	see comment	not estimable	(0 studies)	-	None of the included studies reported on this outcome.
Tardive dyskinesia: deterioration of symptoms	see comment	see comment	not estimable	(0 studies)	-	None of the included studies reported on this outcome.
Mental state	see comment	see comment	not estimable	(0 studies)	-	None of the included studies reported on this outcome.
Adverse effect: any adverse effects follow-up: 40 weeks	see comment	see comment	not estimable	(0 studies)	-	None of the included studies reported on this outcome.
Acceptability of the treatment: leaving the study early	see comment	see comment	not estimable	(0 studies)	-	None of the included studies reported on this outcome.
Social confidence, social inclusion, social networks, or personalised quality of life	see comment	see comment	not estimable	(0 studies)	-	None of the included studies reported on this outcome.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its CI).

CI: Confidence interval; **MAO:** monoamine oxidase; **RR:** Risk Ratio

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ Downgraded one level for risk of bias: the included study did not adequately describe randomisation procedure or allocation concealment, and there was no mention of the study being blinded.

² Downgraded two levels for imprecision: very small sample size (n = 20).

³ Downgraded two levels for imprecision: very wide CI that includes appreciable benefit for both groups; very small sample size (n = 20).

⁴ Downgraded one level for indirectness: leaving the study early can give an indication, but is not a direct measurement, of treatment acceptability.

Summary of findings 2. Anticholinergic medication compared with other treatments for antipsychotic-induced tardive dyskinesia

Anticholinergic medication compared with other treatments for antipsychotic-induced tardive dyskinesia

Patient or population: chronic schizophrenia patients with antipsychotic-induced tardive dyskinesia

Settings: outpatients in the USA.

Intervention: procyclidine (anticholinergic), 5 mg twice/day

Comparison: isocarboxazid (MAO-inhibitor), 10 mg twice/day

Outcomes	Illustrative comparative risks* (CI)		Relative effect (CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	risk with MAO-inhibitor	risk with anticholinergic drugs				
Tardive dyskinesia: Not improved to a clinically important extent follow-up: 40 weeks	200 per 1000	840 per 1000 (280 to 1000)	RR 4.20 (1.40 to 12.58)	20 (1 study)	⊕⊕⊕⊕ very low ^{1 2}	
Tardive dyskinesia: deterioration of symptoms	see comment	see comment	not estimable	(0 studies)	-	None of the included studies reported on this outcome.

Mental state	see comment	see comment	not estimable	(0 studies)	-	None of the included studies reported on this outcome.
Adverse effect: any adverse effects follow-up: 40 weeks	100 per 1000	33 per 1000 (2 to 732)	RR 0.33 (0.02 to 7.32)	20 (1 study)	⊕⊕⊕⊕ very low ^{1 3}	
Acceptability of the treatment: leaving the study early follow-up: 40 weeks	100 per 1000	33 per 1000 (2 to 732)	RR 0.33 (0.02 to 7.32)	20 (1 study)	⊕⊕⊕⊕ very low ^{1 3 4}	
Social confidence, social inclusion, social networks, or personalised quality of life	see comment	see comment	not estimable	(0 studies)	-	None of the included studies reported on this outcome.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its CI).

CI: Confidence interval; **MAO:** monoamine oxidase; **RR:** Risk Ratio

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ Downgraded one level for risk of bias: the included study did not adequately describe randomisation procedure or allocation concealment, and there was no mention of the study being blinded.

² Downgraded two levels for imprecision: very small sample size (n = 20).

³ Downgraded two levels for imprecision: very wide CI that includes appreciable benefit for both groups; very small sample size (n = 20).

⁴ Downgraded one level for indirectness: leaving the study early can give an indication, but is not a direct measurement, of treatment acceptability.

Summary of findings 3. Withdrawal of anticholinergic medication compared to continuing anticholinergic medication for antipsychotic-induced tardive dyskinesia

Withdrawal of anticholinergic medication compared to continuing anticholinergic medication for antipsychotic-induced tardive dyskinesia

Patient or population: chronic schizophrenia patients with antipsychotic-induced tardive dyskinesia

Setting: Germany (1 study)

Intervention: withdrawal of biperiden (stopping after 1 week)

Comparison: continuing biperiden (stopping after 4 weeks)

Outcomes	Anticipated absolute effects* (CI)	Relative effect (CI)	Nº of participants	Quality of the evidence	Comments
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	Risk with con- tinuation of anticholinergic drugs	Risk with with- drawal of an- ticholinergic drugs	(studies)				(GRADE)
Tardive dyskinesia: not improved to a clinically important extent	see comment	see comment	not estimable	0 (0 studies)	-		None of the included studies re- ported on this outcome.
Tardive dyskinesia: deterioration of symptoms	see comment	see comment	not estimable	0 (0 studies)	-		None of the included studies re- ported on this outcome.
Mental state	see comment	see comment	not estimable	0 (0 studies)	-		None of the included studies re- ported on this outcome.
Adverse effects	see comment	see comment	not estimable	0 (0 studies)	-		None of the included studies re- ported on this outcome.
Acceptability of the treatment: leav- ing the study early follow-up: 7 weeks	0 per 1,000	0 per 1,000 (0 to 0)	RR 2.14 (0.11 to 42.52)	10 (1 RCT)	⊕⊕⊕⊕ very low ^{1 2 3}		
Social confidence, social inclusion, social networks, or personalised quality of life	see comment	see comment	not estimable	0 (0 studies)	-		None of the included studies re- ported on this outcome.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its CI).

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

¹ Downgraded one level for risk of bias: the included study did not adequately describe randomisation procedure or allocation concealment.

² Downgraded one level for indirectness: leaving the study early can give an indication, but is not a direct measurement, of treatment acceptability. In addition, the continuation of anticholinergic medication group stopped biperiden after 4 weeks but the results were measured after 7 weeks.

³ Downgraded two levels for imprecision: very wide CI that includes appreciable benefit for both groups; very small sample size (n = 10).

BACKGROUND

Description of the condition

Since the 1950s antipsychotic (neuroleptic) medication has been used extensively to treat people with chronic mental illnesses, such as schizophrenia. These drugs can effectively control symptoms such as abnormal perceptions (hallucinations), disordered thinking and fixed false beliefs (delusions). In addition, maintenance therapy with antipsychotics is associated with a reduced risk of relapses (Schooler 1993). However, antipsychotic medication has also been associated with a wide range of adverse effects, including movement disorders. The appearance of these disorders can be extremely disfiguring, compounds stigma, and is associated with poor compliance to antipsychotic treatment (Barnes 1993; Tarsy 2011).

Tardive dyskinesia (TD) is one such movement disorder and is characterised by abnormal, repetitive and involuntary movements. TD is a chronic condition of insidious onset, the severity of which spontaneously fluctuates (APA 1992). The clinical features include tongue protrusion, side-to-side or rotatory movement of the jaw, lip smacking, puckering and pursing, and rapid eye blinking (Casey 1994). In some people rapid movements of the arms, legs, and trunk may also occur. Studies on the natural history of TD have reported widely variable remission rates (1% to 62%) depending on patient age, psychiatric diagnosis, course of the psychiatric disorder, and duration of therapy (Bergen 1989; Fernandez 2001; Glazer 1990). It occurs in more than 20% of those using antipsychotic medication continually for longer than three months. Every year 4% to 5% of adults and 25% to 30% of elderly persons who continually use these drugs begin to show signs of TD (APA 1992; Correll 2004). This disorder can result in considerable social and physical disability (Barnes 1993).

The prevalence of TD is often thought to be decreasing based on the use of second generation antipsychotics (SGA) in place of first generation antipsychotics (FGA) (Cloud 2014). A systematic review found that the incidence of TD associated with SGAs (2% to 4%) was significantly lower than that for FGAs (5% to 8%) (Correll 2008). Despite this, widespread use of SGAs in clinical settings may still result in an overall increase in the number of cases of TD (Glazer 2000).

Although the most frequent cause of TD is the use of antipsychotic medication it is striking that dose reduction can lead to a temporary exacerbation in symptoms. Conversely, increasing the dose is often associated with a temporary remission (Cavallaro 1993; Smith 1980). Antipsychotic drugs block certain chemical receptor sites in the brain — one of these is specific for dopamine (Casey 1994). One hypothesis explaining the cause of antipsychotic-induced TD is that chronic blockade of dopamine receptors in specific cells of the brain (neurones from the nigrostriatum) causes an overgrowth of these receptors (Casey 1994). Consequently, interactions between antipsychotic drugs and dopamine receptors in the brain have been proposed as both the mechanisms for their beneficial effects in psychoses as well as the cause of the movement disorder side effects, including TD (Jeste 1982). In addition, there is evidence to suggest that an imbalance between cells that use dopamine and cells that use acetylcholine may be a cause of TD (Alphs 1983; Casey 1994).

Description of the intervention

Drugs that reduce the activity of the cholinergic cells (anticholinergic drugs) are widely used to help treat other antipsychotic-induced movement disorders such as parkinsonism and dystonia (APA 1992). Many acutely psychotic patients who receive antipsychotic medication also receive anticholinergic drugs in order to reduce some of the movement side effects associated with antipsychotic medication. However, anticholinergic drugs can cause many undesirable side effects, such as dryness of mouth, constipation, blurring of vision, and confusion (APA 1992).

How the intervention might work

The rationale for the use of anticholinergic drugs in TD is less clear, as there is a suggestion from animal experiments that the chronic administration of anticholinergics could increase the supersensitivity of dopamine receptors and consequently cause TD (Kane 1994). As a result these drugs have not been widely used for the treatment of antipsychotic-induced TD.

Why it is important to do this review

Several SGAs have been produced in the last decades that are claimed to cause less or no TD (Lieberman 1996). These claims may or may not be true: certainly evidence does indicate that thoughtful use of older generation drugs is not associated with more TD than occurs with newer treatments (Chouinard 2008). Furthermore it is likely that the less expensive and more familiar drugs — such as chlorpromazine or haloperidol — will continue to be the mainstay of treatment of people with schizophrenia in a global context (WHO Essential List 2010). Use of drugs such as these is associated with emergence of TD and therefore this condition will remain a problem for years to come.

Given the high incidence and prevalence of TD among people taking antipsychotic medication, the need for prevention or treatment is clear. Unfortunately, there has been sparse evidence to guide clinicians (NICE 2014; Taylor 2009). Although many treatments have been tested, no one intervention has been shown clearly to be effective. Cessation or reduction of the dose of antipsychotic medication is the ideal management for TD. In clinical practice this is not always possible, not least because in many individuals such a reduction would lead to relapse. This review focuses on whether the addition or withdrawal of anticholinergic drugs to those already receiving antipsychotic medication is likely to help TD.

This review is one in a series of Cochrane Reviews (see Table 1) evaluating treatments for antipsychotic-induced TD, and is an update of a Cochrane Review first published in 1997 (Soares-Weiser 1997).

OBJECTIVES

To determine whether the use or the withdrawal of anticholinergic drugs (benzhexol, bantzropine, biperiden, orphenadrine, procyclidine, scopolamine, or trihexyphenidyl) are clinically effective for the treatment of people with both antipsychotic-induced tardive dyskinesia and schizophrenia or other chronic mental illnesses.

METHODS

Criteria for considering studies for this review

Types of studies

All relevant randomised controlled trials. Where a trial was described as 'double-blind' but it implied that the study was randomised and the demographic details of each group were similar, we included it. We had planned to exclude quasi-randomised studies, such as those allocated by using alternate days of the week (see [Differences between protocol and review](#)).

Types of participants

Adults, however defined, with schizophrenia or related disorders, including schizophreniform disorder, schizoaffective disorder and delusional disorder, by any means of diagnosis. We are interested in making sure that information is as relevant as possible to the current care of people with schizophrenia, so if information was available we highlighted the current clinical state of participants (acute, early post-acute, partial remission, remission), 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 illnesses).

Types of interventions

- i. Anticholinergic drugs (benzhexol, benzotropine, biperiden, dextimide, orphenadrine, procyclidine, scopolamine, trihexyphenidyl) compared to placebo, or no intervention;
- ii. anticholinergic drugs (as above) compared to any other intervention to treat TD; or
- iii. the withdrawal of the above anticholinergic drugs compared with the continuation of the treatment.

Types of outcome measures

We have defined clinical efficacy as an improvement in the symptoms of TD of more than 50%, on any scale. We grouped outcomes into short term (less than 6 weeks), medium term (between 6 weeks and six months) and long term (more than six months).

Primary outcomes

1. Tardive dyskinesia

No clinically important improvement in the symptoms of individuals, defined as more than 50% improvement on any TD scale – any time period.

2. Adverse effects

No clinically significant extrapyramidal adverse effects – any time period.

Secondary outcomes

1. Tardive dyskinesia (TD)

- 1.1 Any improvement in the symptoms of individuals on any TD scale, as opposed to no improvement.
- 1.2 Deterioration in the symptoms of individuals, defined as any deleterious change on any TD scale.
- 1.3 Average change in severity of TD during the trial period.
- 1.4 Average difference in severity of TD at the end of the trial.

2. General mental state changes

- 2.1 Deterioration in general psychiatric symptoms (such as delusions and hallucinations) defined as any deleterious change on any scale.
- 2.2 Average difference in severity of psychiatric symptoms at the end of the trial.

3. Acceptability of the treatment

- 3.1 Acceptability of the intervention to the participant group as measured by numbers of people dropping out during the trial.

4. Adverse effects

- 4.1 Use of any anti-parkinsonism drugs.
- 4.2 Average score/change in extrapyramidal adverse effects.
- 4.3 Acute dystonia.

5. Other adverse effects, general and specific

6. Hospital and service utilisation outcomes

- 6.1 Hospital admission.
- 6.2 Average change in days in hospital.
- 6.3 Improvement in hospital status (for example: change from formal to informal admission status, use of seclusion, level of observation).

7. Economic outcomes

- 7.1 Average change in total cost of medical and mental health care.
- 7.2 Total indirect and direct costs.

8. Social confidence, social inclusion, social networks, or personalised quality of life measures

- 8.1. No significant change in social confidence, social inclusion, social networks, or personalised quality of life measures.
- 8.2 Average score/change in social confidence, social inclusion, social networks, or personalised quality of life measures.

9. Behaviour

- 9.1 Clinically significant agitation.
- 9.2 Use of adjunctive medication for sedation.
- 9.3 Aggression to self or others.

10. Cognitive state

- 10.1 No clinically important change.
- 10.2 No change, general and specific.

'Summary of findings' table

We used the GRADE approach to interpret findings ([Schünemann 2008](#)); and [GRADEPRO](#) to import data from [Review Manager](#) to create 'Summary of findings' tables. These tables provide outcome-specific information concerning the overall quality of evidence from each included study in the comparison, the magnitude of effect of the interventions examined, and the sum of the available data on all outcomes we rated as important to patient care and decision making. This summary was used to guide our conclusions and recommendations. We selected the following main outcomes for inclusion in the 'Summary of findings' table.

1. Tardive dyskinesia

- 1.1 Improved to a clinically important extent.
- 1.2 Deteriorated.

2. Mental state

2.1 Deterioration.

3. Adverse effects

3.1 Any adverse event.

3.2 Adverse effects: no clinically significant extrapyramidal adverse effects.

4. Acceptability of treatment

4.1 Leaving the study early.

5. Social confidence, social inclusion, social networks, or personalised quality-of-life measures*

5.1 No significant change in social confidence, social inclusion, social networks, or personalised quality of life measures for either recipients of care or caregivers.

* Outcome designated important to patients. We wished to add perspectives from people's personal experience with TD to the research agenda. A consultation with service users was planned where a previously published version of a review in the Cochrane TD series and a lay overview of that review gave the foundation for the discussions (Soares-Weiser 2011; Table 1). The session was planned to provide time to reflect on current research on TD and consider gaps in knowledge. The report is not completed but we will add a link to it within this review. In the meantime we have added one figure showing a service user's feelings concerning this neglected area of research (Figure 1). Informed by the results of the consultation, for this review we included outcomes important to service users to the 'Summary of findings' table.

Figure 1. Message from one of the participants of the Public and patient involvement consultation of service user perspectives on tardive dyskinesia research.

Search methods for identification of studies

Electronic searches

The 2017 review update was carried out in parallel with updating eight other TD reviews: see Table 1 for details. The search covered all nine TD reviews.

Cochrane Schizophrenia Group's Study-Based Register of Trials

On 16 July 2015 and 26 April 2017, the Information Specialist searched the register using the following search strategy:

Tardive Dyskinesia in Health Care Condition Field of STUDY

In such study-based registers, 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, 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.

Anticholinergic medication for antipsychotic-induced tardive dyskinesia (Review)

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Searching other resources

1. Reference searching

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

2. Personal contact

Where necessary, we contacted the first author of each included study for information regarding unpublished trials. We noted the outcome of this contact in the [Included studies](#) or [Studies awaiting classification](#) tables.

Data collection and analysis

Selection of studies

For the 2017 update, reviewers RA and AG (see [Acknowledgements](#)) inspected all abstracts of studies identified as above for potentially relevant reports. We resolved disagreement by discussion; or, where there was still doubt, we acquired the full article for further inspection. We acquired the full articles of relevant reports/abstracts meeting initial criteria for reassessment and carefully inspected for a final decision on inclusion (see [Criteria for considering studies for this review](#)). RA and AG were not blinded to the names of the authors, institutions or journal of publication. Where difficulties or disputes arose, we asked author HB for help; and where it was impossible to decide or if adequate information was not available to make a decision, we added these studies to [Studies awaiting classification](#) and contacted the authors of the papers for clarification.

Data extraction and management

1. Extraction

For the 2017 update, reviewers RA and HB independently extracted data from all included studies. Again, we discussed any disagreement and documented decisions. KSW helped clarify issues with any remaining problems and we documented these final decisions. We extracted data presented only in graphs and figures whenever possible, but included them only if two reviewers independently had the same result. We attempted to contact authors through an open-ended request in order to obtain missing information or for clarification whenever necessary. If studies were multi-centre, where possible we extracted data relevant to each component centre separately.

2. Management

2.1 Forms

For the 2017 update we extracted data to simple forms. Extracted data are available [here](#) with a link to the original source PDF for each item.

2.2 Scale-derived data

We included 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 should be 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

included sub-scores from mental state scales measuring positive and negative symptoms of schizophrenia.

Ideally the measuring instrument should either be i. a self-report or ii. completed by an independent rater or relative (not the therapist). We realise that this is not often reported clearly; we noted in [Description of studies](#) if this was the case or not.

2.3 Endpoint versus change data

There are advantages of both endpoint and change data. Change data can remove a component of between-person variability from the analysis. On the other hand calculation of change needs two assessments (baseline and endpoint) which can be difficult in unstable and difficult-to-measure conditions such as schizophrenia. We decided to primarily use endpoint data, and only use change data if the former were not available. We combined endpoint and change data in the analysis as we preferred to use mean differences (MD) rather than standardised mean differences throughout ([Higgins 2011](#)).

2.4 Skewed data

Continuous data on clinical and social outcomes are often not normally distributed. To avoid the pitfall of applying parametric tests to non-parametric data, we applied the following standards to relevant data before inclusion; see (a) and (b) below.

Please note: we would have entered data from studies of at least 200 participants in the analysis, because skewed data pose less of a problem in large studies. We also would have entered 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 data are skewed or not.

For endpoint data from studies of fewer than 200 participants:

(a) when a scale starts from the finite number zero, we planned to subtract the lowest possible value from the mean, and divide this by the standard deviation. If this value was lower than 1, it strongly suggests a skew and we would have excluded these data. If this ratio was higher than 1 but below 2, there is suggestion of skew. We would have entered these data and tested whether its inclusion or exclusion changed the results substantially. Finally, if the ratio was larger than 2 we would have included these data, because skew is less likely ([Altman 1996](#); [Higgins 2011](#)).

(b) if a scale starts from a positive value (such as the Positive and Negative Syndrome Scale (PANSS), ([Kay 1986](#))) which can have values from 30 to 210), we would have modified the calculation described above to take the scale starting point into account. In these cases skew is present if $2SD > (S - S_{min})$, where S is the mean score and 'S min' is the minimum score.

2.5 Common measure

Where relevant, to facilitate comparison between trials we would have converted 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 converted continuous 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 Positive and Negative Syndrome Scale (PANSS, [Kay 1986](#)), this can be considered as a clinically significant response ([Leucht 2005a](#), [Leucht 2005b](#)). If data based on these thresholds were not available, we used the primary cut-off presented by the original authors.

2.7 Direction of graphs

Where possible, we entered data in such a way that the area to the left of the line of no effect indicated a favourable outcome for anticholinergic medication. Where keeping to this made it impossible to avoid outcome titles with clumsy double-negatives (e.g. 'Not un-improved') we presented data where the left of the line indicates an unfavourable outcome and noted this in the relevant graphs.

Assessment of risk of bias in included studies

Reviewers RA and HB independently assessed risk of bias within the included studies by using criteria described in the *Cochrane Handbook for Systematic Reviews of Interventions* to assess trial quality ([Higgins 2011](#)). This set of criteria is based on evidence of associations between overestimate of effect and high risk of bias of the article such as sequence generation, allocation concealment, blinding, incomplete outcome data and selective reporting.

If the raters disagreed, we made the final rating by consensus, with the involvement of another member of the review group. Where inadequate details of randomisation and other characteristics of trials were provided, we contacted authors of the studies in order to obtain further information. If non-concurrence occurred, we reported this.

We noted the level of risk of bias in the text of the review and in [Figure 2](#), [Figure 3](#), [Summary of findings 3](#) and [Summary of findings 2](#).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Bucci 1971	?	?	-	-	+	-	?
Greil 1984	?	?	+	?	+	-	?

Measures of treatment effect

1. Binary data

For binary outcomes we calculated a standard estimation of the risk ratio (RR) and its 95% confidence interval (CI). It has been shown that RR is more intuitive than odds ratios (Boissel 1999), as odds ratios tend to be interpreted as RR by clinicians (Deeks 2000).

2. Continuous data

For continuous outcomes we estimated mean difference (MD) between groups. We preferred not to calculate effect size measures (standardised mean difference (SMD)). However, if scales of very considerable similarity were used, we presumed there is a small difference in measurement, and calculated effect size and transformed the effect back to the units of one or more of the specific instruments.

Unit of analysis issues

1. Cluster trials

Studies increasingly employ 'cluster randomisation' (such as randomisation by clinician or practice) but analysis and pooling of clustered data can be a problem. Authors often fail to account for intra-class correlation in clustered studies, leading to a 'unit of analysis' error (Divine 1992), whereby P values are spuriously low, confidence intervals unduly narrow and statistical significance overestimated. This causes type I errors (Bland 1997; Gulliford 1999).

If any of the included trials had randomised participants by clusters, and where clustering is not accounted for in primary studies, we would have presented such data in a table, with a (*) symbol to indicate the presence of a probable 'unit of analysis' error. In subsequent versions of this review we will seek to contact first authors of studies to obtain intra-class correlation coefficients for their clustered data and to adjust for this by using accepted methods (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.

We have sought statistical advice and have been advised that the binary data as presented in a report should be divided by a 'design effect'. This is calculated using the mean number of participants per cluster (m) and the intra-class correlation coefficient (ICC) (Design effect = $1 + (m - 1) * ICC$) (Donner 2002). If the ICC is not reported it will be assumed to be 0.1 (Ukoumunne 1999).

If cluster studies have been appropriately analysed taking into account intra-class correlation coefficients and relevant data documented in the report, synthesis with other studies would be possible using the generic inverse variance technique.

2. Cross-over trials

A major concern of cross-over trials is the carry-over effect. It occurs if an effect (pharmacological, physiological or psychological) of the treatment in the first phase is carried over to the second phase. As a consequence on entry to the second phase the participants can differ systematically from their initial state despite a wash-out phase. For the same reason cross-over trials are not appropriate if the condition of interest is unstable (Elbourne 2002). As both effects are very likely in severe mental illness, we only used data of 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 presented the additional treatment arms in comparisons. If data were binary we simply added and combined within the two-by-two table. If data were continuous we combined data following the formula in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We did not use data where the additional treatment arms were not relevant.

Dealing with missing data

1. Overall loss of credibility

At some degree of loss to follow-up, data must lose credibility (Xia 2009). We chose that, for any particular outcome, should more than 50% of data be unaccounted for, we would not reproduce these data or use them within analyses. If, however, more than 50% of those in one arm of a study were lost, but the total loss was less than 50%, we addressed this within the 'Summary of findings' table/s by down-rating quality. We also downgraded quality within the 'Summary of findings' table/s should loss be 25% to 50% in total.

2. Binary

In the case where attrition for a binary outcome is between 0% and 50% and where these data are not clearly described, we presented data on a 'once-randomised-always-analyse' basis (an 'intention to treat' analysis). We assumed all those leaving the study early had no improvement. We undertook a sensitivity analysis testing how prone the primary outcomes were to change by comparing data only from people who completed the study to that point to the 'intention to treat' analysis using the above assumptions.

3. Continuous

3.1 Attrition

We reported and used data where attrition for a continuous outcome was between 0% and 50%, and data only from people who completed the study to that point were reported.

3.2 Standard deviations

If standard deviations were not reported, we first tried to obtain the missing values from the authors. If not available, where there were missing measures of variance for continuous data but an exact standard error and confidence intervals available for group means, and either P value or t value available for differences in mean, we calculated them according to the rules described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011): when only the standard error (SE) is reported, standard deviations (SDs) are calculated by the formula $SD = SE * \sqrt{n}$. Chapters 7.7.3 and 16.1.3 of the *Cochrane Handbook for Systematic Reviews of Interventions* present detailed formulae for estimating SDs from P, t or F values, confidence intervals, ranges or other statistics (Higgins 2011). If these formulae did not apply, we calculated the SDs according to a validated imputation method which is based on the SDs of the other included studies (Furukawa 2006). Although some of these imputation strategies can introduce error, the alternative would be to exclude a given study's outcome and thus to lose information. We nevertheless examined the validity of the imputations in a sensitivity analysis excluding imputed values.

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

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

Assessment of heterogeneity

1. Clinical heterogeneity

We considered all included studies initially, without seeing comparison data, to judge clinical heterogeneity. We simply inspected all studies for clearly outlying people or situations which we had not predicted would arise and discussed in the text if they arose.

2. Methodological heterogeneity

We considered all included studies initially, without seeing comparison data, to judge methodological heterogeneity. We simply inspected all studies for clearly outlying methods which we

had not predicted would arise and discussed in the text if they arose.

3. Statistical heterogeneity

3.1 Visual inspection

We visually inspected graphs to investigate the possibility of statistical heterogeneity.

3.2 Employing the I^2 statistic

We investigated heterogeneity between studies by considering the I^2 method alongside the χ^2 P value. The I^2 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 i. magnitude and direction of effects and ii. strength of evidence for heterogeneity (e.g. P value from χ^2 test, or a confidence interval for I^2). An I^2 estimate equal to or greater than around 50% accompanied by a statistically significant χ^2 statistic can be interpreted as evidence of substantial levels of heterogeneity (Section 9.5.2 *Cochrane Handbook for Systematic Reviews of Interventions*; Higgins 2011). We explored and discussed in the text potential reasons for substantial levels of 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 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We are aware that funnel plots may be useful in investigating reporting biases but are of limited power to detect small-study effects. We would not have used funnel plots for outcomes where there were 10 or fewer studies, or where all studies were of similar sizes. In future versions of this review, if funnel plots are possible we will seek statistical advice in their interpretation.

Data synthesis

We understand that there is no closed argument for preference of fixed-effect models over random-effects models, or vice versa. 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 chose the fixed-effect model for all analyses.

Subgroup analysis and investigation of heterogeneity

1. Subgroup analyses

1.1 Primary outcomes

We anticipated one sub-group analysis to test the hypothesis that the modification of anticholinergic medication is most effective for those with early onset TD (less than five years). We had hoped to present data for this subgroup for the primary outcomes.

1.2 Clinical state, stage or problem

We proposed to undertake this review and provide an overview of the effects of anticholinergic medication for people with schizophrenia in general. In addition, however, we had wanted to report data on subgroups of people in the same clinical state, stage and with similar problems.

2. Investigation of heterogeneity

We would have reported when inconsistency was high. First we would have investigated whether data were entered correctly. Second, if data were correct, we would have visually inspected the graph and successively removed studies from the company of the rest to see if homogeneity was restored. For this review we decided that should this occur with data contributing to the summary finding of no more than around 10% of the total weighting, we would present data. If not, we would not pool such data but would discuss issues. We know of no supporting research for this 10% cut off but are investigating use of prediction intervals as an alternative to this unsatisfactory state.

When unanticipated clinical or methodological heterogeneity were obvious, we simply discussed. We did not undertake sensitivity analyses relating to these.

Sensitivity analysis

1. Implication of randomisation

If trials were described in some way as to imply randomisation we undertook a sensitivity analysis for the primary outcomes. We included these studies in the analyses and if there was no substantive difference when the implied randomised studies were added to those with better description of randomisation, then we used relevant data from these studies.

2. Assumptions for lost binary data

Where assumptions had to be made regarding people lost to follow-up (see [Dealing with missing data](#)) we compared the findings of the primary outcomes when we used our assumption compared with 'completer' data only. If there was a substantial difference, we reported and discussed these results but continued to employ our assumption.

Where assumptions have to be made regarding missing SDs data (see [Dealing with missing data](#)), we compared the findings on primary outcomes when we used our assumption compared with 'completer' data only. We undertook a sensitivity analysis testing how prone results were to change when 'completer' data only were compared to the imputed data using the above assumption. If there was a substantial difference, we reported and discussed these results but continued to employ our assumption.

3. Risk of bias

We analysed the effects of excluding trials that we judged to be at high risk of bias across one or more of the domains of randomisation (implied as randomised with no further details available), allocation concealment, blinding and outcome reporting for the meta-analysis of the primary outcome. If the exclusion of trials at high risk of bias did not substantially alter the direction of effect or the precision of the effect estimates, we included data from these trials in the analysis.

4. Imputed values

Had cluster trials been included, we would have undertaken a sensitivity analysis to assess the effects of including data from trials where we used imputed values for ICC in calculating the design effect.

If we found substantial differences in the direction or precision of effect estimates in any of the sensitivity analyses listed above, we did not pool data from the excluded trials with the other trials contributing to the outcome, but presented them separately.

5. Fixed and random effects

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

RESULTS

Description of studies

Please see [Characteristics of included studies](#); [Characteristics of excluded studies](#); [Characteristics of studies awaiting classification](#).

Results of the search

The 2015 and 2017 update searches were part of an update search of nine Cochrane Reviews; see [Table 1](#). The 2015 search retrieved 704 references for 344 studies; see [Figure 4](#) for study flow diagram. After excluding irrelevant references at title and abstract screening, we screened full texts of 31 references (25 studies). As a result of updating the methods and outcomes considered in this review, we have now included two studies that we previously excluded because of a lack of placebo control ([Bucci 1971](#)), and uncertainty around the number of participants ([Greil 1984](#)); see [Included studies](#). These two studies are the only studies included in this review. One study is awaiting classification ([Zeng 1996](#)).

Figure 4. Study flow diagram for 2015 and 2017 searches.

The 2017 search found eight records (five studies). Editorial base of Cochrane Schizophrenia screened these records and no new studies were relevant to this review. They could be relevant to the other reviews in this series of TD reviews (see [Table 1](#)), and have been put into 'Studies awaiting classification' of the [Soares-Weiser 2003](#) 'miscellaneous treatments' review.

Included studies

The review now includes two studies with 30 participants, published in 1971 and 1984.

1. Methods

Both studies were stated to be randomised and [Greil 1984](#) also reported being double blind. For further details, please see [Risk of bias in included studies](#) (below) on allocation and blinding.

2. Design

Both studies presented a parallel longitudinal design.

3. Duration

The study by [Greil 1984](#) lasted for 7 weeks while [Bucci 1971](#) lasted 40 weeks.

4. Participants

Participants, totalling 30 people, were mostly women in their 50s, with diagnoses of chronic schizophrenia. All were reported to have antipsychotic-induced TD; however, no criteria for the diagnosis of TD were reported. The number of participants ranged from 10 ([Greil 1984](#)) to 20 ([Bucci 1971](#)).

5. Setting

One study was performed in hospital outpatients in the USA ([Bucci 1971](#)); the other was set in Germany but did not report whether participants were out- or inpatients ([Greil 1984](#)).

6. Interventions

6.1 Anticholinergic medications

6.1.1 Procyclidine

Procyclidine was used by [Bucci 1971](#) in a 5 mg dose, twice daily.

6.1.2 Biperiden

Biperiden was used by [Greil 1984](#) in the same dose that participants received before the trial. This trial compared the withdrawal of biperiden after 1 week and 4 weeks.

6.2 Comparison group

[Greil 1984](#) compared the withdrawal of biperiden over two time periods. [Bucci 1971](#) used isocarboxazid — a monoamine oxidase inhibitor — 10 mg twice per day as a control.

7. Outcomes

7.1 TD symptoms

Only one study provided useable data on TD symptoms ([Bucci 1971](#)). This appears to be a clinical assessment and not a validated scale.

7.2 Adverse events

Only one study provided useable data on adverse events as a result of medication ([Bucci 1971](#)). This was reported simply as the number of events in both groups.

Studies awaiting classification

We identified one study, published in Chinese ([Zeng 1996](#)). We have contacted the study authors to determine if participants were diagnosed with TD but at the time of preparing this review we had not had a response.

Ongoing studies

We have identified no ongoing studies.

Excluded studies

There are 22 excluded studies. Twelve studies were not randomised ([Casey 1977](#); [Gardos 1984](#); [Gerlach 1976](#); [Gerlach 1978](#); [Jus 1974](#); [Konig 1996](#); [Lejoyeux 1993](#); [Smith 1979](#); [Tamminga 1977](#); [Wirshing 1989a](#); [Wirshing 1989b](#); [Zwanikken 1976](#)). Four studies were randomised but included participants with schizophrenia but not TD ([DiMascio 1976](#); [Double 1993](#); [Elie 1972](#); [Fann 1976](#)). One study did not report data separately on the minority of participants with TD and the author confirmed that these data are unavailable ([Klett 1972](#)). Four studies were cross-over trials that did not provide data before the first phase before crossing over to the next treatment. We contacted authors of three of these studies and received no data ([Friis 1983](#); [Lieberman 1988](#); [NDSG 1986](#)). For one of these studies we were not able to identify up-to-date contact details, and we consider it is very unlikely that we will receive a reply with data so many years later ([Silver 1995](#)). One study did not provide any usable data, despite our making contact with the authors ([Ludatscher 1989](#)).

Risk of bias in included studies

Please refer to [Figure 2](#) and [Figure 3](#) for graphical overviews of the risk of bias in the included studies.

Allocation

While both studies claimed to be randomised, neither described explicitly how the randomisation sequence was generated or how allocation concealment was ensured. As a result we have rated them as having unclear risk of bias.

Blinding

Although [Greil 1984](#) was conducted on a double-blind basis, only blinding of the treatment provider was explicitly described. [Bucci 1971](#) did not mention blinding of providers, participants, or outcome assessors.

Incomplete outcome data

In each included study there was one person who did not complete the study. In all cases, however, we tried to ensure that every person randomised was analysed.

Selective reporting

All data in this review originates from published reports. The expected outcomes (impact on TD symptoms) were not reported sufficiently by [Greil 1984](#). Both studies did not fully report outcomes that were measured during the study and were rated at high risk of

reporting bias. Attempts to contact authors of trials for additional data were unsuccessful.

Other potential sources of bias

Both studies had very small sample sizes. There was very little information reported on which to base further concerns regarding risk of bias.

Effects of interventions

See: [Summary of findings for the main comparison Anticholinergic medication compared with placebo for antipsychotic-induced tardive dyskinesia](#); [Summary of findings 2 Anticholinergic medication compared with other treatments for antipsychotic-induced tardive dyskinesia](#); [Summary of findings 3 Withdrawal of anticholinergic medication compared to continuing anticholinergic medication for antipsychotic-induced tardive dyskinesia](#)

1. Comparison 1: anticholinergic drugs versus placebo or no treatment

No studies were identified that assessed this comparison.

2. Comparison 2: anticholinergic drugs versus other compounds

2.1 TD symptoms

We had chosen 'any improvement in TD symptoms of more than 50% on any TD scale – any time period' as a primary outcome. Although the data we found in trials did not fit this exactly we feel that the outcome 'not improved to a clinically important extent' fits best with what we had hoped to find.

2.1.1 Not improved to a clinically important extent

One study found a significant difference on 'no clinically important improvement in TD symptoms favouring isocarboxazid (MAO-inhibitor) compared with procyclidine (anticholinergic) after 40 weeks' (low-quality evidence, 1 trial, 20 people; RR 4.20, 95% CI 1.40 to 12.58; [Analysis 1.1](#)).

2.1.2 Not any improvement

For the outcome of 'not any improvement in TD symptoms', procyclidine resulted in a worse outcome than isocarboxazid after 40 weeks (low-quality evidence, 1 trial, 20 people; RR 7.00, 95% CI 1.57 to 31.15; [Analysis 1.2](#)).

2.2 Adverse effects

2.2.1 Any adverse effects

There was no significant difference in the incidence of any adverse effects between procyclidine and isocarboxazid after 40 weeks (very low quality evidence, 1 trial, 20 people; RR 0.33, 95% CI 0.02 to 7.32; [Analysis 1.3](#)).

2.3 Leaving the study early

Using procyclidine did not significantly affect the chances of a person leaving the study early compared to isocarboxazid after 40 weeks (very low quality evidence, 1 trial, 20 people; RR 0.33, 95% CI 0.02 to 7.32; [Analysis 1.4](#)).

We did not identify any studies that reported on hospital and service utilisation outcomes, economic outcomes, social

confidence, social inclusion, social networks, personalised quality of life, behaviour, or cognitive state.

3. Comparison 3: continuation versus withdrawal of anticholinergic drugs

3.1 Leaving the study early

The only usable data showed no significant difference on leaving the study early between withdrawal of biperiden after 1 week compared with continuation of the drug for 4 weeks (very low quality evidence, 1 trial, 10 people; RR 2.14, 95% CI 0.11 to 42.52; [Analysis 2.1](#)).

We did not identify any studies that reported on TD symptoms, adverse events, hospital and service utilisation outcomes, economic outcomes, social confidence, social inclusion, social networks, personalised quality of life, behaviour, or cognitive state.

4. Subgroup analyses

4.1 Clinical stage: recent onset TD

It was not possible to evaluate whether those with recent onset TD responded differently to those with more established problems, since no trial reported data for groups with different durations of TD that could be extracted for separate analyses, and since only one study per comparison was included.

4.2 Duration of follow-up

It was not possible to evaluate whether the effect of anticholinergic drugs changed in relation to duration of follow-up; only one study per comparison was included.

5. Heterogeneity

Only one study per comparison was included. Therefore, investigation into heterogeneity was not relevant, and we could not detect clinical, methodological or statistical heterogeneity as described in [Assessment of heterogeneity](#).

6. Sensitivity analyses

6.1 Implication of randomisation

We aimed to include trials in a sensitivity analysis if they were described in some way as to imply randomisation. We have not undertaken this sensitivity analysis as only one study was included per comparison, and both studies were stated to be randomised.

6.2 Assumptions for lost binary data

Where assumptions had to be made regarding people lost to follow-up (see [Dealing with missing data](#)) we compared the findings when we used our assumption with 'completer' data only. Using 'completer' data only for anticholinergic drugs (procyclidine) versus isocarboxazid, we found that there was no substantial alteration to the direction of effect or the precision of the effect estimates for the primary outcome 'no clinically important improvement' (1 trial, 19 people; RR 3.82, 95% CI 1.30 to 11.26; analysis not shown).

6.3 Risk of bias

It was not possible to evaluate whether excluding trials that we judged to be at high risk of bias across one or more of the domains

would alter the effect estimate; only one study was included per comparison.

6.4 Imputed values

We would have undertaken a sensitivity analysis to assess the effects of including data from cluster randomised trials where we used imputed values for ICC in calculating the design effect. However, no cluster randomised trials were included.

6.5 Fixed and random effects

We also synthesised data for the primary outcome using a random-effects model. This did not alter the results.

DISCUSSION

Summary of main results

1. The search

This area of research does not seem to be active. The 2017 update has identified additional data, but all trials predate 1990. This could be because of reasons such as less concern with TD, or less emergence of the problem in research-active communities because of more thoughtful use of antipsychotic drugs.

2. Few data

Only 30 people were included in this review. For this reason it is very likely that real — and important — effects have not been highlighted because of the necessarily wide CIs of the findings. Many outcomes were not measured at all, including several of our pre-stated outcome measures (see [Overall completeness and applicability of evidence](#)).

3. Comparison 1: anticholinergic drugs versus placebo or no treatment

We found no included study that compared the efficacy or safety of an anticholinergic drug compared with placebo or no treatment ([Summary of findings for the main comparison](#)).

4. Comparison 2: anticholinergic drugs versus other compounds

We identified one very small trial reporting few outcomes ([Summary of findings 2](#)). There were no data on mental state or social outcomes.

4.1 TD symptoms

One study found that more participants on isocarboxazid (MAO-inhibitor) than on procyclidine (anticholinergic) improved to a clinically important level at long term (RR 4.20, 95% CI 1.40 to 12.58; N = 20). However, the quality of the evidence is very low and therefore we have very little confidence in the effect estimate and CIs — the true effect is likely to be substantially different.

4.2 Adverse effects

One study found no clear difference in adverse events between procyclidine (anticholinergic) (0/10) and isocarboxazid (MAO-inhibitor) (1/10) (RR 0.33, 95% CI 0.02 to 7.32; N = 20). Evidence was of very low quality, therefore we are uncertain about the result.

4.3 Leaving the study early

One study found no clear difference in leaving the study early between procyclidine (anticholinergic) (0/10) and isocarboxazid (MAO-inhibitor) (1/10) (RR 0.33, 95% CI 0.02 to 7.32; N = 20). Evidence was of very low quality, therefore we are uncertain about the result.

5. Comparison 3. continuation versus withdrawal of anticholinergic drugs

We identified one very small trial reporting few outcomes ([Summary of findings 3](#)). There were no data on tardive dyskinesia, adverse effects, mental state or social outcomes.

5.1 Leaving the study early

One study found no significant difference in leaving the study early between anticholinergic withdrawal after 1 week (1/6) and anticholinergic continuation for 4 weeks (0/4) (RR 2.14, 95% CI 0.11 to 42.52; N = 10). Evidence was of very low quality, therefore we are uncertain about the result.

Overall completeness and applicability of evidence

1. Completeness

Only two small studies with few useable data were included, not sufficient to address whether the use or withdrawal of anticholinergic drugs was associated with an improvement in antipsychotic-induced TD in people with schizophrenia or other chronic mental illness, let alone to examine whether there was a differential effect among the different anticholinergic drugs. We only identified usable data on TD symptoms from a study comparing anticholinergic medication with another compound, the antidepressant isocarboxazid, a drug which is experimental in the treatment of TD. We found few usable data on adverse events, and none on mental state, social confidence, social inclusion, social networks, or personalised quality of life. If reporting had been better we might have been able to include more data from these studies, and we might have had some data to present from the excluded studies ([Friis 1983](#); [Lieberman 1988](#); [Ludatscher 1989](#); [NDSG 1986](#); [Silver 1995](#)).

2. Applicability

Trials included both in- and outpatients who were mostly women in their 50s with schizophrenia. They were people who would be recognisable in everyday care. The interventions in question — anticholinergic drugs — are readily accessible and most outcomes are understandable in terms of clinical practice. Should anticholinergic drugs have had important effects the findings might well have been applicable.

Quality of the evidence

We cannot draw any robust conclusions regarding the effects of anticholinergic drugs on TD: only two studies with 30 participants could be included, which severely limited the quality of the evidence. The larger trial randomised only 20 people: a trial of this size is unable to detect subtle, yet important, differences due to an intervention with any confidence. In order to detect a 20% difference between groups, probably about 150 people are needed in each arm of the study (alpha 0.05, beta 0.8). Overall the quality of reporting of these trials was poor (see [Figure 3](#)). Allocation concealment was not described, generation of the sequence was

not explicit, studies were not clearly blinded, and data were not fully reported. The small sample size and the poor reporting means that we have very little confidence in the effect estimates, and the true effects are likely to be substantially different from the estimates of the effects.

Potential biases in the review process

1. Missing studies

We made every effort to identify relevant trials. However, these studies are both small and it is likely that we have failed to identify other studies of limited power. It is likely that such studies would also not be in favour of the anticholinergics group: if they had been so, it is more likely that they would have been published in accessible literature. We do not, however, think it likely that we have failed to identify large relevant studies.

2. Introducing bias

We have tried to be balanced in our appraisal of the evidence but could have inadvertently introduced bias. We welcome comments or criticisms. New methods and innovations now make it possible to report data where, in the past, we could not report data at all or had to report data in a different way. We believe 'Summary of findings' table is a valuable innovation but problematic to those not 'blind' to the outcome data: it is possible to 'cherry pick' significant findings for presentation in this table. We have tried to decrease the chance of doing this by asking a new reviewer (HB) to select outcomes relevant for this table before becoming familiar with the data.

Agreements and disagreements with other studies or reviews

The only other relevant quantitative review we know of is the previous Cochrane Review (Soares-Weiser 1997). This update identified two studies to include (as discussed in [Results of the search](#) and [Potential biases in the review process](#)), but the very sparse and low-quality evidence lead to no substantial change in the conclusions.

AUTHORS' CONCLUSIONS

Implications for practice

1. For people with TD

Based on the currently available data, this systematic review can provide no useful information for service-users about the use of anticholinergics (benzhexol, benztropine, biperiden, orphenadrine, procyclidine, scopolamine or trihexylphenidyl) for the treatment of antipsychotic-induced TD. In addition, there is no evidence to support the suggestion that the withdrawal of these medications may benefit people with TD. People with TD could consider these as other experimental treatments for which very little supportive data exist. Few data exist for any treatment for TD.

2. For clinicians

Anticholinergics have been widely used in modern psychiatry for the treatment of extrapyramidal side effects (EPS). There is some suggestion that they may exacerbate TD symptoms; however, the link between the use of anticholinergics and the emergence of TD may be only an epiphenomenon, since people who develop EPS are thought to be more likely to receive anticholinergics and also

to develop TD (APA 1992). Nevertheless, based on this systematic review there is no solid evidence to support or discourage the use or withdrawal of these medications as a treatment for TD. There is a real place for clinician-driven research, with prescription within the context of a randomised trial and routine data collection on outcomes of relevance to people with TD and their clinicians.

3. Policy makers or managers

This is one of the reviews in the series of Cochrane Reviews on treatments for antipsychotic-induced TD (see [Table 1](#)). No evidence is convincing that addition or withdrawal of another drug helps with the symptoms of TD. There are, however, many unanswered questions in this area. This unattractive adverse effect is caused, to a greater or lesser extent, by antipsychotic drugs. Clinicians and researchers should feel responsible enough to continue to try to help it. Those compiling guidance could encourage supportive activity and more research into this neglected area.

Implications for research

1. General

The power of this review would have been greatly enhanced by better reporting of data. For example, none of the trials made explicit how randomisation was undertaken. We realise that the work for these trials predates CONSORT, which was first published in 1996 (Begg 1996), and that it is only too easy to judge studies of the past by standards of today. Future studies, however, should report to a much higher standard.

2. Specific

From the theoretical background, there is some evidence to suggest that withdrawal of anticholinergics may benefit people with antipsychotic-induced TD. Well-designed randomised controlled trials, involving a large number of participants over protracted periods of time, are needed if we are to see if anticholinergics or anticholinergic withdrawal could have a role in prevention and treatment of TD. Such studies are of importance to people with the problem and have long been ignored ([Figure 1](#)).

2.1 Use of cross-over design

Trialists find it difficult to identify people with both TD and schizophrenia to participate in trials. Randomised cross-over design is used in the hope of improving the power of the study to find outcomes of interest. This design initially asks participants to be randomised to one of the experimental interventions, and then, at a pre-specified time, to be crossed over to the treatment that they did not at first receive. Conditions with a more stable time course than TD are better suited for cross-over studies (Fleiss 1984). Further difficulties are the carry-over effect and a related neuroreceptor issue. Unless cross-over studies include a mid-study washout period (where the person is free of treatment before starting the next arm of the study), any effect of anticholinergic drugs may continue into the second half placebo arm of the trial — the 'carry-over effect'. Also, carry-over may involve the re-growth or retreat of neuroreceptors. This slow re-balancing, if started, could continue long after all traces of intervention drugs are gone, so physiological half life of the experimental treatment may not be the only variable to consider when thinking through the issues of carry-over. TD is also an unstable condition and people with TD may not remain compliant with medication. All these factors make the

arguments for not using cross-over methodology strong, despite the initial attraction (Armitage 1991; Fleiss 1984; Pocock 1983).

2.2 Sample size calculation

None of the trials explained how they calculated their sample size. However, the results suggest that larger sample size should be used to provide more precise estimates of effect.

2.3 Length of study

One of the studies included in this review used the intervention for 40 weeks (Bucci 1971). TD is a chronic condition of insidious onset, the severity of which fluctuates spontaneously (APA 1992). Even if anticholinergics or anticholinergic withdrawal has a swift effect, which is unlikely, it is the long-term outcomes that must be considered of most clinical value.

2.4 Outcomes

Many of the outcomes we initially desired when we started this review have not been investigated. In addition, a service user consultation also informed the addition of outcomes of special importance to patients. We have reconsidered all these outcomes in case they were too ambitious and tried to tailor them to a real-world pragmatic trial design (see Table 2).

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Previous versions

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2017 Update

Parts of this review were generated using RevMan HAL v 4.0. You can find more information about RevMan HAL [here](#).

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REFERENCES

References to studies included in this review

Bucci 1971 {published data only}

Bucci L. The dyskinesias: a new therapeutic approach. *Diseases of the Nervous System* 1971;**32**(5):324-7.

Greil 1984 {published data only}

Greil W, Haag H, Rossnagl G, Rther E. Effect of anticholinergics on tardive dyskinesia. A controlled discontinuation study. *British Journal of Psychiatry* 1984;**145**:304-10.

References to studies excluded from this review

Casey 1977 {published data only}

Casey DE, Denney D. Pharmacological characterization of tardive dyskinesia. *Psychopharmacology* 1977;**54**(1):1-8.

DiMascio 1976 {published data only}

DiMascio A, Bernardo DL, Greenblatt DJ, Marder JE. A controlled trial of amantadine in drug-induced extrapyramidal disorders. *Archives of General Psychiatry* 1976;**33**(5):599-602.

DiMascio A, Bernardo DL, Greenblatt DJ, Marder JE. A controlled trial of amantadine in drug-induced extrapyramidal disorders. *Psychopharmacology Bulletin* 1977;**13**(3):31-3.

Double 1993 {published data only}

Double DB, Warren GC, Evans M, Rowlands MP. Efficacy of maintenance use of anticholinergic agents. *Acta Psychiatrica Scandinavica* 1993;**88**(5):381-4.

Elie 1972 {published data only}

Elie R, Morin L, Tetreault M. Effects of ethopropazine and of trihexyphenidyl on several parameters of the neuroleptic syndrome. *Encephale* 1972;**61**(1):32-52.

Fann 1976 {published data only}

Fann WE, Lake CR. Amantadine versus trihexyphenidyl in the treatment of neuroleptic-induced parkinsonism. *American Journal of Psychiatry* 1976;**133**(8):940-3.

Friis 1983 {published data only}

Friis T, Christensen R, Gerlach J. Sodium valproate and biperiden in neuroleptic-induced akathisia, parkinsonism and hyperkinesia. *Acta Psychiatrica Scandinavica* 1983;**67**(3):178-87.

Gardos 1984 {published data only}

Gardos G, Cole JO, Rapkin RM, LaBrie RA, Baquelod E, Moore P, et al. Anticholinergic challenge and neuroleptic withdrawal. Changes in dyskinesia and symptom measures. *Archives of General Psychiatry* 1984;**41**(11):1030-5.

Gerlach 1976 {published data only}

Gerlach J. The relationship between parkinsonism and tardive dyskinesia. *American Journal of Psychiatry* 1977;**134**(7):781-4.

Gerlach J, Thorsen K. The movement pattern of oral tardive dyskinesia in relation to anticholinergic and antidopaminergic treatment. *Internal Pharmacopsychiatry* 1976;**11**(1):1-7.

Gerlach 1978 {published data only}

Gerlach J, Simmelsgaard H. Tardive dyskinesia during and following treatment with haloperidol, haloperidol and biperiden, thioridazine and clozapine. *Psychopharmacology* 1978;**59**(2):105-12.

Jus 1974 {published data only}

Jus K, Jus A, Gautier J, Villeneuve A, Pires P, Pineau R, et al. Studies on the action of certain pharmacological agents on tardive dyskinesia and on the rabbit syndrome. *International Journal of Clinical Pharmacology, Therapy, and Toxicology* 1974;**9**(2):138-45.

Klett 1972 {published data only}

Klett CJ, Caffey E. Evaluating the long-term need for antiparkinson drugs by chronic schizophrenics. *Archives of General Psychiatry* 1972;**26**(4):374-9.

Konig 1996 {published data only}

Konig P, Chwatal K, Havelec L, Riedl F, Schubert H, Schultes H. Amantadine versus biperiden - a double-blind study of treatment efficacy in neuroleptic extrapyramidal movement disorders. *Neuropsychobiology* 1996;**33**(2):80-4. [MEDLINE: 8927233]

Lejoyeux 1993 {published data only}

Lejoyeux M, Gorwood P, Stalla-Bourdillon A, Ades J. Translation and application of the Simpson and Angus Scale of Extrapyramidal Symptoms [Traduction et utilisation de l'echelle de Simpson et Angus de symptmes extra-pyramidaux]. *L'Encphale* 1993;**19**(1):17-21.

Lieberman 1988 {published data only}

Lieberman J, Pollack S, Lesser M, Kane J. Pharmacologic characterization of tardive dyskinesia. *Journal of Clinical Psychopharmacology* 1988;**8**(4):254-60.

Ludatscher 1989 {published data only}

Ludatscher JI. Stable remission of tardive dyskinesia by L-dopa. *Journal of Clinical Psychopharmacology* 1989;**9**(1):39-41.

NDSG 1986 {published data only}

Gerlach J. Tardive dyskinesia: pathophysiological mechanisms and clinical trials. *L'Encephale* 1988;**XIV**:227-32.

Gerlach J, Ahfors UG, Amthor KF. Effect of different neuroleptics in tardive dyskinesia and parkinsonism. A video-controlled multicenter study with chlorprothixene, perphenazine, haloperidol and haloperidol and biperiden. *Psychopharmacology* 1986;**90**(4):423-9.

Nordik Dyskinesia Study Group. Effect of different neuroleptics in tardive dyskinesia and parkinsonism. *Psychopharmacology* 1986;**90**(4):423-9.

Povlsen UJ, Noring U, Meidahl B, Korsgaard S, Waehrens J, Gerlach J. Not available [Neuroleptikas virkning pa tardive dyskinesier]. *Ugeskr Laeger* 1987;**149**(25):1682-5.

Silver 1995 {published data only}

Silver H, Geraisy N, Schwartz M. No difference in the effect of biperiden and amantadine on parkinsonian- and tardive dyskinesia-type involuntary movements: A double-blind crossover, placebo-controlled study in medicated chronic schizophrenic patients. *Journal of Clinical Psychiatry* 1995;**56**(9):435.

* Silver H, Geraisy N, Schwartz M. No difference in the effect of biperiden and amantadine on parkinsonian- and tardive dyskinesia-type involuntary movements: a double-blind crossover, placebo-controlled study in medicated chronic schizophrenic patients. *Journal of Clinical Psychiatry* 1995;**56**(4):167-70.

Smith 1979 {published data only}

Smith JS, Kiloh LG. Six-month evaluation of thiopropazate hydrochloride in tardive dyskinesia. *Journal of Neurology, Neurosurgery and Psychiatry* 1979;**42**(6):576-9.

Tamminga 1977 {published data only}

Tamminga CA, Smith RC, Ericksen SE, Chang S, Davis JM. Cholinergic influences in tardive dyskinesia. *American Journal of Psychiatry* 1977;**134**(7):769-74.

Wirshing 1989a {published data only}

Wirshing WC, Freidenberg DL, Cummings JL, Bartzokis G. Effects of anticholinergic agents on patients with tardive dyskinesia and concomitant drug-induced parkinsonism. *Journal of Clinical Psychopharmacology* 1989;**9**(6):407-11.

Wirshing 1989b {published data only}

Wirshing WC, Freidenberg DL, Cummings JL, Bartzokis G. Effect of anticholinergic agents on patients with tardive dyskinesia and concomitant drug-induced parkinsonism. *Journal of Clinical Psychopharmacology* 1989;**9**(6):407-11. [MEDLINE: 2574192]

Zwanikken 1976 {published data only}

Zwanikken GJ, Oei TT, Kimya S, Amery W. Safety and efficacy of prolonged treatment with Tremblex (dextetamide), an antiparkinsonian agent. A controlled study. *Acta Psychiatrica Belgica* 1976;**76**(3):467-79. [MEDLINE: 1020682]

References to studies awaiting assessment

Zeng 1996 {published data only}

Zhaoxiang Z, Fenglian C, Lin L. A Clinical Research of Dextetamide and Benzhexol for Treatment of Drug-induced Tremor. *Herald of Medicine* 1996;**15**(3):130-1.

Additional references

Alabed 2011

Alabed S, Latifeh Y, Mohammad HA, Rifai A. Gamma-aminobutyric acid agonists for neuroleptic-induced tardive dyskinesia. *Cochrane Database of Systematic Reviews* 2011, Issue 4. [DOI: [10.1002/14651858.CD000203.pub3](https://doi.org/10.1002/14651858.CD000203.pub3)]

Alphs 1983

Alphs LD, Davis JM. Cholinergic treatments for tardive dyskinesia. *Modern Problems in Pharmacopsychiatry* 1983;**21**:168-86.

Altman 1996

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

APA 1992

American Psychiatric Association. Tardive dyskinesia: a task force report of the American Psychiatric Association. Washington DC: American Psychiatric Association, 1992.

Armitage 1991

Armitage P. Should we cross off the crossover?. *Journal of Clinical Pharmacology* 1991;**32**(1):1-2.

Barnes 1993

Barnes TRE, Edwards JG. The side-effects of antipsychotic drugs. I. CNS and neuromuscular effects. In: Barnes TRE editor(s). Antipsychotic drugs and their side-effects. London: Harcourt Brace & Company, 1993.

Begg 1996

Begg C, Cho M, Eastwood S, Horton R, Moher D, Olkin I, et al. Improving the quality of reporting of randomized controlled trials: the CONSORT statement. *JAMA* 1996;**276**(8):637-9.

Bergen 1989

Bergen JA, Eyland EA, Campbell JA. The course of tardive dyskinesia in patients on long-term neuroleptics. *British Journal of Psychiatry* 1989;**154**:523-8.

Bhoopathi 2006

Bhoopathi PS, Soares-Weiser K. Benzodiazepines for neuroleptic-induced tardive dyskinesia. *Cochrane Database of Systematic Reviews* 2006, Issue 3. [DOI: [10.1002/14651858.CD000205.pub2](https://doi.org/10.1002/14651858.CD000205.pub2)]

Bland 1997

Bland JM, Kerry SM. 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'efficacité]. *Thérapie* 1999;**54**(4):405-11. [PUBMED: 10667106]

Casey 1994

Casey DE. Tardive dyskinesia: pathophysiology. In: Bloom FE, Kupfer DJ editor(s). Psychopharmacology. The Fourth Generation of Progress. New York: Raven Press, 1994.

Cavallaro 1993

Cavallaro R, Regazzetti MG, Mundo E, Brancato V, Smeraldi E. Tardive Dyskinesia Outcomes: Clinical and

Pharmacologic Correlates of Remission and persistence. *Neuropsychopharmacology* 1993;**8**(3):233-9.

Chouinard 2008

Chouinard G, Chouinard VA. Atypical antipsychotics: CATIE study, drug-induced movement disorder and resulting iatrogenic psychiatric-like symptoms, supersensitivity rebound psychosis and withdrawal discontinuation syndromes. *Psychotherapy and Psychosomatics* 2008;**77**(2):69-77.

Cloud 2014

Cloud LJ, Zutshi D, Factor SA. Tardive dyskinesia: therapeutic options for an increasingly common disorder. *Neurotherapeutics* 2014;**11**(1):166-76.

Correll 2004

Correll CU, Leucht S, Kane JM. Lower Risk for Tardive Dyskinesia Associated With Second-Generation Antipsychotics: A Systematic Review of 1-Year Studies. *American Journal of Psychiatry* 2004;**161**(3):414-25.

Correll 2008

Correll CU, Schenka EM. Tardive dyskinesia and new antipsychotics. *Current Opinion in Psychiatry* 2008;**21**(2):151-6.

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.

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

El-Sayeh 2006

El-Sayeh HG, Lyra da Silva JP, Rathbone J, Soares-Weiser K. Non-neuroleptic catecholaminergic drugs for neuroleptic-induced tardive dyskinesia. *Cochrane Database of Systematic Reviews* 2006, Issue 1. [DOI: [10.1002/14651858.CD000458.pub2](https://doi.org/10.1002/14651858.CD000458.pub2)]

Elbourne 2002

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

Essali 2011

Essali A, Deirawan H, Soares-Weiser K, Adams CE. Calcium channel blockers for neuroleptic-induced tardive dyskinesia.

Cochrane Database of Systematic Reviews 2011, Issue 11. [DOI: [10.1002/14651858.CD000206.pub3](https://doi.org/10.1002/14651858.CD000206.pub3)]

Fernandez 2001

Fernandez HH, Krupp B, Friedman JH. The course of tardive dyskinesia and parkinsonism in psychiatric inpatients: 14-year follow-up. *Neurology* 2001;**56**:805-7.

Fleiss 1984

Fleiss JL. The crossover study. The Design and Analysis of Clinical Experiments. Chichester: John Wiley & Sons, 1984.

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**(7):7-10.

Glazer 1990

Glazer WM, Morgenstern H, Schooler N, Berkman CS, Moore DC. Predictors of improvement in tardive dyskinesia following discontinuation of neuroleptic medication. *British Journal of Psychiatry* 1990;**157**:585-92.

Glazer 2000

Glazer WM. Review of incidence studies of tardive dyskinesia associated with typical antipsychotics. *Journal of Clinical Psychiatry* 2000;**61**(suppl 4):15-20.

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 JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.0.2 (updated September 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Jeste 1982

Jeste DV, Wyatt RJ. Understanding and treating tardive dyskinesia. New York: The Guilford Press, 1982.

Kane 1994

Kane JM. Tardive dyskinesia: epidemiological and clinical presentation. In: Bloom FE, Kupfer DJ editor(s). *Psychopharmacology. The Fourth Generation of Progress*. New York: Raven Press, 1994.

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 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]

Leucht 2005b

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]

Lieberman 1996

Lieberman JA, Fleishacker W. Introduction. *British Journal of Psychiatry* 1996;**168**(Supplement 29):7-8.

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.

Mulrow 1999

Mulrow CD, Oxman AD. Cochrane Collaboration Handbook [updated September 1999]. Cochrane Database of Systematic Reviews. Oxford: Update Software; 1996-. Updated quarterly, 1991, issue 2. [DOI: [ATD020600](https://doi.org/10.1002/ATD020600)]

NICE 2014

NICE. Psychosis and schizophrenia in adults: treatment and management. NICE clinical guideline 178 (guidance.nice.org.uk/cg178) 2014.

Overall 1962

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

Pocock 1983

Pocock SJ. Crossover trials. Clinical trials. A practical approach. Chichester: John Wiley & Sons, 1983.

Schooler 1993

Schooler NR, Keith SJ. The clinical research base for the treatment of schizophrenia. *Psychopharmacology Bulletin* 1993;**29**(4):431-46.

Schünemann 2008

Schünemann HJ, Oxman AD, Vist GE, Higgins JPT, Deeks JJ, Glasziou P, et al. Chapter 12: Interpreting results and drawing conclusions. In: Higgins JPT, Green S (editors), *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. *BiolImpacts* 2017;**7**(4):209-17.

Smith 1980

Smith JM, Balessarini RJ. Changes in prevalence, severity and recovery in tardive dyskinesia with age. *Archives of General Psychiatry* 1980;**37**(12):1368-73.

Soares-Weiser 2003

Soares-Weiser K, Joy C. Miscellaneous treatments for neuroleptic-induced tardive dyskinesia. *Cochrane Database of Systematic Reviews* 2003, Issue 2. [DOI: [10.1002/14651858.CD000208](https://doi.org/10.1002/14651858.CD000208)]

Soares-Weiser 2006

Soares-Weiser K, Rathbone J. Neuroleptic reduction and/or cessation and neuroleptics as specific treatments for tardive dyskinesia. *Cochrane Database of Systematic Reviews* 2006, Issue 1. [DOI: [10.1002/14651858.CD000459.pub2](https://doi.org/10.1002/14651858.CD000459.pub2)]

Soares-Weiser 2011

Soares-Weiser K, Maayan N, McGrath J. Vitamin E for neuroleptic-induced tardive dyskinesia. *Cochrane Database of Systematic Reviews* 2011, Issue 2. [DOI: [10.1002/14651858.CD000209.pub2](https://doi.org/10.1002/14651858.CD000209.pub2)]

Tammenmaa 2002

Tammenmaa I, McGrath J, Sailas E, Soares-Weiser K. Cholinergic medication for neuroleptic-induced tardive dyskinesia. *Cochrane Database of Systematic Reviews* 2002, Issue 3. [DOI: [10.1002/14651858.CD000207](https://doi.org/10.1002/14651858.CD000207); MEDLINE: 22133093]

Tarsy 2011

Tarsy D, Lungu C, Baldessarini RJ. Epidemiology of tardive dyskinesia before and during the era of modern antipsychotic drugs. *Handbook of Clinical Neurology* / Edited by P.J. Vinken and G.W. Bruyn 2011;**100**:601-16.

Taylor 2009

Taylor D, Paton C, Kapur S. The Maudsley Prescribing Guidelines (10th Edition). London: Informa Healthcare, 2009.

Ukoumunne 1999

Ukoumunne OC, Gulliford MC, Chinn S, Sterne JAC, Burney PGJ. Methods for evaluating area-wide and organisation-based intervention in health and health care: a systematic review. *Health Technology Assessment* 1999;**3**(5):1-75.

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.

References to other published versions of this review

Soares-Weiser 1997

Soares-Weiser K, Mobsy C, Holliday E. Anticholinergic medication for neuroleptic-induced tardive dyskinesia.

Cochrane Database of Systematic Reviews 1997, Issue 2. [DOI:
10.1002/14651858.CD000204]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Bucci 1971

Methods	Allocation: random, further details not reported. Blindness: not reported. Duration: 40 weeks. Design: parallel. Setting: outpatients, USA.
Participants	Diagnosis: chronic schizophrenia treated with phenothiazine for several years and demonstrating obvious dyskinetic manifestations. Duration of tardive dyskinesia (TD): ≥ 2 years. N = 20. Sex: 16 female, 4 male. Age: range 45 to 62 years.
Interventions	1. Procyclidine (anticholinergic), 5 mg B.I.D. + chlorpromazine, 100 mg T.I.D. N = 10. 2. Isocarboxazid (MAO inhibitor), 10 mg B.I.D. + chlorpromazine, 100 mg T.I.D. N = 10. Continuous phenothiazine-antiparkinsonian treatment for at least 2 years. Other concomitant medication: not reported.
Outcomes	TD symptoms: improvement (clinical evaluation, scale not reported). Leaving the study early. Adverse events. Unable to use - <ul style="list-style-type: none"> Mental state (data not reported for both groups).
Notes	Sponsorship source: not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The patients were divided at random into groups of 10 each", no further details reported.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding of participants and personnel not reported.

Bucci 1971 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessment not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	“One male patient on chlorpromazine and isocarboxazid was discontinued after 6 weeks as he became increasingly tense, apprehensive and sleepless.”
Selective reporting (reporting bias)	High risk	Unclear if all outcomes have been reported. A protocol is not available for verification. Adverse effects reported only as those related to treatment. Mental state data not reported for group 2.
Other bias	Unclear risk	Insufficient information to make a judgement.

Greil 1984

Methods	Allocation: "randomly assigned" no further details. Blind: "double-blind" no further details. Design: parallel group. Setting: not reported if inpatients or outpatients or both; Germany. Duration: 7 weeks.
Participants	Diagnosis: chronic schizophrenics (ICD-9) with tardive dyskinesia based on the presence of a 'typical' bucco-linguo-masticatory syndrome and the absence of other adequate explanations for the movement disorder. Duration of tardive dyskinesia: ≥ 1 year, severity of the symptoms stable for at least one month before admission to the study. N = 10. Sex: 7 female, 3 male. Age: mean 56.6 (SD 9.2) years; range 35 to 65 years.
Interventions	1. Biperiden (same dose as before the trial) stopped after 4 weeks followed by placebo for 3 weeks. N = 4. 2. Biperiden (same dose as before the trial) stopped after 1 week followed by placebo for 6 weeks. N = 6. All stable on antipsychotics and anticholinergics for at least 5 months before entry and during the trial. Other concomitant medication: not reported.
Outcomes	Leaving the study early. Unable to use (results not reported per randomised group) - <ul style="list-style-type: none"> TD symptoms: Abnormal Involuntary Movements Scale (AIMS). EP symptoms: Simpson-Angus Scale. Study author was contacted for additional data but no reply was received.
Notes	Sponsorship source: not reported. Knoll AG supplied placebo.

Greil 1984 (Continued)

Declarations of interest: not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly assigned", further details not reported.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-blind" "investigators were not informed about the study design"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of raters was not mentioned.
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Nine patients completed the trial. One patient dropped out one week after biperiden withdrawal because of severe parkinsonism; in this patient, only one rating could be carried out while on the placebo."
Selective reporting (reporting bias)	High risk	TD symptoms data were not reported per randomised group, but before biperiden removal versus after biperiden removal.
Other bias	Unclear risk	Insufficient information to make a judgement.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Casey 1977	Allocation: not randomised, controlled clinical study.
DiMascio 1976	Allocation: randomised. Participants: no TD measure at baseline, not stable dose of antipsychotics.
Double 1993	Allocation: randomised. Participants: no TD symptoms at baseline.
Elie 1972	Allocation: randomised. Participants: people with chronic schizophrenia, no TD.
Fann 1976	Allocation: randomised. Participants: no TD symptoms at baseline.
Friis 1983	Allocation: randomised. Participants: antipsychotic-induced akathisia, parkinsonism and hyperkinetic movements, 11/15 participants had tardive dyskinesia. Intervention: valproate vs biperiden vs placebo. Outcomes: two period crossover – no data about allocation in first period.

Study	Reason for exclusion
	Dr Gerlach (author) contacted and replied promptly. Data were destroyed and no more information is available.
Gardos 1984	Allocation: not randomised, controlled clinical trial.
Gerlach 1976	Allocation: not randomised, controlled clinical trial.
Gerlach 1978	Allocation: not randomised - randomisation was only in one arm of the study "haloperidol + biperiden for 4 weeks (phase 2 and phase 3 in randomized sequence)"; all other arms were not randomised (thioridazine for 3 months, haloperidol for 4 weeks, thioridazine for 4 weeks, clozapine for 4 weeks).
Jus 1974	Allocation: not randomised, controlled clinical trial.
Klett 1972	Allocation: randomised. Participants: no information about those with TD symptoms at baseline. Intervention: benztropine withdrawal vs maintenance. Dr Klett (author) contacted and replied promptly. Data were destroyed and no more information is available.
Konig 1996	Allocation: not randomised, controlled clinical trial.
Lejoyeux 1993	Allocation: not randomised, controlled clinical trial.
Lieberman 1988	Allocation: randomised. Participants: schizophrenia, schizoaffective disorder, major affective disorder attention deficit disorder and TD (criteria of Schooler & Kane). Intervention: physostigmine vs bromocriptine vs benztropine vs haloperidol. Outcomes: no outcome data were been provided for the first period before crossover. Study author was contacted for data; no additional information was received and as this study is over 25 years old, we excluded this trial.
Ludatscher 1989	Allocation: randomised. Participants: people with chronic schizophrenia who had symptoms of severe persistent TD and who had been treated with antipsychotic drugs. Intervention: L-dopa 500 mg + carbidopa 50 mg/d + low dose antipsychotics (N = 35) vs placebo + anticholinergic medication + low dose antipsychotic (N = 25). Outcomes: no outcome data could be used. The study is over 25 years old and we were unable to identify contact details for the author.
NDSG 1986	Allocation: randomised crossover. Participants: psychiatric inpatients with TD. Intervention: chlorprothixene vs haloperidol vs perphenazine or haloperidol + biperiden with placebo periods in between phases. Outcomes: no outcome data has been provided for the first period before crossover. Author was contacted but did not reply. Study is over 30 years old and we excluded it.
Silver 1995	Allocation: randomised.

Study	Reason for exclusion
	<p>Participants: people with schizophrenia (DSM-III-R), with and without TD.</p> <p>Interventions: biperiden vs amantadine.</p> <p>Outcomes: no outcome data has been provided for the first period before crossover.</p> <p>We were unable to find up-to-date contact details for the authors and, as this study is over 20 years old, we excluded this trial.</p>
Smith 1979	Allocation: not randomised, controlled clinical trial.
Tamminga 1977	Allocation: not randomised, ABA design.
Wirshing 1989a	Allocation: not randomised, controlled clinical trial.
Wirshing 1989b	Allocation: not randomised, controlled clinical trial.
Zwanikken 1976	Allocation: not randomised, controlled clinical trial.

Characteristics of studies awaiting assessment *[ordered by study ID]*

Zeng 1996

Methods	Allocation: randomised.
Participants	Diagnosis: schizophrenia with drug-induced tremor. N = 68.
Interventions	<p>1. Dextimide. N = 36.</p> <p>2. Benzhexol. N = 32.</p>
Outcomes	<p>Movement disorder: clinical response.</p> <p>Adverse events: TESS.</p>
Notes	<p>Language: Chinese – assessed by Sai Zhao.</p> <p>Study authors have been contacted to find out if participants were diagnosed with tardive dyskinesia.</p>

TESS – Treatment Emergent Symptom Scale

DATA AND ANALYSES

Comparison 1. Anticholinergic medications versus other compounds

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 TD symptoms: no clinically significant improvement	1		Risk Ratio (IV, Fixed, 95% CI)	Subtotals only
1.1 procyclidine vs isocarboxazid	1	20	Risk Ratio (IV, Fixed, 95% CI)	4.2 [1.40, 12.58]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 TD symptoms: not any improvement	1		Risk Ratio (IV, Fixed, 95% CI)	Subtotals only
2.1 procyclidine vs isocarboxazid	1	20	Risk Ratio (IV, Fixed, 95% CI)	7.0 [1.57, 31.15]
3 Adverse effects	1		Risk Ratio (IV, Fixed, 95% CI)	Subtotals only
3.1 procyclidine vs isocarboxazid	1	20	Risk Ratio (IV, Fixed, 95% CI)	0.33 [0.02, 7.32]
4 Leaving the study early	1		Risk Ratio (IV, Fixed, 95% CI)	Subtotals only
4.1 procyclidine vs isocarboxazid	1	20	Risk Ratio (IV, Fixed, 95% CI)	0.33 [0.02, 7.32]

Analysis 1.1. Comparison 1 Anticholinergic medications versus other compounds, Outcome 1 TD symptoms: no clinically significant improvement.

Analysis 1.2. Comparison 1 Anticholinergic medications versus other compounds, Outcome 2 TD symptoms: not any improvement.

Analysis 1.3. Comparison 1 Anticholinergic medications versus other compounds, Outcome 3 Adverse effects.

Analysis 1.4. Comparison 1 Anticholinergic medications versus other compounds, Outcome 4 Leaving the study early.

Comparison 2. Continuation versus withdrawal of anticholinergic medications

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Leaving the study early	1		Risk Ratio (IV, Fixed, 95% CI)	Subtotals only
1.1 biperiden: withdrawal after 1 week vs withdrawal after 4 weeks	1	10	Risk Ratio (IV, Fixed, 95% CI)	2.14 [0.11, 42.52]

Analysis 2.1. Comparison 2 Continuation versus withdrawal of anticholinergic medications, Outcome 1 Leaving the study early.

ADDITIONAL TABLES

Table 1. Other reviews in the series

Interventions	Reference
Anticholinergic medication	This review
Benzodiazepines	Bhoopathi 2006 ; update to be published
Calcium channel blockers	Essali 2011 ; update to be published
Cholinergic medication	Tammenmaa 2002 ; update to be published
Gamma-aminobutyric acid agonists	Alabed 2011 ; update to be published
Miscellaneous treatments	Soares-Weiser 2003 ; update to be published
Neuroleptic reduction and/or cessation and neuroleptics	Soares-Weiser 2006 ; update to be published
Non-neuroleptic catecholaminergic drugs	El-Sayeh 2006 ; update to be published
Vitamin E	Soares-Weiser 2011 ; update to be published

Table 2. Suggestions for design of future study

Methods	Allocation: randomised, with sequence generation and concealment of allocation clearly described. Blindness: double, tested. Duration: 12 months beyond end of intervention at least. Raters: independent.
Participants	People with antipsychotic-induced tardive dyskinesia.* Age: any. Sex: both. History: any. N = 300.**
Interventions	1. Anticholinergic withdrawal (N = 150) versus anticholinergic continuation (N = 150). OR 2. Specific anticholinergic (N = 150) versus placebo (N = 150).
Outcomes	Tardive dyskinesia: any clinically important improvement in TD, any improvement, deterioration.*** Adverse effects: no clinically significant extrapyramidal adverse effects – any time period***, use of any antiparkinsonism drugs, other important adverse events. Leaving the study early. Service outcomes: admitted, number of admissions, length of hospitalisation, contacts with psychiatric services. Compliance with drugs. Economic evaluations: cost-effectiveness, cost-benefit. General state: relapse, frequency and intensity of minor and major exacerbations. Social confidence, social inclusion, social networks, or personalised quality of life: binary measure Distress among relatives: binary measure. Burden on family: binary measure.

Table 2. Suggestions for design of future study (Continued)

Notes	<p>* This could be diagnosed by clinical decision. If funds were permitting, all participants could be screened using operational criteria; otherwise a random sample should suffice.</p> <p>** Size of study with sufficient power to highlight about a 10% difference between groups for primary outcome.</p> <p>*** Primary outcome. The same applies to the measure of primary outcome as for diagnosis. Not everyone may need to have operational criteria applied if clinical impression is proved to be accurate.</p>
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APPENDICES

Appendix 1. Previous methods and searches

Criteria for considering studies for this review

Types of studies

We attempted to identify all relevant randomized controlled trials.

Types of participants

People with schizophrenia or schizoaffective disorder or any other chronic mental illnesses, diagnosed by any criteria, irrespective of gender, age or nationality who;

- i. required the use of neuroleptics for more than three months;
- ii. developed tardive dyskinesia (diagnosed by any criteria at baseline and at least one other occasion) during neuroleptic treatment; and
- iii. for whom the dose of neuroleptic medication had been stable for one month or more (the same applies for those free of neuroleptics).

Types of interventions

- i. Anticholinergic drugs (benzhexol, benzotropine, biperiden, dexetimide, orphenadrine, procyclidine, scopolamine, trihexylphenidyl) compared to placebo, or no intervention; or
- ii. the withdrawal of the above anticholinergic drugs compared with the continuation of the treatment.

Types of outcome measures

Clinical efficacy was defined as an improvement in the symptoms of TD of more than 50%, on any scale, after at least six weeks of intervention.

The outcomes of interest were:

A. Tardive dyskinesia changes

- i. The number of people per treatment group that did not show an improvement in the symptoms of individuals of more than 50% on any TD scale;
- ii. the number of people per treatment group that did not show any improvement in the symptoms of individuals on any TD scale, as opposed to some improvement;
- iii. deterioration in the symptoms of individuals, defined as any deleterious change on any TD scale;
- iv. any adverse effect, other than deterioration of symptoms of TD, as reported in the trials;
- v. average change in severity of TD during the trial period; and
- vi. average difference in severity of TD at the end of the trial.

B. General mental state changes

- i. Deterioration in general psychiatric symptoms (such as delusions and hallucinations) defined as any deleterious change on any scale; and
- ii. average difference in severity of psychiatric symptoms at the end of the trial.

C. Acceptability of the treatment

Acceptability of the intervention to the participant group as measured by numbers of people dropping out during the trial.

When feasible, the outcomes were grouped into time periods - short term (less than 6 weeks), medium term (between 6 weeks and 6 months) and long term (over 6 months).

Search methods for identification of studies

1. Electronic searching

Relevant randomized trials were identified by searching the following electronic databases:

1.1 Biological Abstracts on Silverplatter WinSPIRS 4.0 (January 1982 to March 2000) was searched using the Cochrane Schizophrenia Group's phrase for randomized controlled trials (see Group search strategy) combined with:

[AND (tardive near (dyskine* or diskine*)) or (abnormal near movement* near disorder*) or (involuntar* near movement*))]

This downloaded set of reports was handsearched for possible trials and researched, within the bibliographic package ProCite, with the phrase [anticholinergic* or antiparkinsonian* or benzhexol or benztropine or biperiden or dextetamide or orphenadrine or procyclidine or scopolamine or trihexyphenidyl]

1.2 CINAHL on Silverplatter WinSPIRS 4.0 (1982 - April 2000) was searched using the Cochrane Schizophrenia Group's phrase for randomized controlled trials (see Group search strategy) combined with:

[AND (explode "Movement-Disorders"/ all topical subheadings / all age subheadings) or (explode "Movement-Disorders"/ all topical subheadings / all age subheadings) or (tardive near (dyskine* or diskine*)) or (abnormal* near movement* near disorder*) or (involuntar* near movement*) near movement*)]

This downloaded set of reports was handsearched for possible trials and researched, within the bibliographic package ProCite, with the phrase [anticholinergic* or antiparkinsonian* or benzhexol or benztropine or biperiden or dextetamide or orphenadrine or procyclidine or scopolamine or trihexyphenidyl]

1.3 CCTR/CENTRAL of the Cochrane Library (Issue 2, 2000) was searched using the phrase:

[((movement-disorders*:me) or (dyskinesia-drug-induced:me) or (anti-dyskinesia-agents*:me) or (tardive near (dyskine* or dyskine*)) or (neuroleptic near dyskine*) or (abnormal* near movement* near disorder*) or (involuntar* near movement*)) and (anticholinergic* or antiparkinsonian* or benzhexol* or benztropine or biperiden or dextetamide or orphenadrine or procyclidine or scopolamine or trihexyphenidyl)]

1.4 Cochrane Schizophrenia Group's Register was searched using the phrase:

[anticholinergic* or antiparkinsonian* or benzhexol or benztropine or biperiden or dextetamide or orphenadrine or procyclidine or scopolamine or trihexyphenidyl]

1.5 EMBASE on Silverplatter WinSPIRS 4.0 (January 1980 to May 2000) was searched using the Cochrane Schizophrenia Group's phrase for randomized controlled trials (see Group search strategy) combined with:

[AND (("tardive-dyskinesia"/ all subheadings) or ("dyskinesia"/ all subheadings) or ("motor dysfunction"/ all subheadings) or (tardive near (dyskines* or diskines*)) or (abnormal* near movement* near disorder*) or involuntar* near movement*))]

This downloaded set of reports was handsearched for possible trials and researched, within the bibliographic package ProCite, with the phrase [anticholinergic* or antiparkinsonian* or benzhexol or benztropine or biperiden or dextetamide or orphenadrine or procyclidine or scopolamine or trihexyphenidyl]

1.6 LILACS (January 1982 to September 1996) was searched using the CSG's phrase for randomized controlled trials (see Group search strategy) combined with the phrase:

[AND ((tardive or (dyskinesia* or diskinesia*)) or (drug induced movement disorders in thesaurus))]

This downloaded set of reports was handsearched for possible trials and researched, within the bibliographic package ProCite, with the phrase [anticholinergic* or antiparkinsonian* or benzhexol or benztropine or biperiden or dextetamide or orphenadrine or procyclidine or scopolamine or trihexyphenidyl]

1.7 MEDLINE on Silverplatter WinSPIRS 4.0 (January 1966 to June 2000) was searched using the Cochrane Schizophrenia Group's phrase for randomized controlled trials (see Group search strategy) combined with:

[AND ((explode "movement-disorders" in MeSH / all subheadings) or (explode "anti-dyskinesia-agents" in MeSH / all subheadings) or (explode "dyskinesia-drug-induced" in MeSH / all subheadings) and (explode "psychotic-disorders" in MeSH / all subheadings) or (explode "schizophrenic disorders" in MeSH / all subheadings) or (tardive near (dyskine* or diskine*)) or (abnormal* near movement* near disorder*) or (involuntar* near movement*))]

This downloaded set of reports was handsearched for possible trials and researched, within the bibliographic package ProCite, with the phrase [anticholinergic* or antiparkinsonian* or benzhexol or benztropine or biperiden or dextimide or orphenadrine or procyclidine or scopolamine or trihexyphenidyl]

1.8 PsycLIT on Silverplatter WinSPIRS 4.0 (January 1974 to March 2000) was searched using the Cochrane Schizophrenia Group's phrase for randomized controlled trials (see Group search strategy) combined with the phrase:

[AND ((explode "movement-disorders") or ("tardive-dyskinesia" in DE) or (tardive near (dyskine* or diskine*)) or (abnormal* near movement* near disorder*) or (involuntar* near movement*))]

This downloaded set of reports was handsearched for possible trials and researched, within the bibliographic package ProCite, with the phrase [anticholinergic* or antiparkinsonian* or benzhexol or benztropine or biperiden or dextimide or orphenadrine or procyclidine or scopolamine or trihexyphenidyl]

1.9 SCISEARCH - Science Citation Index

Each of the included studies was sought as a citation on the SCISEARCH database. Reports of articles that had cited these studies were inspected in order to identify further trials.

1.10 Cochrane Schizophrenia Group Trials Register

The Trials Search Co-ordinator searched the Cochrane Schizophrenia Group's Trials Register (November 11, 2013)

[(((*Akineton* or *Anticholinergic* or *Antimuscarinic* or *Aparkan* or *Arpicolin* or *Artane* or *Atropine* or *Banflex* or *Benapr* or *Benzatropine* or *Benzhexol* or *Benztropine* or *Biperiden* or *Biorphen* or *Bornaprine* or *Broflex* or *Buscopan* or *Cholinergic* or *Cogentin* or *Cycrimine* or *Darifenacin* or *Dicycloverine* or *Diphenhydramine* or *Disipal* or *Elantrine* or *Ethopropazine* or *Flavoxate* or *Flexon* or *Hyoscine* or *Kemadrin* or *Mephenamin* or *Muscarinic* or *Norflex* or *Oxybutynin* or *Parkin* or *Parsid* or *Orphenadrine* or *Pro-banthine* or *Procyclidine* or *Profenamine* or *Propantheline* or *Propiverine* or *Scopolamine* or *Solifenacin* or *Tolterodine* or *Trihexyphenidyl* or *Tropium*) in title abstract or index terms of REFERENCE)) and ((*dyskinesia* in title abstract or index terms of REFERENCE) and (Tardive dyskinesia in health care conditions of STUDY))]

The Cochrane Schizophrenia Group's Trials Register is compiled by systematic searches of major databases, handsearches of journals and conference proceedings (see [Group Module](#)). Incoming trials are assigned to existing or new review titles.

2. Reference searching

The references of all identified studies were also inspected for more studies.

3. Personal contact

The first author of each included study was contacted for information regarding unpublished trials.

Data collection and analysis

[For definitions of terms used in this, and other sections, please refer to the Glossary.]

The abstract of each reference identified by the search was inspected, independently, by both reviewers, to see if the study was likely to be relevant. For articles that could possibly have been RCTs, or in cases of disagreement between the two reviewers, the full article was obtained. In turn, these articles were then inspected, independently, to assess their relevance to this review. Again, where resolving disagreement by discussion was not possible, the article was added to those awaiting assessment and the authors of the study were contacted for clarification.

The reviewers independently evaluated the quality of all included trials. A rating was given for each trial based on the three quality categories as described in the Cochrane Collaboration Handbook ([Mulrow 1999](#)). Only trials stated to be randomized (category A or B of the Handbook) were included in this review.

Data were independently extracted by both reviewers. Again, any disagreement was discussed, the decisions documented and, where necessary, the authors of the studies were contacted for clarification. Justification for excluding references from the review was documented. If insufficient information could be extracted from the publication, a letter was sent to the first author for further clarification. These references were allocated to the 'Awaiting assessment' list. In the absence of specific details, the reviewers assumed that subjects dropped out because they had no improvement in their TD. The results were recalculated without these assumptions in order to test the sensitivity of the results.

We expected that many trials would use a crossover design. In order to exclude the potential additive effect in the second or more stages on these trials, only data from the first stage were analysed.

Dichotomous outcomes were analysed by calculating odds ratios for each trial with the uncertainty in each result being expressed using confidence intervals. The odds ratios from the individual trials were combined using appropriate methods of meta-analysis. When overall

results were significant the number needed to treat to produce (or prevent) one outcome was calculated by combining the overall odds ratio with an estimate of the prevalence of the event in the control groups of the trials.

Continuous outcomes were analysed according to their difference in mean treatment effects and its standard deviation. Meta-analytical methods for continuous data assume that the underlying distribution of the measurements is Normal. The ratio of the mean to its standard deviation gives a crude way of assessing skew: if this ratio was less than 1.65 for any group in a trial and this can be resolved by log-transformation, the data then becoming normally distributed. It was proposed to undertake this procedure before including skewed data from any study in the analysis.

Heterogeneity in the results of the trials was assessed both by inspection of graphical presentations and by calculating a test of heterogeneity. Two possible reasons for heterogeneity were pre-specified: (i) that response differs according to different lengths of follow-up; (ii) that response differs according to the different drugs. These were assessed by looking at separate subgroups of trials [(i) and (ii)].

FEEDBACK

Crossover studies

Summary

Category: Methods

A general comment regarding the use and interpretation of data obtained from crossover studies. The statistical questions remain unanswered and thus only data from the first treatment period can legitimately be used. However this data is rarely presented in reports of such trials leading to their exclusion from the systematic review. The author of the comment mentions that the chronic and unstable nature of TD should not disfavour a crossover trial design as suggested by the reviewers. The review would be enhanced if the authors made some recommendations on the characteristics of a crossover study that would allow its inclusion in a systematic review such as this one.

Reply

In the TD reviews data were pooled from the first period where it was possible to do so. When impossible the results were reported without pooling. Most of the crossover trials lasted less than six weeks. Recently we have analysed data from studies using placebo and found 37.3% improved their TD symptoms. We suggest that future RCTs investigating the treatment of TD should utilise a parallel group design.

Contributors

Comment received from Jon Deeks, Oxford, UK, August 1997.

Reply from Karla Soares, Barcelona, Spain, December 1997.

WHAT'S NEW

Date	Event	Description
4 October 2017	New citation required but conclusions have not changed	Results from latest searches have not altered the conclusions of this review.
26 April 2017	New search has been performed	Update search run 26 April 2017. Eight records found and assessed by Cochrane Schizophrenia editorial base, no new studies relevant to this review found. The 8 records added to Miscellaneous Treatments this series of Tardive Dyskinesia reviews; (see also Results of the search)
18 November 2016	Amended	Title changed from 'Anticholinergic medication for neuroleptic-induced tardive dyskinesia'. Two new included trials added (Bucci 1971 ; Greil 1984), analyses and text updated, outcomes list updated due to patient consultation, 'Summary of findings' table added, conclusions not substantially changed.

HISTORY

Protocol first published: Issue 2, 1996

Review first published: Issue 3, 1997

Date	Event	Description
16 July 2015	Amended	Update search run July 15 2015. 704 records found and assessed by review authors.
11 November 2013	Amended	Search was updated and 58 possibly related references were sent to the author.
6 August 2012	Amended	Update search of Cochrane Schizophrenia Group's Trial Register (see Search methods for identification of studies), 8 studies added to Studies awaiting classification .
4 August 2010	Amended	Contact details updated.
14 April 2010	Amended	Contact details updated.
25 April 2008	Amended	Converted to new review format.
14 February 1997	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

HB - trial selection, data extraction and assimilation, 'Summary of findings' tables, report writing.

KSW - protocol writing, searching, trial selection, data extraction and assimilation, report writing.

DECLARATIONS OF INTEREST

Hanna Bergman worked for Enhance Reviews Ltd. during preparation of this review and was paid for her contribution to this review. Enhance Reviews Ltd. is a private company that performs systematic reviews of literature. HB works for Cochrane Response, an evidence consultancy linked to Cochrane that take commissions from healthcare guideline developers and policy makers.

Karla Soares-Weiser is the Deputy Editor-in-Chief for Cochrane and Cochrane Innovations. When the NHIR HTA programme grant was awarded that included provision to update this review, Karla was the Managing Director of Enhance Reviews Ltd.

SOURCES OF SUPPORT

Internal sources

- CAPES - Ministry of Education, Brazil.
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- Enhance Reviews Ltd., UK.

Logistics support for Hanna Bergman

External sources

- NIHR HTA Project Grant, reference number: 14/27/02, UK.

Salary support for Hanna Bergman.
Support for patient involvement consultation.
Support for traceable data database.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The protocol as published with this review has evolved over time. The revisions of protocol are in line with the development of RevMan and in keeping with Cochrane guidance. We think the revisions have greatly improved and enhanced this review. We do not think, however, that it has materially affected our conduct of the review or interpretation of the results.

There was a substantial update to the protocol in the 2017 review update with main changes being as follows.

1. Broadening the inclusion criteria, and adding the comparison 'Anticholinergic medication vs any other intervention'.
2. Changing the title from 'Anticholinergic medication for neuroleptic-induced tardive dyskinesia' to the current title.
3. Rewording of the objectives.
4. Updating list of outcomes following consultation with consumers.
5. Adding 'Summary of findings' tables.

The previous methods are reproduced in [Appendix 1](#).

NOTES

Cochrane schizophrenia Group internal peer review complete (see Module).
External peer review scheduled.

INDEX TERMS

Medical Subject Headings (MeSH)

Antipsychotic Agents [*adverse effects]; Biperiden [adverse effects] [therapeutic use]; Cholinergic Antagonists [adverse effects] [*therapeutic use]; Dyskinesia, Drug-Induced [*drug therapy] [etiology]; Isocarboxazid [adverse effects] [therapeutic use]; Procyclidine [adverse effects] [therapeutic use]; Randomized Controlled Trials as Topic; Schizophrenia [drug therapy]; Withholding Treatment

MeSH check words

Humans