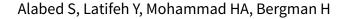


Cochrane Database of Systematic Reviews

Gamma-aminobutyric acid agonists for antipsychotic-induced tardive dyskinesia (Review)



Alabed S, Latifeh Y, Mohammad HA, Bergman H. Gamma-aminobutyric acid agonists for antipsychotic-induced tardive dyskinesia. *Cochrane Database of Systematic Reviews* 2018, Issue 4. Art. No.: CD000203. DOI: 10.1002/14651858.CD000203.pub4.

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[Intervention Review]

Gamma-aminobutyric acid agonists for antipsychotic-induced tardive dyskinesia

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ABSTRACT

Background

Chronic antipsychotic drug treatment may cause tardive dyskinesia (TD), a long-term movement disorder. Gamma-aminobutyric acid (GABA) agonist drugs, which have intense sedative properties and may exacerbate psychotic symptoms, have been used to treat TD.

Objectives

1. Primary objective

The primary objective was to determine whether using non-benzodiazepine GABA agonist drugs for at least six weeks was clinically effective for the treatment of antipsychotic-induced TD in people with schizophrenia, schizoaffective disorder or other chronic mental illnesses.

2. Secondary objectives

The secondary objectives were as follows.

To examine whether any improvement occurred with short periods of intervention (less than six weeks) and, if this did occur, whether this effect was maintained at longer periods of follow-up.

To examine whether there was a differential effect between the various compounds.

To test the hypothesis that GABA agonist drugs are most effective for a younger age group (less than 40 years old).

Search methods

We searched the Cochrane Schizophrenia Group Trials Register (last searched April 2017), inspected references of all identified studies for further trials, and, when necessary, contacted authors of trials for additional information.

Selection criteria

We included randomised controlled trials of non-benzodiazepine GABA agonist drugs in people with antipsychotic-induced TD and schizophrenia or other chronic mental illness.



Data collection and analysis

Two review authors independently selected and critically appraised studies, extracted and analysed data on an intention-to-treat basis. Where possible and appropriate we calculated risk ratios (RRs) and their 95% confidence intervals (CIs). For continuous data we calculated mean differences (MD). We assumed that people who left early had no improvement. We contacted investigators to obtain missing information. We assessed risk of bias for included studies and created a 'Summary of findings' table using GRADE.

Main results

We included 11 studies that randomised 343 people. Overall, the risk of bias in the included studies was unclear, mainly due to poor reporting; allocation concealment was not described, generation of the sequence was not explicit, participants and outcome assessors were not clearly blinded. For some studies we were unsure if data were complete, and data were often poorly or selectively reported.

Data from six trials showed that there may be a clinically important improvement in TD symptoms after GABA agonist treatment compared with placebo at six to eight weeks follow-up (6 RCTs, n = 258, RR 0.83, CI 0.74 to 0.92; *low-quality evidence*). Data from five studies showed no difference between GABA agonist treatment and placebo for deterioration of TD symptoms (5 RCTs, n = 136, RR 1.90, CI 0.70 to 5.16; very low-quality evidence). Studies reporting adverse events found a significant effect favouring placebo compared with baclofen, sodium valproate or progabide for dizziness/confusion (3 RCTs, n = 62 RR 4.54, CI 1.14 to 18.11; *very low-quality evidence*) and sedation/drowsiness (4 RCTS, n = 144, RR 2.29, CI 1.08 to 4.86; *very low-quality evidence*). Studies reporting on akathisia (RR 1.05, CI 0.32 to 3.49, 2 RCTs, 80 participants), ataxia (RR 3.25, CI 0.36 to 29.73, 2 RCTs, 95 participants), nausea/vomiting (RR 2.61, CI 0.79 to 8.67, 2 RCTs, 64 participants), loss of muscle tone (RR 3.00, CI 0.15 to 59.89, 1 RCT, 10 participants), seizures (RR 3.00, CI 0.24 to 37.67, 1 RCT, 2 participants), hypotension (RR 3.04, CI 0.33 to 28.31, 2 RCTs, 119 participants) found no significant difference between GABA drug and placebo (*very low-quality evidence*). Evidence on mental state also showed no effect between treatment groups (6 RCTS, n = 121, RR 2.65, CI 0.71 to 9.86; *very low-quality evidence*) as did data for leaving the study early (around 10% in both groups, 6 RCTS, n = 218, RR 1.47, CI 0.69 to 3.15; *very low-quality evidence*). No study reported on social confidence, social inclusion, social networks, or personalised quality of life, a group of outcomes selected as being of particular importance to patients.

Authors' conclusions

We are uncertain about the evidence of the effects of baclofen, progabide, sodium valproate or tetrahydroisoxazolopyridinol (THIP) for people with antipsychotic-induced TD. Evidence is inconclusive and unconvincing. The quality of data available for main outcomes ranges from very low to low. Any possible benefits are likely to be outweighed by the adverse effects associated with their use.

PLAIN LANGUAGE SUMMARY

Gamma-aminobutyric acid agonists for antipsychotic-induced tardive dyskinesia

Review question.

To determine the effects of gamma-aminobutyric acid (GABA) agonist drugs in the treatment of tardive dyskinesia for people with schizophrenia or similar mental health problems.

Background.

People with schizophrenia often hear voices and see things (hallucinations) and have strange beliefs (delusions). The main treatment of schizophrenia is 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 or high-dose antipsychotic drugs, is difficult to treat and can be incurable. GABA agonist drugs have been used to treat tardive dyskinesia but have intense sedative properties and may make mental health or psychotic symptoms worse. GABA agonist drugs include baclofen, progabide, sodium valproate, and tetrahydroisoxazolopyridinol (THIP).

Study characteristics.

The review includes 11 studies investigating the use of GABA agonist drugs compared with placebo. All studies involved small numbers of participants (2 to 80 people) with schizophrenia or other chronic mental illnesses who had also developed antipsychotic-induced tardive dyskinesia.

Key results.

Evidence of the effects of GABA agonist drugs in the treatment of tardive dyskinesia is not conclusive and not convincing. Any possible benefits of GABA agonist drugs are likely to be outweighed by the adverse effects associated with their use.

Quality of the evidence.

Evidence is weak, short term, small scale and poorly reported. It is not possible to recommend these drugs as a treatment for tardive dyskinesia.



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

SUMMARY OF FINDINGS

Summary of findings for the main comparison. GABA DRUGS for antipsychotic-induced tardive dyskinesia

GABA DRUGS for antipsychotic-induced tardive dyskinesia

Patient or population: patients with antipsychotic-induced TD

Settings: Inpatients and outpatients

Intervention: GABA drugs

Outcomes	Illustrative compara	tive risks* (95% CI)	Relative effect (95% CI)	No of Partici- pants	Quality of the evidence	Comments
	Assumed risk	Corresponding risk	(33 /0 61)	(studies)	(GRADE)	
	Control	GABA drugs				
Tardive dyskinesia: Not improved to a	Medium risk populat	ion ¹	RR 0.83 (0.74 to 0.92)	258 (3 studies)	⊕⊕⊝⊝ low ^{2,3}	Studies on baclofen, progabide and sodium
clinically important extent	929 per 1000	771 per 1000 (687 to 854)	(-1 1 1 1 1 1 1 1.	(= =====,		valproate contributed to this outcome.
follow-up: 6-8 weeks						
Tardive dyskine- sia: Deterioration of	Medium risk populat	ion ¹	RR 1.90 (0.70 to 5.16)	136 (5 studies)	⊕⊝⊝⊝ very low ^{2,4}	Studies on baclofen and sodium valproate
symptoms	71 per 1000	136 per 1000	(======================================	(= ======	very tour	contributed to this outcome.
follow-up: 3-6 weeks		(50 to 369)				outcome.
Adverse events		dizziness/confusion (RR 4.54 CI 1.14 t		284	⊕⊝⊝⊝	Studies on baclofen,
follow-up: 3-8 weeks	ticipants) and sedation/drowsiness (RR 2.29 CI 1.08 to 4.86, 4 RCTs, 144 participants) found a significant effect favouring placebo compared with baclofen, sodium valproate or progabide. Studies reporting on akathisia (RR 1.05 CI 0.32 to 3.49, 2 RCTs, 80 participants), ataxia (RR 3.25 CI 0.36 to 29.73, 2 RCTs, 95 participants), nausea/vomiting (RR 2.61 CI 0.79 to 8.67, 2 RCTs, 64 participants), loss of muscle tone (RR 3.00 CI 0.15 to 59.89, 1 RCT, 10 participants), seizures (RR 3.00 CI 0.24 to 37.67, 1 RCT, 2 participants), hypotension (RR 3.04 CI 0.33 to 28.31, 2 RCTs, 119 participants) found no significant difference between GABA drug and placebo.		(9 studies)	very low ^{2,4}	progabide, sodium val- proate and THIP con- tributed to this out- come.	
Mental state: Deterio- ration	Medium risk populat	ion ¹	RR 2.65 (0.71 to 9.86)	121 (6 studies)	⊕⊝⊝⊝ very low ^{2,4}	Studies on baclofen, progabide, sodium val-
follow-up: 3-6 weeks	18 per 1000	46 per 1000 (12 to 173)			•	proate and THIP con-

						tributed to this outcome.
Acceptability of treatment: Leaving	Medium risk popu	ılation ¹	RR 1.47 (0.69 to 3.15)	218 (6 studies)	⊕⊝⊝⊝ very low ^{2,4,5}	Studies on baclofen, progabide and sodium
the study early	75 per 1000 111 per 1000	(0.03 to 0.15)	(o scaares)	very tow-	valproate contributed to this outcome.	
follow-up: 3-6 weeks		(52 to 238)				to this outcome.
Social confidence, so- cial inclusion, social networks, or person- alised quality of life measures	No studies reporte	d 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 95% CI).

CI: Confidence interval; **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 This risk approximately equates with control risk of trial participants.
- ² Downgraded one step for risk of bias.
- ³ Downgraded one step for imprecision: number of events and participants is small.
- ⁴ Downgraded two steps for imprecision: number of events and participants is small, and 95% CIs are wide and include both no effect and appreciable benefit or harm for the intervention.
- ⁵ Downgraded one step for indirectness: Leaving the study early can give an indication of, but is not a direct measure of, acceptability of the treatment.



BACKGROUND

Description of the condition

Tardive dyskinesia (TD) is a movement disorder characterised by abnormal, repetitive and involuntary movements primarily including tongue protrusion, side-to-side or rotatory movement of the jaw, lip smacking, puckering and pursing, and rapid eye blinking (Casey 1999). Its occurrence is estimated to be 20% to 50% of those on long-standing therapy with conventional antipsychotics depending on the characteristics of the population studied (Glazer 2000). Every year 4% to 5% of those who continually use these drugs begin to show signs of TD (APA 1992). Elderly patients are at five to six times greater risk to develop TD (Jeste 2000). This disorder can result in considerable social and physical disability (Barnes 1993).

The exact mechanisms of the pathophysiology of TD are unknown. Many preclinical models, one of them being the dopamine receptor hypersensitivity hypothesis, have been developed to explain the underlying pathophysiology, but none has yet provided an unequivocal explanation (Casey 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. Antipsychotic drugs block certain chemical receptor sites in the brain - one of these is specific for dopamine (Casey 1994). The interaction between antipsychotic drugs and the

dopamine cells has been proposed as the mechanism for their beneficial effects in psychoses as well as the cause of the movement side effects (Jeste 1982). The most interesting and consistent findings regarding candidate gene studies of TD have focused on the dopamine D3 receptor gene (DRD3). Several groups have reported an association between a serineto-glycine polymorphism in exon 1 of the DRD3 gene and TD (Bakker 2006). Specifically, each group found that either the glycine/glycine genotype or the glycine allele conferred an elevated risk for TD compared with serine/serine homozygotes. One study found a high frequency of this type of homozygosity (22% to 24%) among patients with TD compared with the relative under-representation (4% to 6%) of this genotype in patients without TD (Steen 1997). This may be an explanation to the susceptibility for TD development in some but not most patients.

Description of the intervention

There are many drugs in the gamma-aminobutyric acid (GABA) family. Baclofen (Figure 1), gamma-vinyl-GABA, gamma-acetylenic-GABA, progabide, muscimol (Figure 2), sodium valproate (Figure 3), and tetrahydroisoxazolopyridine (THIP) are the focus of this review, and the benzodiazepines, a large group in themselves, have been reviewed elsewhere (Bergman 2018). The GABA agonist drugs have been trialled as a treatment for people with TD, despite their sedative properties, and the possibility that they may exacerbate psychotic symptoms (Barnes 1988; Gardos 1994).

Figure 1. Baclofen

Figure 2. Muscimol



Figure 3. Sodium valproate

How the intervention might work

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). This, in turn, leads to inactivity in another set of cells in the brain, which employ another neurochemical, GABA (Barnes 1993). The GABA agonists supplement the function of these underactive cells. There is also evidence from animal experiments to suggest that GABA dysfunction may be associated with movement disorders (Gunne 1984).

Why it is important to do this review

Several atypical antipsychotic drugs have been produced in the last decades that claim to cause less or no TD (Lieberman 1996). These claims may or may not be true, and certainly evidence does point to the fact that thoughtful use of older generation drugs is not associated with any more problems of TD than with newer treatments (Chouinard 2008). However, in a global context, 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 (WHO Essential List 2010). Use of drugs such as these is associated with emergence of TD and, therefore, TD 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 of benzodiazepines 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 2000 (Soares-Weiser

2000), and previously updated in 2001 (Soares-Weiser 2001), in 2004 (Rathbone 2004) and in 2011 (Alabed 2011).

OBJECTIVES

1. Primary objective

The primary objective was to determine whether using non-benzodiazepine gamma-aminobutyric acid (GABA) agonist drugs for at least six weeks was clinically effective for the treatment of antipsychotic-induced tardive dyskinesia (TD) in people with schizophrenia, schizoaffective disorder or other chronic mental illnesses.

2. Secondary objectives

The secondary objectives were as follows.

- To examine whether any improvement occurred with short periods of intervention (less than six weeks) and, if this did occur, whether this effect was maintained at longer periods of followup.
- 2. To examine whether there was a differential effect between the various compounds.
- 3. To test the hypothesis that GABA agonist drugs are most effective for a younger age group (less than 40 years old).

METHODS

Criteria for considering studies for this review

Types of studies

All relevant randomised controlled trials (RCTs). Where a trial was described as 'double-blind' but it was implied that the study was randomised and the demographic details of each group were similar, we have included it. We excluded quasi-randomised studies, such as those allocated by using alternate days of the week.

Types of participants

People with schizophrenia or other chronic mental illness, diagnosed by any criteria, irrespective of gender, age or nationality who:



- 1. required the use of antipsychotics for more than three months;
- 2. developed TD (diagnosed by any criteria at baseline and at least one other occasion) during antipsychotic treatment; and
- for whom the dose of antipsychotic medication had been stable for one month or more (the same applies for those free of antipsychotics).

Types of interventions

1. The non-benzodiazepine GABA agonist drugs

This includes baclofen, gamma-vinyl-GABA (GVG), gamma-acetylenic-GABA (GAG), muscimol, progabide, sodium valproate and tetrahydroisoxazolopyridinol (THIP): any dose or means of administration

compared with:

a. placebo or no intervention

or

b. any other intervention for the treatment of tardive dyskinesia (TD)

For this current update a post hoc decision was made to also include studies evaluating the above mentioned non-benzodiazepine GABA agonist drugs compared with any other intervention for the treatment of TD.

Types of outcome measures

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

Primary outcomes

1. Tardive dyskinesia (TD)

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

Other than deterioration of symptoms of TD, as reported in the trials - 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.
- $1.4\,\mbox{Average}$ 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. Hospital and service utilisation outcomes

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

6. Economic outcomes

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

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

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

8. Behaviour

- 8.1 Clinically significant agitation.
- 8.2 Use of adjunctive medication for sedation.
- 8.3 Aggression to self or others.

9. Cognitive state

- 9.1 No clinically important change.
- 9.2 No change, general and specific.

'Summary of findings' table

We used the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach to interpret findings (Schünemann 2011) and used GRADEpro to export data from this review to create a 'Summary of findings' table. These tables provide outcome-specific information concerning the overall quality of evidence from each included study in the comparison, the magnitude of effects of interventions examined and the sum of available data on all outcomes rated as important to patient care and decision making. 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 Any improvement
- 1.3 Deteriorated
- 2. Mental state
- 2.1 Deteriorated
- 3. Adverse effect
- 3.1 Any adverse event
- 4. Acceptability of treatment
- 4.1 Leaving the study early



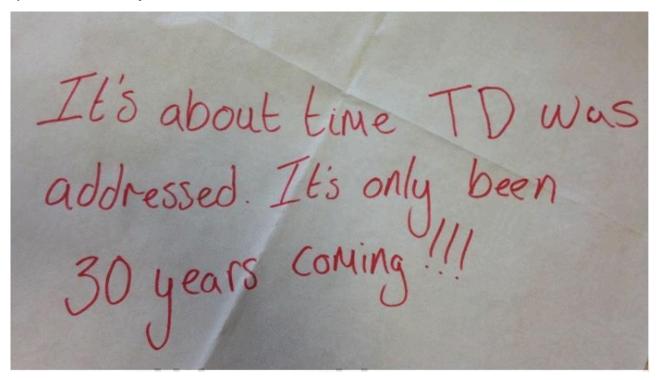
- Social confidence, social inclusion, social networks, or personalised quality of life measures*
- 5.1 No significant change in social confidence, social inclusion, social networks, or personalised quality of life measures for either recipients of care or caregivers

This summary table was used to guide our conclusions and recommendations.

* 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 TD series (Soares-Weiser 2018; Table 1) and a lay overview of the review gave the foundation for the discussions. 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 and have added one figure showing service user expression of frustration concerning this neglected area of research (Figure 4). Informed by the results of the consultation, for this review, we updated outcomes for the 'Summary of findings' table

Figure 4. 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 searches in 2015 and 2017 were carried out in parallel with the updating of eight other TD reviews, see Table 1 for details. The searches covered all nine TD reviews.

1. Cochrane Schizophrenia Group's Register

We searched Cochrane Schizophrenia Group's Study-Based Register of Trials on 16 July 16, 2015 and April 26, 2017 using the following string: *Tardive Dyskinesia* in Healthcare Condition Field of Study. In such a study-based register, searching the major concept retrieves all the synonym keywords and relevant studies because all the studies have already been organised based on their interventions and linked to the relevant topics. The Cochrane Schizophrenia Group's Register of Trials is compiled by systematic searches of major resources (including AMED, BIOSIS, CINAHL, Embase, MEDLINE, PsycINFO, PubMed, and registries of clinical trials) and their monthly updates, handsearches, grey literature, and conference proceedings (see Group's Module). There is no

language, date, document type, or publication status limitations for inclusion of records into the register.

2. Details of previous electronic searches

See Appendix 1.

Searching other resources

1. Reference searching

We searched references of all identified 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 Characteristics of included studies table.



Data collection and analysis

Data collection and analyses methods used by review authors for the 2015 and 2017 searches are listed below. For previous methods please see Appendix 1.

Selection of studies

Rosie Asher (RA) and Antonio Grande (AG) (see Acknowledgements) inspected all abstracts of studies identified as above and identified potentially relevant reports. We resolved disagreements by discussion, or where there was still doubt, we acquired the full-text article for further inspection. We acquired the full-text 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 review author Hanna Bergman (HB) for help and where it was impossible to decide or if adequate information was not available to make a decision, we initially added these studies to those awaiting assessment and contacted the authors of the papers for clarification.

Data extraction and management

1. Extraction

RA and HB independently extracted data from all included studies. Again, we discussed any disagreement and documented decisions. With remaining problems Karla Soares-Weiser (KSW) helped clarify issues and we documented these final decisions. We extracted data presented only in graphs and figures whenever possible, but included only if two review authors 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 this 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); and
- the measuring instrument has not been written or modified by one of the trialists for that particular trial.

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 primarily to 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 (SMD) 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.

Please note, we 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 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 < 200 participants:

(a) when a scale starts from the finite number zero, we subtracted the lowest possible value from the mean, and divided this by the standard deviation (SD). If this value was lower than 1, it strongly suggests a skew and we excluded these data. If this ratio was higher than one but below 2, there is suggestion of skew. We entered these data and tested whether their inclusion or exclusion changed the results substantially. Finally, if the ratio was larger than 2 we 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 modified the calculation described above to take the scale starting point into account. In these cases skew is present if 2 SD > (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 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 2005; Leucht 2005a). 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 GABA agonist drugs. 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

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 5; Figure 5 and Summary of findings for the main comparison.



Figure 5. '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
Ananth 1987	?	?	•	?	•	•	?
Burner 1989	?	?	•	?	•	•	?
Fisk 1987	•	•	•	•	•	•	?
Gerlach 1978	?	?	•	?	?	?	?
Glazer 1985	?	?	?	?	•	•	•
Linnoila 1976	?	?	•	?	•		?
Mei 2008	•	?	•	•	•	?	•
Nair 1978	?	?	?	•	?	•	?
Stewart 1982	?	?	?	?	?	•	?
Thaker 1987	?	?	?	•	•	•	?
Yin 2004	?	?	•	?	•	?	•



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 (Boissel 1999) than odds ratios 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 was 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 poses problems. Firstly, 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 had not been 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 (ICCs) 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 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 ICCs 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 (e.g. 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 involved 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-bytwo table. If data were continuous, we combined data following the formula in section 7.7.3.8 (Combining groups) of 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 of 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 by down-rating quality. We also downgraded quality within the 'Summary of findings' table should loss be 25%-50% in total.

2. Binary

In the case where attrition for a binary outcome was between 0% and 50% and where these data were not clearly described, we presented data on a 'once-randomised-always-analyse' basis (an intention-to-treat (ITT) analysis). We assumed all those leaving the study early had no improvement. We undertook a sensitivity analysis to test how prone the primary outcomes were to change by comparing data only from people who completed the study to that point to the ITT 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 (SDs) 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 (SE) and confidence intervals available for group means, and either a 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 SE is reported, sSDs are calculated by the formula SD = SE * square root (n). Chapters 7.7.3 and 16.1.3 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011) present detailed formulae for estimating SDs from P values, t or F values, confidence intervals, ranges or other statistics. 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 latter methods seem to be somewhat better than LOCF (Leon 2006), we feel that the high percentage of participants leaving the studies early and differences 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 the statistical approach used. However, we preferred to use the more sophisticated approaches. (e.g. MMRM or multipleimputation) 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 I² statistic

We investigated heterogeneity between studies by considering the I² method alongside the Chi² P value. The I² provides an estimate of the percentage of inconsistency thought to be due to chance (Higgins 2003). The importance of the observed value of I² depends on i. magnitude and direction of effects and ii. strength of evidence for heterogeneity (e.g. P value from Chi² test, or a confidence interval for I²). An I² estimate greater than or equal to around 50% accompanied by a statistically significant Chi² 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 did not use 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 for use of fixed-effect or random-effects models. The random-effects method incorporates an assumption that the different studies are estimating different, yet related, intervention effects. This often seems to be true to us and the random-effects model takes into account differences between studies even if there is no statistically significant heterogeneity. There is, however, a disadvantage to the random-effects model. It puts added weight onto small studies which often are the most biased ones. Depending on the direction of effect, these studies can either inflate or deflate the effect size. We chose the fixed-effect model for all analyses.

Subgroup analysis and investigation of heterogeneity

1. Subgroup analyses

1.1 GABA agonist compound

As different GABA agonist compounds may have differential effects on antipsychotic-induced TD, we performed a subgroup analysis to compare the effects of different GABA agonists. We proposed to undertake comparisons only for primary outcomes to minimise the risk of multiple comparisons.

1.2 Younger participants

We anticipated a subgroup analysis to test the hypothesis that the use of GABA agonists is most effective in younger patients (less than 40 years old). We had hoped to present data for this subgroup for the primary outcomes.

1.3 Duration of treatment

We also anticipated a subgroup analysis to examine whether any improvement occurred with short periods of intervention (less than six weeks) and, if this did occur, whether this effect was maintained at longer periods of follow-up.

2. Investigation of heterogeneity

We reported when inconsistency was high. First, we investigated whether data were entered correctly. Second, if data were correct, we visually inspected the graph and successively removed outlying studies 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 discuss the 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 these. 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 analyses 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 followup (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 had 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 to test 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-effect 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

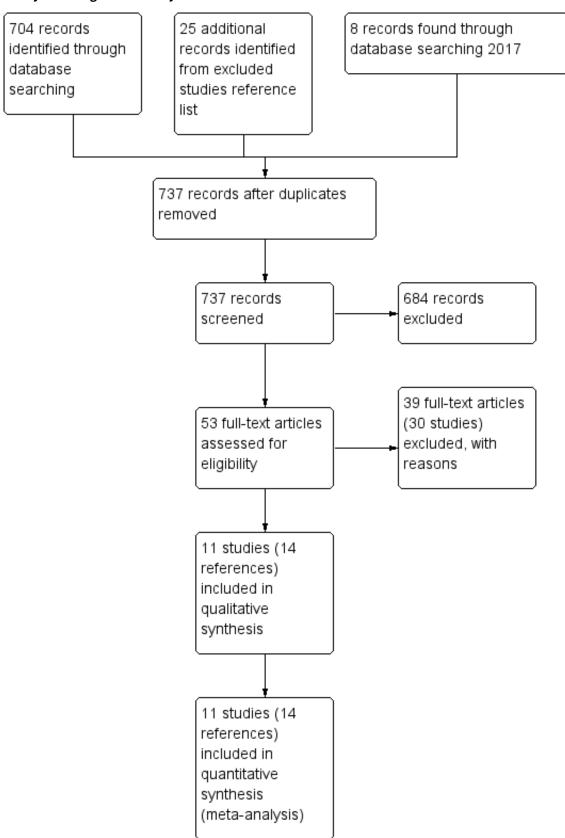
Please see Characteristics of included studies and Characteristics of excluded studies.

Results of the search

The 2015 and 2017 updated searches were part of an update of nine Cochrane reviews, see Table 1. The 2015 search retrieved 704 references for 344 studies, see Figure 6 for study flow diagram. After having excluded irrelevant references at title and abstract screening, we screened full texts of 53 references (41 studies). Two of these studies (Mei 2008; Yin 2004) are new additions in Chinese to the eight already included studies of this review. Another study was previously excluded because only completers were analysed and numbers randomised were not available (Glazer 1985), however, in this update we decided to include it as we thought it might add value to the evidence. As a precaution we conducted sensitivity analyses excluding it (see Effects of interventions). We could also group four previously excluded references into one excluded study (Sikich 1999). The review now contains 30 excluded studies (39 references) and 11 included (14 references); no studies await assessment. As far as the review authors are aware there are no ongoing studies that would be relevant to this review.



Figure 6. Study flow diagram for study selection.





The 2017 search found eight records (five studies). The editorial base of Cochrane Schizophrenia screened these records and no new studies were considered relevant to this review. They could be relevant to the other reviews in this series of tardive dyskinesia (TD) reviews (see Table 1), and have been put into awaiting assessment reference section of the *Miscellaneous treatments for neuroleptic-induced tardive dyskinesia* review Soares-Weiser 2003.

Included studies

The current update of this review now includes 11 studies with 343 participants published between 1976 and 2008. Three of these included studies are new to this update (Glazer 1985; Mei 2008; Yin 2004).

1. Methods

All studies were stated to be randomised and double-blind. In general, however, allocation was poorly described. For further details please see sections below on Allocation and Blinding.

2. Design

All included studies presented a parallel longitudinal design. Five of the 11 studies used a cross-over design (Ananth 1987; Gerlach 1978; Linnoila 1976; Nair 1978, Thaker 1987) with two periods. We had considered this as likely when embarking on the review and have used only the data from before the first cross-over for the reasons outlined above (Unit of analysis issues).

3. Duration

Overall, the length of the trials were short. No study followed people up for longer than eight weeks and five of the 11 relevant studies fell into the short-term category (less than six weeks). Six trials just fell into the medium term category (six to 26 weeks) and lasted between six (Burner 1989; Fisk 1987; Glazer 1985; Stewart 1982; Yin 2004) and eight weeks (Mei 2008).

4. Participants

Participants, now totaling 343 people with diagnoses of various chronic psychiatric disorders, but mainly schizophrenia. All had antipsychotic-induced TD diagnosed using various methods. The number of participants ranged from two to 80 (median 31). People included in relevant trials were commonly quite elderly, with an average age of 50 and over.

5. Setting

Most trials were conducted with hospital inpatients. The studies themselves were from around the world, with four conducted in the USA (Glazer 1985; Nair 1978; Stewart 1982; Thaker 1987), two in China (Mei 2008; Yin 2004), and one each in Finland (Linnoila 1976), Denmark (Gerlach 1978), Canada (Ananth 1987), Switzerland (Burner 1989) and the UK (Fisk 1987).

6. Interventions

6.1 Non-benzodiazepine gamma-aminobutyric acid (GABA) agonist drugs

6.1.1 Baclofen

Baclofen was used in five trials. Ananth 1987 used it in a dose increasing over three days to 40 mg/day, whereas Gerlach 1978 used it in a dose increasing over two weeks to 120 mg/day max; range 20 mg to 120 mg/day. Glazer 1985 used a maximum baclofen

dose of 90 mg/day. It was also used by Nair 1978 in a dose increasing gradually to 90 mg/day. In the Stewart 1982 study the dose was increased over four weeks to 90 mg/day unless efficacy was observed.

6.1.2 Gamma-aminobutyric acid

Two gamma-aminobutyric acid capsules three times per day was used by Mei 2008. the dose was not specified further.

6.1.3 Progabide

Progabide was used by Burner 1989 in the doses 20 mg, 30 mg or 45 mg/kg/day.

6.1.4 Sodium valproate

Sodium valproate was used by Linnoila 1976 in a fixed dose of 900 mg/day and by Fisk 1987 in a dose increasing over six days to 1500 mg/day. Yin 2004 applied doses of between 200 mg/day and 400 mg/day.

6.1.5 THIP

Thaker 1987 used tetrahydroisoxazolopyridinol (THIP) in a dose increasing over five days to 120 mg/day in the first patient and to 60 mg/day in the second patient.

6.2 Comparison group

All studies used placebo as a comparison. None of the included studies compared GABA agonists with another active intervention.

Participants remained on stable schizophrenia treatment antipsychotic medication during the trials.

7. Outcomes

7.1 General

Some outcomes were presented only in graphs, with inexact P values of differences, or a statement of significant or non-significant difference. This made it impossible to acquire raw data for synthesis. Some continuous outcomes could not be extracted due to missing numbers of participants or missing means, standard deviations, or standard errors. All included studies used the LOCF strategy for the ITT analysis of dichotomous data. Details of the scales used in this review to quantify both TD and psychiatric symptoms are provided below. Data from these scales were reported either in continuous form or as binary figures where study authors have stipulated a cut-off point at which they feel an outcome is reached (for example, 'Tardive dyskinesia: not improved to an important extent'). We have accepted these judgements and not cross-checked the cut-off points.

7.2 Scales used to measure TD symptoms

7.2.1 Abnormal Involuntary Movement Scale (AIMS)

This 12-item scale consists of a standard examination followed by questions rating the orofacial, extremity and trunk movements, the dental status, and three global measurements (Guy 1976). Each of these items can be scored from zero (none) to four (severe). The AIMS ranges from four to 40 with higher scores indicating greater severity. This scale was used in Ananth 1987, Glazer 1985, Mei 2008; Nair 1978; Stewart 1982 and Yin 2004.



7.2.2 Abbreviated Dyskinesia Rating Scale - Simpson Rating Scale (SRS)

This 15-item scale measures the movements around the orofacial region, neck, trunk and extremities (Simpson 1979). Each of these items can be scored from one (absent) to six (severe). This scale ranges from 10 to 102 with higher scores indicating greater severity, and was used in Burner 1989.

7.2.3 Gerlach Scoring Scale for Oral Tardive Dyskinesia

This is a videotape technique where the oral movements (lingual and masticatory) are recorded for 10 minutes and evaluated according to their frequency zero to 18), amplitude (zero to six) and duration (zero to three) (Gerlach 1976). This scale was used in Gerlach 1978.

7.3 Scales used to measure mental state and behaviour

7.3.1 Brief Psychiatric Rating Scale (BPRS)

The BPRS is an 18-item scale measuring positive symptoms, general psychopathology and affective symptoms (Overall 1962). The original scale has 16 items, although a revised 18-item scale is commonly used. Total scores can range from zero to 126. Each item is rated on a seven-point scale, with high scores indicating more severe symptoms. This scale was used in Mei 2008.

7.4 Scales used to measure adverse events

7.4.1 Treatment Emergent Symptom Scale (TESS)

This checklist assesses a variety of characteristics for each adverse event, including severity, relationship to the drug, temporal characteristics, contributing factors, course, and action taken to counteract the effect (Guy 1976). Symptoms can be listed a priori or can be recorded as observed by the investigator. High scores indicate worse symptoms. TESS was used in Yin 2004.

Studies awaiting classification

No studies await classification.

Ongoing studies

We know of no ongoing trials.

Excluded studies

We excluded 30 studies (39 references), 16 of which were not randomised: in four RCTs participants did not have TD (Gulmann 1976; Raptis 1990; Sikich 1999; Tamminga 1978), in two RCTs use of antipsychotics was not in stable dosages (Cassady 1992; Tamminga 1979), and two RCTs did not use a relevant intervention, i.e. a GABA agonist (Chiu 2006; Nordic 1986). We excluded other randomised trials including relevant participants and interventions because it was impossible to extract first period data from five cross-over trials (Chien 1978; Friis 1983; Korsgaard 1976; Nasrallah 1986; Tamminga 1983), and because we could extract no data at all from one trial (Frangos 1980). We contacted the authors of five of these studies; one author confirmed the data had been destroyed (Friis 1983), one author replied but did not provide any more data (Tamminga 1983), and three authors did not reply (Frangos 1980; Korsgaard 1976; Nasrallah 1986). We could not identify up-to-date contact details for authors of one of the studies published over 35 years ago (Chien 1978); it was also excluded as we assumed it very unlikely to receive data so many years later.

Risk of bias in included studies

Please refer to Figure 5 for graphical overview of the risk of bias in the included studies.

Allocation

Only one study (Mei 2008) reported explicit details about how randomisation was undertaken (random number table). One set of authors kindly provided information on how randomisation was carried out (stratified, computer program co-ordinated by hospital pharmacists) (Fisk 1987). As a result, we could judge only these two studies to be of reasonable quality within this category. The other nine studies were not explicit about how allocation was achieved other than using the word "randomized"; we classified them as unclear risk of selection of bias.

Blinding

Although all studies stated that they were conducted on a double-blind basis, only seven studies (Ananth 1987; Burner 1989; Fisk 1987; Gerlach 1978; Linnoila 1976; Mei 2008; Yin 2004) explicitly described how this was undertaken and were rated at low risk of performance bias. Only four studies (Fisk 1987; Mei 2008; Nair 1978; Thaker 1987) explicitly described how outcome assessors were blinded and were rated at low risk of detection bias. The remaining studies were rated as unclear risk of performance and detection bias. None of the included studies tested the blindness of raters, clinicians and trial participants.

Incomplete outcome data

No study had a greater than 30% loss to follow-up. Fisk 1987 reported in a mixed population that 24% of participants dropped-out before the end of the intervention. Glazer 1985 did not explicitly state the number of participants enrolled and randomised. These two studies were at high risk of attrition bias.

Selective reporting

The majority of data in this review originates from published reports. Expected outcomes (impact on TD symptoms) were reported for most of the trials, however, in eight trials (Ananth 1987; Burner 1989; Fisk 1987; Glazer 1985; Linnoila 1976; Nair 1978; Stewart 1982; Thaker 1987) the data were insufficiently reported and these studies were rated at high risk of reporting bias. We have had no opportunity to see protocols of the trials to compare the outcomes reported in the full-text publications with what was measured during the conduct of the trial, therefore, the remaining trials were at unclear risk of reporting bias.

Other potential sources of bias

Taking into account the poor description of randomisation and blinding, these studies did not fully minimise the introduction of bias so all findings should be viewed with caution. Many of the studies used small, and sometimes extremely small, sample sizes, which increases the likelihood of treatment effects going undetected. Five of the studies also used a cross-over design (Ananth 1987; Gerlach 1978; Linnoila 1976; Nair 1978, Thaker 1987).

Effects of interventions

See: Summary of findings for the main comparison GABA DRUGS for antipsychotic-induced tardive dyskinesia



1. Comparison: GABA drugs versus placebo

1.1 TD symptoms

We had chosen 'any improvement in tardive dyskinesia symptoms of more than 50% on any tardive dyskinesia 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.

1.1.1 Not improved to a clinically important extent

The overall results for 'clinically relevant improvement' found a small benefit in favour of GABA agonist drugs against placebo across all time points (six to eight weeks) and types of GABA agonist drugs (low-quality evidence, 6 RCTs, n = 258, RR 0.83, CI 0.74 to 0.92, $I^2 = 0\%$, Analysis 1.1).

1.1.2 Not any improvement

For the outcome of 'not any improvement in TD symptoms', again added across all time periods and types of GABA agonist drugs, we found a small difference in favour of GABA agonist drugs against placebo (8 RCTs, n = 271, RR 0.72, CI 0.60 to 0.86, $I^2 = 57\%$, Analysis 1.2).

1.1.3 Average endpoint/change scores

TD symptoms were also measured on different scales (see Included studies above) by five studies. We did not combine data on symptom scores, both endpoint scores and change ratings, as trials used different scales to assess TD that are not directly comparable. Two trials suggested a significant effect for the GABA drugs and three did not (see Analysis 1.3; Analysis 1.4).

1.1.4 Deterioration of symptoms

There was no difference in deterioration of symptoms between GABA agonist drugs compared with placebo (very low-quality evidence, 5 RCTs, n = 136, RR 1.90, CI 0.70 to 5.16, $I^2 = 0\%$, Analysis 1.5).

1.2 Adverse effects

1.2.1 Specific adverse effects

Nine of the 11 trials reported specific adverse effects that are included in the analysis (Analysis 1.6). Ananth 1987 reported that none of the 10 included people suffered adverse effects (baclofen versus placebo study). Unfortunately the reporting of adverse effects in Linnoila 1976 was ambiguous and we could not present data (sodium valproate versus placebo study). Compared with placebo, GABA agonist drugs (baclofen, progabide) resulted in increased dizziness/confusion (3 RCTs, n = 62, RR 4.54, 95% CI 1.14 to 18.11, $I^2 = 0\%$), increased sedation/drowsiness (4 RCTs, n = 144, RR 2.29, 95% CI 1.08 to 4.86, $I^2 = 0\%$), and low platelets (1 RCT, n = 79, RR 17.43 95% CI 1.04 to 291.96). For all other adverse effects (ataxia, loss of muscle tone, nausea/vomiting, restlessness/akathisia, seizures, hypotension, leucocyte decrease) there were no statistically significant differences between GABA agonist drugs and placebo.

In one trial (Thaker 1987) the presence of tonic-clonic seizures after withdrawal of THIP led to the termination of the study (n = 2).

1.3 Mental state

Six trials reported 'deterioration in mental state' as an outcome, two of the trials reported no events. No difference was found for this outcome between GABA agonist drugs and placebo (very low-quality evidence, 6 RCTs, n = 121, RR 2.65, CI 0.71 to 9.86, Analysis 1.7).

One study reported average endpoint Brief Psychiatric Rating Scale (BPRS) score and found no significant difference between GABA agonist and placebo (1 RCT, n = 40, MD 0.03, CI -3.29 to 3.35; Analysis 1.8).

1.4 Leaving the study early

A greater proportion of people allocated GABA medication failed to complete the trial compared with those allocated placebo (13% versus 8%) but this difference was not statistically significant (very low-quality evidence, 6 RCTs, n = 218, RR 1.47 CI 0.69 to 3.15, Analysis 1.9).

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.

1.5 Subgroup analysis

1.5.1 GABA agonist compound

We stratified the primary outcome by type of GABA agonist drug. There was no significant heterogeneity between baclofen, progabide, sodium valproate and GABA ($I^2=0\%$, P=0.54, Analysis 1.1). However, studies evaluating sodium valproate (2 RCTs, n=141, RR 0.86, CI 0.76 to 0.96; $I^2=53\%$) and GABA (RR 0.67, CI 0.45 to 0.98; 40 participants; 1 study) found significant differences favouring GABA drug, whereas studies evaluating baclofen (2 RCTs, n=64, RR 0.89, CI 0.70 to 1.13; $I^2=0\%$) and progabide (1 RCT, n=13, RR 0.68, CI 0.36 to 1.25) found no significant differences.

1.5.2 Younger participants

It was not possible to evaluate whether those younger than 40 years old responded differently compared to older participants, since no trial reported data for different age groups that could be extracted for separate analyses.

1.5.3 Duration of treatment

It was not possible to ascertain the medium- or long-term effects of these drugs since all trials reporting data on the primary outcome reported at medium term (six to eight weeks).

1.6 Heterogeneity

Data were homogeneous. We did not detect clinical, methodological or statistical heterogeneity as described in Assessment of heterogeneity.

1.7 Sensitivity analyses

1.7.1 Implication of randomisation

We aimed to include trials in a sensitivity analysis if they were described in some way as to imply randomisation. As all studies were stated to be randomised we did not undertake this sensitivity analysis.



1.7.2 Assumptions for lost binary data

The above results are based on data as presented in the original study reports, with the assumption that those who left early before the end of the trial had not improved (see Dealing with missing data). When the sensitivity of the results to this assumption was tested, we found no appreciable differences in the results. Using completer-only data for no clinically important improvement in TD symptoms, we found that the direction of effect in favour of GABA agonist drugs did not change, though there was a minor shift in the effect estimate and the precision of the effect estimate (RR 0.81, Cl 0.72 to 0.91; 239 participants; six studies, analysis not shown). If there had been a substantial difference, we would have reported results and discussed them but continued to employ our assumption.

1.7.3 Risk of bias

When excluding two trials that we judged to be at high risk of bias across one or more of the domains (Fisk 1987; Glazer 1985), there was no substantial alteration to the direction of effect or the precision of the effect estimates (4 RCTs, n = 165, RR 0.78, Cl 0.67 to 0.90; analysis not shown).

1.7.4 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 intra-class correlation coefficients (ICCs) in calculating the design effect. No cluster-randomised trials were included.

1.7.5 Fixed and random effects

We also synthesised data for the primary outcome using a random-effects model. This did not alter the significance of the results (6 RCTs, n = 258; RR 0.85, CI 0.77 to 0.94).

1.7.6 Study with unknown number of randomised participants

One study (Glazer 1985) had an unknown number of participants randomised, and study authors could not provide this information as data had been destroyed (communicated to review authors of a previous version of this review). For this update we nevertheless decided to include this study, but carried out sensitivity analyses examining the impact of this study. There were no substantial alterations to the direction of effects or the precision of the effect estimates when this study was excluded from analyses.

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 most trials predate the year 2000, only two were carried out after then, published in 2004 and 2008. This could be because of reasons such as less concern with tardive dyskinesia (TD), or less emergence of the problem in research-active communities because of more thoughtful use of antipsychotic drugs, or loss of faith in GABA agonists as a potential treatment.

2. Few data

Only a little under 350 people have been involved in placebo-controlled trials of GABA agonists for TD. It is possible that real, and important, effects have not been highlighted because of the necessarily wide confidence intervals (CIs) of the findings. Many outcomes were not measured at all (see Overall completeness and applicability of evidence), including one of our pre-stated outcome measures. We may have been overambitious in hoping for some of these outcomes in TD trials but simple reporting of satisfaction with care or quality of life still does not seem too demanding and does remain of interest.

3. Comparison 1: GABA agonist drugs versus placebo

3.1 TD symptoms

There was low-quality evidence from six trials that there may be a clinically important improvement in TD symptoms after GABA agonist treatment compared with placebo at six to eight weeks follow-up (6 RCTs, n = 258, RR 0.83, CI 0.74 to 0.92). The evidence on deterioration of TD symptoms was of very low quality (5 RCTs, n = 136, RR 1.90, CI 0.70 to 5.16).

3.2 Adverse effects

All GABA agonist drugs are associated with adverse effects and a possible deleterious (harmful to the mind or body) effect on people's mental state. Even with the very limited data in this review, there are suggestions that these adverse effects could be prohibitive of use of GABA agonist drugs. Adverse effects seem to be a major problem for these drugs when used for people with antipsychotic-induced TD. Traditional reviews have also reported that high side-effect rates limit the use of GABA agonists (APA 1992; Jeste 1988).

3.3 Mental state

Seven trials reported on mental state. Six reported on number of participants that experienced a deterioration in mental state, and one trial used the Brief Psychiatric Rating Scale (BPRS) scale. There was no suggestion that GABA agonists had any more effect on mental state than placebo (very low-quality evidence, RR 2.65, CI 0.71 to 9.86; 6 RCTs, 121 people).

3.4 Leaving the study early

It is always unclear what leaving the study early means. It could be to do with the participant not accepting treatment for a series of reasons, or of participants finding the trial intolerable. It also could be a function of a trial design in which willing participants are still asked to leave because of some degree of protocol violation. In any event, around 10% of people left the study early, and this was not significantly different for those allocated to either group (6 RCTs, n = 218, RR 1.47, CI 0.69 to 3.15).

3.5 Social confidence, social inclusion, social networks, or personalised quality of life

This group of outcomes was selected as being of importance to patients for the 2016 review update following a service user consultation. No studies were identified that reported on any of these outcomes.



Overall completeness and applicability of evidence

1. Completeness

The majority of studies had a duration of less than six weeks, whilst only three actually had a duration of six weeks. Whether the effects of the drugs were maintained at longer periods of follow-up may therefore be under-reported in short-term studies.

Outcome reporting was mainly symptom- and physician-oriented. Patient-oriented global and functional outcomes, such as social functioning, ability to work, patient and carer satisfaction and family burden were not reported. There is clearly a need for studies focusing not only on symptoms, but also on general and social functioning, family burden and patient acceptability.

Overall, sample sizes in relevant studies were particularly small and the completeness of evidence for those suffering from antipsychotic-induced TD is poor.

2. Applicability

The setting of trials were a mixture of inpatient and outpatient, reflecting the situation of most people with antipsychotic-induced TD.

Quality of the evidence

All of the trials are small and prone to multiple biases. The largest trial in this area randomised only 80 people. A trial of this size is unable to detect subtle, yet important differences due to GABA agonists with any confidence. Overall, the quality of reporting of these trials was poor (see Figure 5). Allocation concealment was not described, generation of the sequence was not explicit, studies were not clearly blinded. We are also unsure if data are incomplete or selectively reported or if other biases were operating. The small trial size, along with the poor reporting of trials, would be associated with an exaggeration of effect of the experimental treatment (Jűni 2001) if an effect had been detected. This is only evident for the outcome of 'Tardive dyskinesia: Not improved to a clinically important extent' where there is indeed an effect favouring the GABA agonist drug group. This interesting finding may be real – but could equally be a function of biases or of chance.

Potential biases in the review process

1. Missing studies

Every effort was made to identify relevant trials. However, these studies are all 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 GABA agonist 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 think the 'Summary of findings' table to be 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 review author (HB) to select outcomes relevant for this table before becoming familiar with the data.

Agreements and disagreements with other studies or reviews

This review substantially updates and largely concurs with findings from the previous version of this review (Alabed 2011). Previous reviews concluded that approximately 50% of those who use GABA agonists for TD show some improvement (APA 1992; Jeste 1988). These reviews probably overestimate the positive effects of these treatments. This systematic review suggests that the difference in improvement rates between those who received the GABA intervention and those who received placebo was, if present at all, around 15%.

AUTHORS' CONCLUSIONS

Implications for practice

1. For people with antipsychotic-induced tardive dyskinesia (TD)

Currently, evidence of any positive effect of baclofen, progabide, sodium valproate or THIP (tetrahydroisoxazolopyridinol) for people with antipsychotic-induced TD is weak. It would seem advisable to take such medications only if the problem is intractable and in the context of a well-designed study.

2. For clinicians

Any possible benefits are likely to be outweighed by the adverse effects associated with the use of these drugs. This category of drugs should be used as a last resort and THIP should not be used at all. The experimental use of these drugs, and their current use will always be experimental, should be in the context of a well-designed study.

3. For funders and policy makers

It seems evident that there are better projects for funders to invest support in. These compounds should represent a policy of last resort. 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. Destruction of data

Authors have destroyed data from relevant studies conducted only nine years before being requested for the first version of this review (Ananth 1987; Friis 1983; Glazer 1985 - personal communication). It would be helpful for trialists to archive their data, in perpetuity, to allow them to be used to their full value. This would help give recognition to the important, and often pioneering, work of researchers.

2. Incomplete reporting

Randomised trials in this review were poorly or incompletely reported. Assumptions about the allocation of people who left early



had to be made in order to allow intention-to-treat (ITT) analyses. Only two studies specified how randomisation was undertaken (Fisk 1987; Mei 2008). In one trial, personal communication with the principal investigator clarified that people who left early during the intervention were excluded from final analysis (Glazer 1985), and that it was unclear exactly how many were initially randomised. Complete reporting of both methodological details and information about those who entered but did not complete the study would be helpful.

3. Study design

All included studies used the treatments for no longer than eight weeks and for small groups of people (fewer than 40 people in each group). Half the included trials used a cross-over design. This design is not well-suited to evaluate interventions for TD. Brief interventions make the detection of change difficult to separate out from background variations, and there is a high risk of carryover effects after people have received active treatment. Another problem to be considered is the use of different scales to measure the symptoms of TD. These scales have been validated to measure the severity of the TD symptoms, but their use to measure change directly related to treatment is less clear (Bergen 1984). Poor design influences the estimation of treatment effects in trials and systematic reviews (Schulz 1995). Based on the weak and unpromising evidence of positive effects and the known adverse effects of GABA agonists, we believe that the drugs in this review are not good candidates for future trials and therefore discourage further investigations into them.

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1. Original review

Without John McGrath (Brisbane, Queensland, Australia), it is difficult to know if this review would have happened. He was a

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2. 2010 update

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Throughout the Methods section, the generic text found in the reviews of the Cochrane Schizophrenia Group was used and modified to the needs of this review.

3. 2016 update

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Ananth 1987

Methods	drug baclofen or an ine Design: cross-over (eac	e medication was supplied in identical capsules containing 10 mg of the active ert substance, placebo." h preceded by 1 week washout). ital, St Anne de Bellevue, Quebec, Canada.
Participants	structured neurologica	ia (no criteria). TD on the basis of the chart diagnoses, clinical interviews, and l examinations performed independently by three psychiatrists; buccolingual as its, in addition to involuntary movements in other parts of the body. orted.
	N = 10. Sex: 10 male. Age: mean 39 years, rar	nge 30-58 years
Interventions	1. Baclofen: dose day 1	20 mg/d; dose day 2, 30 mg/d; dose day 3 onwards 40 mg/d for 4 weeks. N = 5
	2. Placebo. N = 5.	
	Stable dose of antipsyo within two months prio	chotic medication: an exclusion criteria was change in the antipsychotic dosage or to inclusion.
	All patients were on an to the study.	tiparkinsonian (trihexyphenidyl or benzotropine) agents at the time of entry in
Outcomes	TD symptoms: AIMS, de Adverse effects.	eterioration of symptoms.
	Leaving the study early Mental state: BPRS.	
Notes	Sponsorship source: Sp	ponsorship source not reported
	No information about of Authors contacted. Date	compliance. a destroyed - no more information available.
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"patients were randomly assigned", further details not reported.



Ananth 1987 (Continued)		
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported.
Blinding of participants and personnel (perfor- mance bias) All outcomes	Low risk	"The medication was supplied in identical capsules containing 10 mg of the active drug baclofen or an inert substance, placebo."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	TD symptoms and mental state: Blinding details of outcome assessors not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants seem to have completed the trial. Results for all 10 participants (in the two periods of the cross-over trial) have been reported.
Selective reporting (reporting bias)	High risk	AIMS, BPRS scores have not been reported as mean (SD) but as total scores.
Other bias	Unclear risk	Insufficient information to make a judgement. Very small sample size.

Burner 1989

Methods	Allocation: randomly allocated, not described. Blindness: double, described, adequate
	Design: parallel group
	Setting: not reported Duration: 6 weeks (preceded by 1 week washout).
Participants	Diagnosis: schizophrenia (ICD-9), manic depressive illness (ICD-9) and antipsychotic induced TD.
	Duration of TD: 2-13 years. N = 13. Sex: 7 male and 5 female, 1 not specified. Age: mean 56 years.
Interventions	1. Progabide: dose 20 mg, 30 mg or 45 mg/kg/day for 6 weeks. N = 10.
	2. Placebo. N = 3.
	Stable but unspecified dose of antipsychotic drugs; benzodiazepines not permitted.
Outcomes	TD symptoms: SRS. Adverse effects. Leaving study early. Mental state: BPRS.
Notes	Sponsorship source: Sponsorship source not reported. However, all but the first author are affiliated with Synthelabo-Recherche.
	Duration of TD longer in placebo group. 1 person left progabide group early (day 19) - confusional state & depressive symptoms. Person with manic-depressive illness (1) not possible to separate from final analysis.
Risk of bias	



Burner 1989 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"patients were randomly enrolled", further details not reported.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported.
Blinding of participants and personnel (perfor- mance bias) All outcomes	Low risk	"double-blind" "They received progabide (20, 30, or 45 mg/kg/day) or placebo as identical capsules for 6 weeks."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Response to treatment was assessed on a weekly basis by the investigator", no further details reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	"One patient dropped out of the progabide group (45 mg/kg/day) on day 19 because of a confusional state and depressive symptoms. This patient was the only one who suffered from manic-depressive psychosis. The other 12 patients completed the study."
		Dropout rate: 8%. 1/10 in the progabide and 0/3 in the placebo group. Reason reported.
Selective reporting (reporting bias)	High risk	"Response to treatment was assessed on a weekly basis by the investigator using the Simpson Rating Scale and the therapeutic effect item from the Clinical Global Impression Scale"
		Data for CGI not reported. Also, SRS and BPRS data not reported as mean (SD).
Other bias	Unclear risk	Very small sample size. The duration of dyskinesia was longer in the placebo group (mean 92 vs. 49.4 months).

Fisk 1987

15K 2501	
Methods	Allocation: randomised, described. Blindness: double, described.
	Design: parallel group
	Duration: 6 weeks baseline, followed by 6 weeks treatment.
	Setting: Inpatients and outpatients from three mental hospitals, UK.
	Compliance: assessed by records or tablet returns.
Participants	Diagnosis: schizophrenia, manic-depressive illness and recurrent depression (no criteria) and antipsychotic induced TD, defined by a score of two or more on the central portion of the BRS. Duration of TD: at least 6 months.
	N = 62. Sex: 42 males and 20 females. Age: mean age 58.1(SD 8.83) years.
Interventions	1. Sodium valproate: dose increasing over 6 days to 1500 mg/day for 12 weeks. People < 50 kg received 1200 mg/day. N = 33.



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2. Placebo. N = 29.

Stable dose of antipsychotic medication: dose (CPE) < 300 mg/day (SV = 12; Pl = 9); 300 mg to 900 mg/ day (SV = 17; Pl = 12); > 900 mg/day (SV = 4; Pl = 8). Benzodiazapines and anticholinergic medication permitted.

Outcomes TD symptoms: BRS, SRS.

Adverse effects. Leaving study early.

Mental state: Krawiecka Scale.

Notes Sponsorship source: Sanofi-Labaz (UK)

Not possible to separate people with manic-depressive psychosis or recurrent depression from the

15 people left early (11 on SV group and 4 on Pl); reasons - protocol violation, poor compliance, ill-

health, pneumonia, unstable medication.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Trial entrants were randomised between SV and placebo treatment groups, with stratification for age, sex, hospital, in-patient or community-based status, and high or low pretrial TD, using a computer program"
Allocation concealment (selection bias)	Low risk	"Hospital pharmacists acted as coordinators of treatment dispensation with emergency access to treatment allocation."
Blinding of participants and personnel (perfor- mance bias) All outcomes	Low risk	"Double-blind procedures were used throughout. Medication was pre packed and labelled with the patient's name." "Hospital pharmacists acted as coordinators of treatment dispensation"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	As treatment was assigned by the central pharmacist and medications were prepackaged, it seems that everybody including the outcome assessors (except the pharmacist) were blind to treatment group. Moreover: "In addition to a 'live' TD rate each patient was videotaped simultaneously, Thus, each patient was videotaped in a standard environment and was given a standard task. The videotapes were used to provide two further blind TD ratings by experienced independent raters."
Incomplete outcome data (attrition bias) All outcomes	High risk	Not possible to separate people with manic-depressive psychosis or recurrent depression from the analysis. 15 people left early (11 in sodium valproate group and 4 on placebo); reasons - protocol violation, poor compliance, ill, pneumonia, unstable medication. Details not reported per intervention group.
Selective reporting (reporting bias)	High risk	TD outcomes not reported as mean (SD); fig 1 report only means. For TD symptoms and mental state, only, improvement and deterioration data reported. Adverse effects fully reported, leaving the study early: reasons not reported per intervention group.
Other bias	Unclear risk	Small sample size; similar baseline characteristics: "A check on randomisation showed no significant difference between SV and placebo treatment groups for age, sex, in-patient vs community-patient status, diagnosis, duration of antipsychotic treatment, maintenance medication level and type of medication."



Methods	Allocation: randomised - no further information.
Metrious	Blindness: double, not described.
	Design: two period cross-over (no washout).
	Duration: 3 weeks in each period.
	Setting: inpatients, Denmark.
Participants	Diagnosis: schizophrenia, manic-depressive illness, dementia and chronic alcoholism (no criteria) and antipsychotic induced TD.
	Duration of TD: not reported.
	N = 20.
	Sex: 15 males and 3 females, 2 not specified.
	Age: median 66 years, range 47- 79 years.
Interventions	1. Baclofen: dose increasing over 2 weeks to 120 mg/day max; range 20 mg to 120 mg/day. N = 10.
	2. Placebo. N = 8.
	Stable but unspecified dose of antipsychotic medication.
	Anticholinergics and benzodiazepines allowed.
Outcomes	TD symptoms: GRS.
	Adverse effects.
	Leaving study early.
	Behaviour: NOSIE.
Notes	Source of support: Baclofen and placebo tablets were supplied by Ciba-Geigy Ltd.
	2 people left study early (refusal to continue medication); unclear about the treatment status of these
	people.
	Not possible to separate people with manic-depressive, dementia or chronic alcoholism from the analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Random allocation", no further details.
Allocation concealment (selection bias)	Unclear risk	No further details.
Blinding of participants and personnel (perfor- mance bias) All outcomes	Low risk	"Double" "Baclofen, 10 mg, and placebo were administered in tablets of identical appearance"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"The patients were evaluated by means of live and video-taped interviews, first before the study, then weekly during the two treatment phases"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Two people left study early (refusal to continue medication); unclear about the treatment status of these people. Not possible to separate people with manic-depressive, dementia or chronic alcoholism from the analysis.



Gerlach 1978 (Continued)		
Selective reporting (reporting bias)	Unclear risk	Unclear if all outcomes have been reported.
Other bias	Unclear risk	The groups seem to have been similar in their baseline characteristics (except for diagnosis). Very small sample size; cross-over design.

Glazer 1985

Methods	Allocation: randomised.
	Blindness: double.
	Design: parallel.
	Duration: 6 weeks.
	Setting: TD Clinic at the Connecticut Mental Health Center, Yale University School of Medicine.
Participants	Diagnosis: schizophrenia (25), schizoaffective disorder (4), other; unspecified (2). antipsychotic medication for at least 6 months; TD (AIMS) for at least 6 months prior to the study.
	Duration of TD: around 2 years.
	N = 31.
	Sex: 16 male and 15 female.
	Age: baclofen, 46.5 (SD 12.2) years; range 27-65 years. Placebo, 47.1 (SD14.1) years; range 26-67 years.
Interventions	1. Baclofen: maximum dose 90 mg/d for 6 weeks. N = 16 (completers).*
	2. Placebo: 6 weeks. N = 15 (completers).*
	Doses of antipsychotic medications stable for at least 4 weeks prior to randomisation. During the study, patients were maintained on the dose of antipsychotic medication that they were on upon entry into the study.
	Concomitant medication: not reported.
Outcomes	TD symptoms: AIMS.
	Mental state.
	Adverse effects.
Notes	Sponsorship source: Supported in part by NIMH and CIBA-GEIGY Corporation.
	"Patients were dropped from the study if poor compliance was suspected."
	*No information about numbers initially randomised (only those completing were analysed); authors contacted and confirmed that those who left early were not included in analyses. No additional data.
Risk of bias	
Rias	Authors' judgement Support for judgement

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomized" Details not reported



Glazer 1985 (Continued)		
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported.
Blinding of participants and personnel (perfor- mance bias) All outcomes	Unclear risk	"double-blind" Details not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	TD symptoms and mental state: "double-blind". Details not reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	Number of participants enrolled and randomised to each group not reported. Only participants who completed were reported and analysed.
Selective reporting (reporting bias)	High risk	TD symptoms (total AIMS scores) reported as means only.
Other bias	Low risk	Mean duration of TD, antipsychotic use (dose), mean duration of psychiatric diagnoses, and psychiatric diagnoses reported for both groups are similar. The study seems to be free of other sources of bias.

Linnoila 1976

Methods	Allocation: randomised, using 2 X 2 Latin square. Blindness: double. Design: two period cross-over (no washout). Duration: 1 week each period. Setting: Psychogeriatric unit of Koskela Geriatric Hospital, Helsinki, Finland.
Participants	Diagnosis: schizophrenia (DSM-III), dementia and other psychosis and antipsychotic-induced TD.
	Duration of TD: at least one year prior to the study. N = 32.
	Sex: 8 males and 23 females, 1 not specified. Age: hospital 1: mean 78 (SD 6) years; hospital 2: mean 62 (SD 13) years.
Interventions	1. Sodium valproate: dose fixed 900 mg/day. N = 16.
	2. Placebo. N = 16.
	Stable but unspecified dose of antipsychotic medication.
	Concomitant medication: not reported.
Outcomes	TD symptoms. Leaving study early. Mental state: BPRS.
Notes	Sponsorship source: Sponsorship source not reported
	Rated orofacial dyskinesia: range 0 (no dyskinesia) - 3 (severe). 1 person left early (valproate). Not possible to separate people with dementia or other psychosis from the analysis.



Linnoila 1976 (Continued)

Authors contacted and provided more information about randomisation procedure. No other data available.

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The patients were allocated to the treatments using a 2 X 2 Latin square design."
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported.
Blinding of participants and personnel (perfor- mance bias) All outcomes	Low risk	"The design of the experiment was double blind, cross-over, and without a wash-out period. The placebo used was lactose in tablets identical with the active drug."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind. Details of outcome assessor blinding not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	"One patient in the geriatric group was not willing to continue sodium valproate after a two-day administration." 3%(1/32) dropout. Group and reason reported. Cross-over period not reported.
Selective reporting (reporting bias)	High risk	TD symptom outcomes (Primary outcome) have not been reported as mean (SD). Adverse effects not reported.
Other bias	Unclear risk	Small sample size; cross-over design.

Mei 2008

Methods	Allocation: "random number table" Blinding: "double-blind" "The interventions were coded as intervention I or II by the researcher. Participants and personnel did not know the allocation result." "The two drugs were contained in capsules with same appearance" "The outcome assessor did not know the group assignment" Duration: 8 weeks Setting: "inpatients", China		
Participants	Diagnosis: Patients with schizophrenia (CCMD-3) and antipsychotics-induced TD (Schooler 1982).		
	Duration of TD: mean 3.6 (2.3) years.		
	N = 40		
	Sex: not reported.		
	Age: mean 43 (SD 7) years old.		
Interventions	1. Gamma-aminobutyric acid: two capsules each time, three times per day for 8 weeks. N = 20		
	2. Placebo Group: two capsules each time, three times per day for 8 weeks. N = 20		
	All participants received stable doses of antipsychotics. Other concomitant medication was not reported.		



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Outcomes TD symptoms: clinical response, AIMS.

Mental state: BPRS.

Adverse events: orthostatic hypotension, diarrhoea.

Notes Funding source: not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"random number table"
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel (perfor- mance bias) All outcomes	Low risk	"double blind" "The interventions were coded as intervention I or II by the researcher. Participants and personnel did not know the allocation result." "The two drugs were contained in capsules with same appearance" Blinding of participants and key study personnel ensured.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The outcome assessor did not know the group assignment." Blinding of outcome assessor ensured.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study.
Selective reporting (reporting bias)	Unclear risk	Unclear if all outcomes have been reported.
Other bias	Low risk	None obvious.

Nair 1978

Methods	Allocation: randomised - no further information. Blindness: double, no details. Design: cross-over. Duration: 8 weeks (3 weeks followed by 2 weeks placebo and then crossed over to another 3 weeks). Setting: Norristown State Hospital, USA.
Participants	Diagnosis: schizophrenia (no criteria) and antipsychotic induced TD. Duration of TD: not reported.
	N = 10. Sex: 5 males, 5 females. Age: average 56 years, range 40-64.
Interventions	1. Baclofen: dose increasing gradually to 90 mg/day. N = 5.
	2. Placebo. N = 5.
	Antipsychotic medication free for > 3 months, other concomitant mediation was not reported.
Outcomes	TD symptoms: AIMS (unable to use - not reported for phase before crossing over separately).



Nair 1978 (Continued)	Adverse effects.			
Notes	Data about improvement and compliance not possible to extract. Authors contacted but have not replied.			
Risk of bias				
Bias	Authors' judgement	Support for judgement		
Random sequence generation (selection bias)	Unclear risk	"Random allocation", no further details.		
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported.		
Blinding of participants and personnel (perfor- mance bias) All outcomes	Unclear risk	"double blind" no details reported.		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Interviews using the Abnormal Involuntary Movement Scale (AIMS) were videotaped to assess response. Coded tapes were rated under blind conditions."		
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Attrition data not reported.		
Selective reporting (reporting bias)	High risk	Data about improvement not possible to extract.		
Other bias	Unclear risk	Very small sample size; cross-over design.		
Stewart 1982				
Methods	Allocation: randomised - sequential assignment determined by prepackaged medication bottles. Blindness: double, no details Design: parallel group. Duration: 6 weeks (no washout).			
	Setting: not reported.			
Participants	Diagnosis: schizophrenia, major depressive disorder and neurosis (no criteria) and antipsychological TD.			
	Duration of TD: not rep N = 36. Sex: 25 males and 11 fe Age: mean 52 years.			
Interventions	1. Baclofen: dose incre	asing over 4 weeks to 90 mg/day unless efficacy observed. N = 14.		
	2. Placebo. N = 19.			
	Stable but unspecified dose of antipsychotic medication.			
	Concomitant medicati	on: not reported.		



Stewart 1982 (Continue	uec	ontinu	(Co	2	36	19	rt	ıa	ew	SI
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Outcomes TD symptoms: AIMS.

Mental state: BPRS.

General improvement: CGI.

Adverse effects. Leaving study early.

Notes Not possible to separate people with major depressive disorder or neurosis from analysis.

3 (1 baclofen) people left study early due to poor compliance, protocol violation, adverse reactions.

Risk of bias

Bias	Authors' judgement	Support for judgement	
Random sequence generation (selection bias)	Unclear risk	"Random allocation", sequential assignment determined by prepackaged medication bottles.	
Allocation concealment (selection bias)	Unclear risk	No details.	
Blinding of participants and personnel (perfor- mance bias) All outcomes	Unclear risk	"double blind" No further details	
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"double blind" No further details	
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	3 (1 baclofen) people left study early due to poor compliance, protocol violation, adverse reactions. No further details were given about these patients.	
Selective reporting (reporting bias)	High risk	BPRS results not reported.	
Other bias	Unclear risk	Small sample size; the base-line characteristics of the 33 patients who entered the double-blind study were similar in both treatment groups.	

Thaker 1987

Methods	Allocation: randomised - no further information. Blindness: double. Duration: 3 weeks each period. Design: two period cross-over (preceded by 1-2 weeks washout). Setting: Inpatients at psychiatric facility, USA
Participants	Diagnosis: schizophrenia (DSM-III) and antipsychotic induced TD, stable dyskinesia ratings (< 20% variation). Duration of TD: not reported.
	N = 9. Sex: 5 male and 4 female. Age: range 22-36.
Interventions	First study



Thaker 1987 (Continued)

1. Gamma-vinyl gamma aminobutyric acid (GVG): dose titrated over 5 days: from 250 mg/d to a maximum dose of 3000 mg/d for three weeks. N = 7.

2. Placebo. N = 7.

Free of antipsychotic medication for > 5 weeks.

Concomitant medication not reported.

Second study

1. THIP: dose increasing over 5 days to 120 mg/day (patient 1); 60 mg/day (patient 2). N = 1.

2. Placebo. N = 1.

Antipsychotic free at least 4 weeks prior to study.

Concomitant medication not reported.

Outcomes TD symptoms: SEPS.

Mental state: BPRS.

Adverse effects.

Notes No person left study early.

THIP produced mental state change and tonic-clonic seizures 8 days after its withdrawal.

Risk of bias

Bias	Authors' judgement	Support for judgement	
Random sequence generation (selection bias)	Unclear risk	"The order of drug and placebo periods was randomized", no further details reported.	
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported	
Blinding of participants and personnel (perfor- mance bias) All outcomes	Unclear risk	"patients, staff, and evaluators were blind to the treatment course." Further blinding details not reported.	
Blinding of outcome assessment (detection bias) All outcomes	Low risk	TD symptoms and Mental state: "evaluators were blind to the treatment course."	
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the trial.	
Selective reporting (reporting bias)	High risk	Not all outcomes have been reported. TD symptoms outcome data reported for the whole population (not per period) in the GVG trial and not reported in the THIP trial. Improvement data not reported for placebo groups.	
Other bias	Unclear risk	Very small sample size; cross-over design. Insufficient information to make a judgement	



/in 2004	
Methods	Allocation: "randomly assigned". Blinding: "double blind" "the sodium valproate and starch placebo were enclosed in capsule with same appearance, the interventions were coded by researchers as drug I and drug II". Duration: 6 weeks.
	Location: inpatients, China.
Participants	Diagnosis: Antipsychotics-induced TD (Schooler criteria).
	Duration of TD: not reported.
	N = 80.
	Sex: 80 male.
	Age: mean 44 (SD 8) years old.
Interventions	1. Sodium valproate group: The initial dosage of sodium valproate was 0.2 g each time, three times per day; after 4 weeks if no adverse events, the dosage was titrated to 0.4 g each time, three times a day for 2 weeks, the treatment lasted for 6 weeks. N = 40.
	2. Placebo group: starch capsule was the placebo treatment for 6 weeks. N = 40.
	All participants received stable doses of antipsychotics. Other concomitant medication was not reported.
Outcomes	TD clinical response. TD: AIMS. Mental state: BPRS. Adverse events: TESS, hypotension and disturbance of consciousness, leukocyte decrease, low platele count.
Notes	Funding source: not reported.
Risk of bias	
Bias	Authors' judgement Support for judgement

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly assigned", no further details
Allocation concealment (selection bias)	Unclear risk	The author did not state the method of allocation concealment.
Blinding of participants and personnel (perfor- mance bias) All outcomes	Low risk	"double blind" "the sodium valproate and starch placebo were enclosed in capsule with same appearance, the interventions were coded by researchers as drug I and drug II": Blinding of participants and key study personnel ensured.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	Low risk	One participant in the treatment group left the study early.
Selective reporting (reporting bias)	Unclear risk	Unclear if all outcomes have been reported.



Yin 2004 (Continued)

Other bias Low risk None obvious.

TD - tardive dyskinesia

TD scales

AIMS - Abnormal Involuntary Movement Scale.

BRS - Barnes & Kidger Rating Scale.

GRS - Gerlach Rating Scale.

SEPS - Smith Extrapyramidal Scale.

SRS - Simpson Rating Scale.

Global state scales

CGI - Clinical Global Improvement

Mental/behaviour state scales

BPRS - Brief Psychiatric Rating Scale

NOSIE - Nurses Observation Scale for Inpatient Evaluation

General scales

TESS - Treatment Emergent Symptom Scale

Medication abbreviations

CPE - chlorpromazine equivalent dosages

GVG - Gamma-vynil GABA

SV - Sodium valproate

THIP - tetrahydroisoxazolopyridinol

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Casey 1979	Allocation: not randomised, cohort study.
Casey 1980	Allocation: not randomised.
Cassady 1992	Allocation: randomised. Participants: people with TD. Intervention: muscimol versus placebo, unstable dose of antipsychotic drugs. Outcomes: only reported after 2 hours
Cassady 1993	Allocation: not randomised, ABA study.
Chien 1978	Allocation: randomised. Participants: people with TD. Intervention: sodium valproate versus oxypertine versus deanol. Outcomes: Unable to extract data from first cross-over phase (TD improvement, AIMS, Leaving the study early). We were unable to identify up-to-date study author contact details for this over 35-year old study.
Chiu 2006	Allocation: randomised, cross-over design. Participants: people with Schizophrenia. Interventions: ginseng versus placebo, not GABA agonist.
Danion 1984	Allocation: not randomised.
Frangos 1980	Allocation: randomised. Participants: people with TD. Intervention: baclofen versus placebo. Outcomes: not possible to extract data; published only as a conference proceeding - authors contacted in 1996 and did not reply.
Friis 1983	Allocation: randomised, cross-over design.



Study	Reason for exclusion
	Participants: people with TD. Interventions: valproate versus biperiden versus placebo. Outcomes: no data from first period; Dr Gerlach contacted and replied promptly; data were destroyed and no more information is available.
Gibson 1978	Allocation: not randomised, cohort study.
Gulmann 1976	Allocation: randomised. Participants: people with schizophrenia, not TD. Interventions: baclofen versus placebo; 19/20 participants were given chlorpromazine.
Korsgaard 1976	Allocation: randomised, cross-over design. Participants: people with antipsychotic-induced TD. Intervention: baclofen versus placebo. Outcomes: not possible to extract data from first period; authors contacted in 1996 and did not reply. The study was excluded as it is over 35 years old and further attempts to contact authors will likely not be fruitful.
Korsgaard 1982	Allocation: not randomised.
Korsgaard 1983	Allocation: not randomised.
Lambert 1982	Allocation: not randomised.
Monteleone 1988	Allocation: not randomised, case-control study.
Morselli 1985	Allocation: not randomised.
Nagao 1979	Allocation: not randomised.
Nasrallah 1985	Allocation: not randomised.
Nasrallah 1986	Allocation: randomised.
	Participants: schizophrenia, paranoid disorder, and schizoaffective disorder + Schooler and Kane criteria for persistent TD.
	Interventions: AMPT vs L-DOPA vs Choline chloride vs Valproic acid vs Hydroxytryptophan
	Outcomes: No outcome data have been provided for the first period before cross-over. Study author was contacted for data; no additional information was received, so this 25-year old study was excluded.
Nordic 1986	Allocation: randomised, cross-over design. Interventions:chlorprothixene, perphenazine, haloperidol and haloperidol + biperiden versus placebo, not GABA agonist.
Raptis 1990	Allocation: randomised. Participants: people with schizophrenia without TD.
Rondot 1987	Allocation: not randomised.
Sikich 1999	Allocation: randomised, double-blind.
	Participants: 8 to 19 year olds with active psychotic symptoms, not TD. Interventions: haloperidol, risperidone, and olanzapine, not GABA agonist.
Simpson 1978	Allocation: not randomised.



Study	Reason for exclusion
Stahl 1985	Allocation: not randomised.
Tamminga 1978	Allocation: double-blind methodology, randomisation not stated.
	Participants: people with schizophrenia without TD.
Tamminga 1979	Allocation: randomised.
	Participants: people free from antipsychotic drugs for < 1 month: dose unstable.
	Intervention: muscimol versus placebo.
	Outcomes: no usable data.
Tamminga 1983	Allocation: randomised, cross-over design. Participants: people with TD. Intervention: GVG versus placebo. Outcomes: not possible to extract data from first period; authors contacted three times in 1996, did reply, but did not provide any further information.
Tell 1981	Allocation: not randomised.

TD - tardive dyskinesia **TD** scales

AIMS - Abnormal Involuntary Movement Scale

GABA - Gamma-aminobutyric acid **GABA** compounds

GVG - Gamma-vynil GABA

GAG - Gamma-acetylenic GABA

THIP - Tetrahydroisoxazolopyridinol

Outcome

SCD - Saccadic distractibility

DATA AND ANALYSES

Comparison 1. GABA AGONIST DRUGS versus PLACEBO

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Tardive dyskinesia: 1. Not improved to a clinically important extent - medium term	6	258	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.74, 0.92]
1.1 baclofen	2	64	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.70, 1.13]
1.2 progabide	1	13	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.36, 1.25]
1.3 sodium valproate	2	141	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.76, 0.96]
1.4 gamma-aminobutyric acid	1	40	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.45, 0.98]
2 Tardive dyskinesia: 2. Not any improvement	8	271	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.60, 0.86]
2.1 baclofen - short term	1	10	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.22, 4.56]



Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.2 baclofen - medium term	1	33	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.27, 3.84]
2.3 progabide - medium term	1	13	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.05, 21.67]
2.4 sodium valproate - short term	1	32	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.32, 0.83]
2.5 sodium valproate - medium term	2	141	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.71, 1.01]
2.6 THIP - short term	1	2	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.03, 4.19]
2.7 gamma-aminobutyric acid - medium term	1	40	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.16, 0.80]
3 Tardive dyskinesia: 3. Average endpoint scores (different scales, high score = poor, data skewed)			Other data	No numeric data
4 Tardive dyskinesia: 4. Average change scores (different scales, high score = poor, data skewed)			Other data	No numeric data
5 Tardive dyskinesia: 5. Deteriora- tion of symptoms	5	136	Risk Ratio (M-H, Fixed, 95% CI)	1.90 [0.70, 5.16]
5.1 baclofen - short term	2	28	Risk Ratio (M-H, Fixed, 95% CI)	2.45 [0.11, 53.25]
5.2 baclofen - medium term	2	61	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.13, 4.30]
5.3 sodium valproate - medium term	1	47	Risk Ratio (M-H, Fixed, 95% CI)	3.41 [0.77, 15.19]
6 Adverse effects	10		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 ataxia (baclofen, sodium val- proate)	2	95	Risk Ratio (M-H, Fixed, 95% CI)	3.25 [0.36, 29.73]
6.2 dizzy/confused (baclofen, progabide)	3	62	Risk Ratio (M-H, Fixed, 95% CI)	4.54 [1.14, 18.11]
6.3 loss of muscle tone (baclofen)	1	10	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.15, 59.89]
6.4 nausea/vomiting (baclofen)	2	64	Risk Ratio (M-H, Fixed, 95% CI)	2.61 [0.79, 8.67]
6.5 restlessness/akathisia (ba- clofen, sodium valproate)	2	80	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.32, 3.49]
6.6 sedation/drowsiness (baclofen, sodium valporate)	4	144	Risk Ratio (M-H, Fixed, 95% CI)	2.29 [1.08, 4.86]
6.7 seizures (THIP)	1	2	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.24, 37.67]
6.8 Hypothension (Gamma- Aminobutyric acid, Sodium Val- proate)	2	119	Risk Ratio (M-H, Fixed, 95% CI)	3.04 [0.33, 28.31]

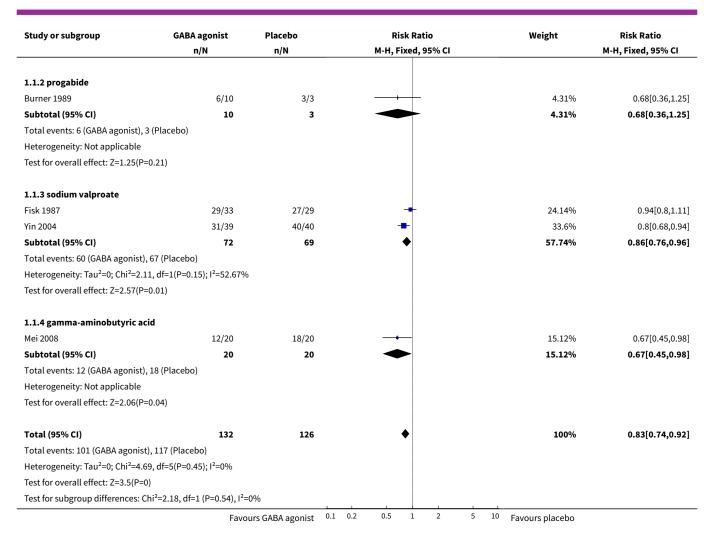


Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
6.9 Diarrhoea (Gamma- Aminobutyric acid)	1	40	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.13, 69.52]
6.10 Leucocyte decrease (sodium valporate)	1	79	Risk Ratio (M-H, Fixed, 95% CI)	3.08 [0.13, 73.27]
6.11 Low platelet (sodium valporate)	1	79	Risk Ratio (M-H, Fixed, 95% CI)	17.43 [1.04, 291.96]
6.12 any - baclofen	1	10	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Mental state: 1. Deterioration	6	121	Risk Ratio (M-H, Fixed, 95% CI)	2.65 [0.71, 9.86]
7.1 baclofen - short term	2	28	Risk Ratio (M-H, Fixed, 95% CI)	4.09 [0.22, 74.78]
7.2 baclofen - medium term	1	31	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.3 progabide - medium term	1	13	Risk Ratio (M-H, Fixed, 95% CI)	1.82 [0.11, 30.27]
7.4 sodium valproate - medium term	1	47	Risk Ratio (M-H, Fixed, 95% CI)	2.27 [0.22, 23.38]
7.5 THIP - short term	1	2	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.24, 37.67]
8 Mental state: 2. Average endpoint score (BPRS, high score = poor)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
8.1 Gamma-Aminobutyric acid - medium term	1	40	Mean Difference (IV, Fixed, 95% CI)	0.03 [-3.29, 3.35]
9 Leaving the study early	6	218	Risk Ratio (M-H, Fixed, 95% CI)	1.47 [0.69, 3.15]
9.1 baclofen	3	63	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.07, 2.24]
9.2 progabide	1	13	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.05, 21.67]
9.3 sodium valproate	2	142	Risk Ratio (M-H, Fixed, 95% CI)	2.48 [0.93, 6.61]

Analysis 1.1. Comparison 1 GABA AGONIST DRUGS versus PLACEBO, Outcome 1 Tardive dyskinesia: 1. Not improved to a clinically important extent - medium term.

Study or subgroup	GABA agonist	Placebo			Ri	sk Rat	io			Weight	Risk Ratio
	n/N	n/N			M-H, F	ixed, 9	5% CI				M-H, Fixed, 95% CI
1.1.1 baclofen											
Glazer 1985	13/16	14/15			-	+				12.14%	0.87[0.66,1.14]
Stewart 1982	10/14	15/19			_	+				10.69%	0.9[0.6,1.36]
Subtotal (95% CI)	30	34				*				22.83%	0.89[0.7,1.13]
Total events: 23 (GABA agonis	st), 29 (Placebo)										
Heterogeneity: Tau ² =0; Chi ² =0	0.03, df=1(P=0.87); I ² =0%										
Test for overall effect: Z=0.99((P=0.32)										
	Favo	urs GABA agonist	0.1	0.2	0.5	1	2	5	10	Favours placebo	

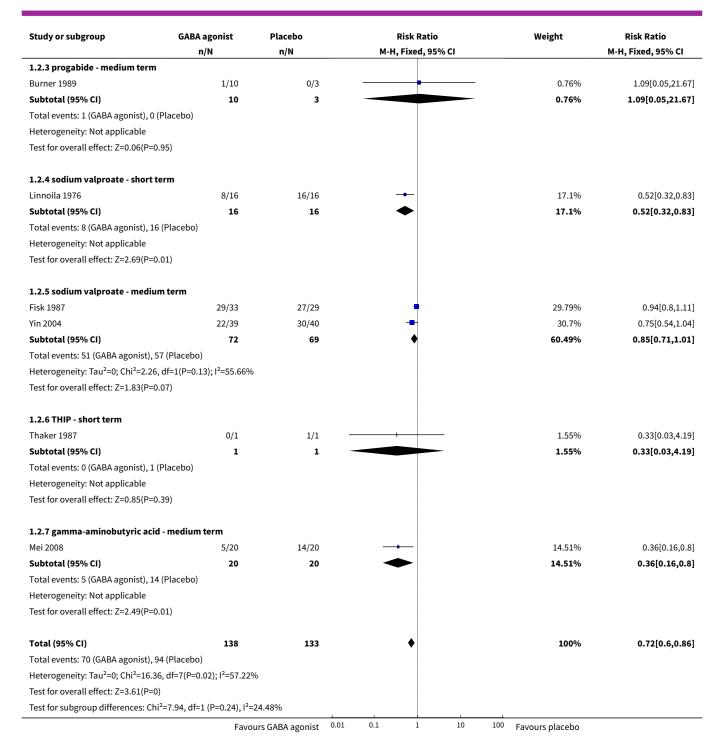




Analysis 1.2. Comparison 1 GABA AGONIST DRUGS versus PLACEBO, Outcome 2 Tardive dyskinesia: 2. Not any improvement.

Study or subgroup	GABA agonist	Placebo			Risk Ratio			Weight	Risk Ratio
	n/N	n/N		М-Н	, Fixed, 95	% CI			M-H, Fixed, 95% CI
1.2.1 baclofen - short term									
Ananth 1987	2/5	2/5		_	-	_		2.07%	1[0.22,4.56]
Subtotal (95% CI)	5	5		-	$\overline{}$	-		2.07%	1[0.22,4.56]
Total events: 2 (GABA agonist), 2 (Plac	cebo)								
Heterogeneity: Not applicable									
Test for overall effect: Not applicable									
1.2.2 baclofen - medium term									
Stewart 1982	3/14	4/19		-	-	-		3.52%	1.02[0.27,3.84]
Subtotal (95% CI)	14	19		-	ightharpoonup	-		3.52%	1.02[0.27,3.84]
Total events: 3 (GABA agonist), 4 (Plac	cebo)								
Heterogeneity: Not applicable									
Test for overall effect: Z=0.03(P=0.98)									
	Favo	urs GABA agonist	0.01	0.1	1	10	100	Favours placebo	





Analysis 1.3. Comparison 1 GABA AGONIST DRUGS versus PLACEBO, Outcome 3 Tardive dyskinesia: 3. Average endpoint scores (different scales, high score = poor, data skewed).

Tardive dyskinesia: 3. Average endpoint scores (different scales, high score = poor, data skewed)

Study	Intervention	Mean	SD	N	Scale	Notes
Gerlach 1978	Baclofen	3.7	2.4	10	Gerlach scale	
Gerlach 1978	Placebo	5.3	2.2	8		



Study	Intervention	Mean	SD	N	Scale	Notes
Mei 2008	GABA	6.02	3.03	20	AIMS	suggests a statisti- cally significant effet in favour of GABA
Mei 2008	Placebo	9.35	4.26	20		
Stewart 1982	Baclofen	11	7.35	13	AIMS	
Stewart 1982	Placebo	12.35	6.79	17		
Yin 2004	Sodium valproate	6.05	3.01	39	AIMS	suggests a statisti- cally significant effet in favour of sodium valproate
Yin 2004	Placebo	9.36	4.16	40		

Analysis 1.4. Comparison 1 GABA AGONIST DRUGS versus PLACEBO, Outcome 4 Tardive dyskinesia: 4. Average change scores (different scales, high score = poor, data skewed).

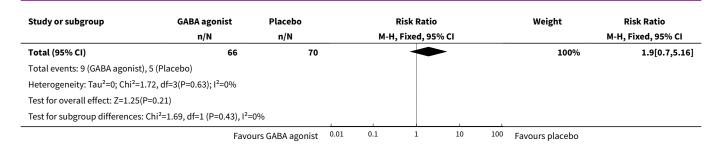
Tardive dyskinesia: 4. Average change scores (different scales, high score = poor, data skewed)

		,		, 	,,	
Study	Intervention	Mean	SD	N	Scale	Notes
Burner 1989	Progabide	7.3 decline	3.9	9	Simpson Rating Scale	
Burner 1989	Placebo	2.6 decline	1.5	3		
Stewart 1982	Baclofen	6.3 decline	5.66	13	AIMS	
Stewart 1982	Placebo	4.2 decline	4.68	17		

Analysis 1.5. Comparison 1 GABA AGONIST DRUGS versus PLACEBO, Outcome 5 Tardive dyskinesia: 5. Deterioration of symptoms.

Study or subgroup	GABA agonist	Placebo	Risk Ratio	Weight	Risk Ratio	
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI	
1.5.1 baclofen - short term						
Ananth 1987	0/5	0/5			Not estimable	
Gerlach 1978	1/10	0/8		10.6%	2.45[0.11,53.25]	
Subtotal (95% CI)	15	13		10.6%	2.45[0.11,53.25]	
Total events: 1 (GABA agonist), 0	(Placebo)					
Heterogeneity: Not applicable						
Test for overall effect: Z=0.57(P=0	0.57)					
1.5.2 baclofen - medium term						
Glazer 1985	1/16	1/15		19.9%	0.94[0.06,13.68]	
Stewart 1982	1/13	2/17		33.41%	0.65[0.07,6.45]	
Subtotal (95% CI)	29	32		53.31%	0.76[0.13,4.3]	
Total events: 2 (GABA agonist), 3	(Placebo)					
Heterogeneity: Tau ² =0; Chi ² =0.04	4, df=1(P=0.84); I ² =0%					
Test for overall effect: Z=0.31(P=0	0.76)					
1.5.3 sodium valproate - mediu	ım term					
Fisk 1987	6/22	2/25	-	36.09%	3.41[0.77,15.19]	
Subtotal (95% CI)	22	25		36.09%	3.41[0.77,15.19]	
Total events: 6 (GABA agonist), 2	(Placebo)					
Heterogeneity: Not applicable						
Test for overall effect: Z=1.61(P=0	0.11)					
	Favo	urs GABA agonist 0.	01 0.1 1 10	100 Favours placebo		





Analysis 1.6. Comparison 1 GABA AGONIST DRUGS versus PLACEBO, Outcome 6 Adverse effects.

Study or subgroup	GABA agonist	Placebo	Risk Ratio	Weight	Risk Ratio	
	n/N		M-H, Fixed, 95% CI		M-H, Fixed, 95% CI	
1.6.1 ataxia (baclofen, sodiu	m valproate)					
Fisk 1987	1/33	0/29	-	55.35%	2.65[0.11,62.56	
Stewart 1982	1/14	0/19	-	44.65%	4[0.17,91.48	
Subtotal (95% CI)	47	48		100%	3.25[0.36,29.73	
Total events: 2 (GABA agonist)	, 0 (Placebo)					
Heterogeneity: Tau²=0; Chi²=0	.03, df=1(P=0.86); I ² =0%					
Test for overall effect: Z=1.04(F	P=0.3)					
1.6.2 dizzy/confused (baclof	en, progabide)					
Burner 1989	1/10	0/3		31.67%	1.09[0.05,21.67	
Gerlach 1978	6/10	0/8	+	23.75%	10.64[0.69,164.43	
Glazer 1985	4/16	1/15	-	44.58%	3.75[0.47,29.87	
Subtotal (95% CI)	36	26		100%	4.54[1.14,18.11	
Total events: 11 (GABA agonis	t), 1 (Placebo)					
Heterogeneity: Tau²=0; Chi²=1	.28, df=2(P=0.53); I ² =0%					
Test for overall effect: Z=2.15(F	P=0.03)					
1.6.3 loss of muscle tone (ba	clofen)					
Nair 1978	1/5	0/5	-	100%	3[0.15,59.89	
Subtotal (95% CI)	5	5		100%	3[0.15,59.89	
Total events: 1 (GABA agonist)	, 0 (Placebo)					
Heterogeneity: Not applicable	:					
Test for overall effect: Z=0.72(F	P=0.47)					
1.6.4 nausea/vomiting (back	ofen)					
Glazer 1985	3/16	0/15	+	16.83%	6.59[0.37,117.77	
Stewart 1982	4/14	3/19	- • 	83.17%	1.81[0.48,6.83	
Subtotal (95% CI)	30	34		100%	2.61[0.79,8.67	
Total events: 7 (GABA agonist)	, 3 (Placebo)					
Heterogeneity: Tau²=0; Chi²=0	.69, df=1(P=0.41); I ² =0%					
Test for overall effect: Z=1.57(F	P=0.12)					
1.6.5 restlessness/akathisia	(baclofen, sodium valproa	te)				
Fisk 1987	1/33	0/29	-	13.75%	2.65[0.11,62.56	
Gerlach 1978	3/10	3/8		86.25%	0.8[0.22,2.94	
Subtotal (95% CI)	43	37	*	100%	1.05[0.32,3.49	
Total events: 4 (GABA agonist)	, 3 (Placebo)					
Heterogeneity: Tau ² =0; Chi ² =0	.5, df=1(P=0.48); I ² =0%					



Study or subgroup (GABA agonist	Placebo	Risk Ratio	Weight	Risk Ratio
Test for overall effect: Z=0.09(P=0.93)	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
rest for overall effect. 2=0.05(r=0.55)					
1.6.6 sedation/drowsiness (baclofen,	sodium valporate	e)			
Fisk 1987	7/33	4/29	- 1	49.69%	1.54[0.5,4.73
Gerlach 1978	7/10	0/8	+	6.42%	12.27[0.81,187.0
Glazer 1985	3/16	2/15		24.09%	1.41[0.27,7.2
Stewart 1982	3/14	2/19		19.8%	2.04[0.39,10.6
Subtotal (95% CI)	73	71	•	100%	2.29[1.08,4.8
Total events: 20 (GABA agonist), 8 (Plac	ebo)				
Heterogeneity: Tau²=0; Chi²=2.3, df=3(F	P=0.51); I ² =0%				
Test for overall effect: Z=2.17(P=0.03)					
1.6.7 seizures (THIP)					
Thaker 1987	1/1	0/1		100%	3[0.24,37.6
Subtotal (95% CI)	1	1		100%	3[0.24,37.6
Total events: 1 (GABA agonist), 0 (Place	bo)				,
Heterogeneity: Not applicable	•				
Test for overall effect: Z=0.85(P=0.39)					
1 6 8 Uynathansian /Camma Aminah	b.wis asid Sadio	um Valmus ats\			
1.6.8 Hypothension (Gamma- Aminol Mei 2008	1/20	-		50.31%	2[0 12 60 5
	•	0/20			3[0.13,69.5
/in 2004	1/39	0/40		49.69%	3.08[0.13,73.2
Subtotal (95% CI)	59	60		100%	3.04[0.33,28.3
Total events: 2 (GABA agonist), 0 (Place					
Heterogeneity: Tau ² =0; Chi ² =0, df=1(P=	0.99); I ² =0%				
Test for overall effect: Z=0.98(P=0.33)					
1.6.9 Diarrhoea (Gamma- Aminobuty	ric acid)				
Mei 2008	1/20	0/20		100%	3[0.13,69.5
Subtotal (95% CI)	20	20		100%	3[0.13,69.5
Total events: 1 (GABA agonist), 0 (Place	bo)				
Heterogeneity: Not applicable					
Test for overall effect: Z=0.69(P=0.49)					
1.6.10 Leucocyte decrease (sodium v	alporate)				
/in 2004	1/39	0/40		100%	3.08[0.13,73.2
Subtotal (95% CI)	39	40		100%	3.08[0.13,73.2
Total events: 1 (GABA agonist), 0 (Place	bo)				
Heterogeneity: Not applicable					
Test for overall effect: Z=0.69(P=0.49)					
I.6.11 Low platelet (sodium valporat	e)				
Yin 2004	8/39	0/40		100%	17.43[1.04,291.9
Subtotal (95% CI)	39	40		100%	17.43[1.04,291.9
Total events: 8 (GABA agonist), 0 (Place		-10		20070	
Heterogeneity: Not applicable	/				
Test for overall effect: Z=1.99(P=0.05)					
1.6.12 any - baclofen					
Ananth 1987	0/5	0/5			Not estimab
Subtotal (95% CI)	0/5 5	0/5 5			Not estimab
		э			NOCESCIIIIAD
Total events: 0 (GABA agonist), 0 (Place	บบ)				



Study or subgroup	GABA agonist	Placebo			Risk Ratio			Weight	Risk Ratio
	n/N	n/N n/N		М-Н	, Fixed, 95	% CI			M-H, Fixed, 95% CI
Heterogeneity: Not applicable									
Test for overall effect: Not applicable				1					
	Fa	avours GABA agonist	0.01	0.1	1	10	100	Favours placeho	

Analysis 1.7. Comparison 1 GABA AGONIST DRUGS versus PLACEBO, Outcome 7 Mental state: 1. Deterioration.

Study or subgroup	GABA agonist	Placebo	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
1.7.1 baclofen - short term					
Ananth 1987	0/5	0/5			Not estimable
Gerlach 1978	2/10	0/8	-		4.09[0.22,74.78]
Subtotal (95% CI)	15	13		20.22%	4.09[0.22,74.78]
Total events: 2 (GABA agonist), 0 (Pla	cebo)				
Heterogeneity: Not applicable					
Test for overall effect: Z=0.95(P=0.34)					
1.7.2 baclofen - medium term					
Glazer 1985	0/16	0/15			Not estimable
Subtotal (95% CI)	16	15			Not estimable
Total events: 0 (GABA agonist), 0 (Plac	cebo)				
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.7.3 progabide - medium term					
Burner 1989	2/10	0/3		26.97%	1.82[0.11,30.27]
Subtotal (95% CI)	10	3		26.97%	1.82[0.11,30.27]
Total events: 2 (GABA agonist), 0 (Plac	cebo)				
Heterogeneity: Not applicable					
Test for overall effect: Z=0.42(P=0.68)					
1.7.4 sodium valproate - medium te	erm				
Fisk 1987	2/22	1/25		34.42%	2.27[0.22,23.38]
Subtotal (95% CI)	22	25		34.42%	2.27[0.22,23.38]
Total events: 2 (GABA agonist), 1 (Pla	cebo)				
Heterogeneity: Not applicable					
Test for overall effect: Z=0.69(P=0.49)					
1.7.5 THIP - short term					
Thaker 1987	1/1	0/1		18.39%	3[0.24,37.67]
Subtotal (95% CI)	1	1		18.39%	3[0.24,37.67]
Total events: 1 (GABA agonist), 0 (Pla	cebo)				
Heterogeneity: Not applicable					
Test for overall effect: Z=0.85(P=0.39)					
Total (95% CI)	64	57		100%	2.65[0.71,9.86]
Total events: 7 (GABA agonist), 1 (Pla	cebo)				
Heterogeneity: Tau ² =0; Chi ² =0.18, df=	3(P=0.98); I ² =0%				
Test for overall effect: Z=1.46(P=0.15)					
Test for subgroup differences: Chi ² =0	.18. df=1 (P=0.98). l ² =	0%			



Analysis 1.8. Comparison 1 GABA AGONIST DRUGS versus PLACEBO, Outcome 8 Mental state: 2. Average endpoint score (BPRS, high score = poor).

Study or subgroup	GAB	A agonist	P	acebo		Me	an Difference	•		Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)		Fi	ixed, 95% CI				Fixed, 95% CI
1.8.1 Gamma-Aminobutyric acid - n	nedium	term									
Mei 2008	20	35.7 (5.3)	20	35.7 (5.4)		_	-			100%	0.03[-3.29,3.35]
Subtotal ***	20		20			-				100%	0.03[-3.29,3.35]
Heterogeneity: Not applicable											
Test for overall effect: Z=0.02(P=0.99)											
			Favours	GABA agonist	-10	-5	0	5	10	Favours placebo)

Analysis 1.9. Comparison 1 GABA AGONIST DRUGS versus PLACEBO, Outcome 9 Leaving the study early.

				_		
Study or subgroup	GABA agonist	Placebo	Risk Ratio	Weight	Risk Ratio	
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI	
1.9.1 baclofen						
Ananth 1987	0/5	0/5			Not estimable	
Gerlach 1978	0/10	2/10 —		25.8%	0.2[0.01,3.7	
Stewart 1982	1/14	2/19		17.52%	0.68[0.07,6.76]	
Subtotal (95% CI)	29	34		43.32%	0.39[0.07,2.24	
Total events: 1 (GABA agonist	t), 4 (Placebo)					
Heterogeneity: Tau ² =0; Chi ² =	0.42, df=1(P=0.52); I ² =0%					
Test for overall effect: Z=1.05	(P=0.29)					
1.9.2 progabide						
Burner 1989	1/10	0/3	-	7.57%	1.09[0.05,21.67]	
Subtotal (95% CI)	10	3		7.57%	1.09[0.05,21.67]	
Total events: 1 (GABA agonist	t), 0 (Placebo)					
Heterogeneity: Not applicabl	e					
Test for overall effect: Z=0.06	(P=0.95)					
1.9.3 sodium valproate						
Fisk 1987	11/33	4/29	 	43.95%	2.42[0.86,6.77]	
Yin 2004	1/40	0/40	+	- 5.16%	3[0.13,71.51]	
Subtotal (95% CI)	73	69		49.11%	2.48[0.93,6.61]	
Total events: 12 (GABA agonis	st), 4 (Placebo)					
Heterogeneity: Tau ² =0; Chi ² =	0.02, df=1(P=0.9); I ² =0%					
Test for overall effect: Z=1.81	(P=0.07)					
Total (95% CI)	112	106	•	100%	1.47[0.69,3.15]	
Total events: 14 (GABA agonis	st), 8 (Placebo)					
Heterogeneity: Tau ² =0; Chi ² =	3.36, df=4(P=0.5); I ² =0%					
Test for overall effect: Z=0.99	(P=0.32)					
Test for subgroup differences	s: Chi ² =3.32, df=1 (P=0.19), I ² =	39.69%				
	Eavo	urs GABA agonist 0.01	0.1 1 10	100 Favours placebo		

ADDITIONAL TABLES



Table 1. Series of related reviews

Review title	Reference
Anticholinergic medication for neuroleptic-induced tardive dyskinesia	Bergman 2018a
Benzodiazepines for neuroleptic-induced tardive dyskinesia	Bergman 2018
Calcium channel blockers for neuroleptic-induced tardive dyskinesia	Essali 2011
Cholinergic medication for neuroleptic-induced tardive dyskinesia	Tammenmaa 2002
Gamma-aminobutyric acid agonists for neuroleptic-induced tardive dyskinesia	This review
Miscellaneous treatments for neuroleptic-induced tardive dyskinesia	Soares-Weiser 2003
Neuroleptic reduction and/or cessation and neuroleptics as specific treatments for tardive dyskinesia	Bergman 2018b
Non-neuroleptic catecholaminergic drugs for neuroleptic induced tardive dyskinesia	El-Sayeh 2006
Vitamin E	Soares-Weiser 2018

APPENDICES

Appendix 1. Previous searches, data collection and analyses

1. Electronic searches

1.1 For the update of 2010

Cochrane Schizophrenia Group Trials Register was searched in June 2010 using the phrase:[((GABA* or baclofen* or gamma-vinyl-GABA* or gamma-acetylenic-GABA* or muscimol* or progabide* or valproate* or THIP* in title) or (* GABA* or *baclofen* or *gamma-vinyl-GABA* or *gamma-acetylenic-GABA* or *muscimol* or *progabide* or *valproate* or *THIP* in title, abstract or index terms of REFERENCE)) or (GABA* or baclofen* or gamma-vinyl-GABA* or gamma-acetylenic-GABA* or muscimol* or progabide* or valproate* or THIP* in interventions of STUDY)]

This register is compiled by systematic searches of major database, hand searches and conference proceedings (see group module).

1.2 For the update of 2006

We searched the Cochrane Schizophrenia Group Trials Register (November 2005) using the phrase:[benzodiazep* or alprazolam or bromazepam or chlordiazepoxide or clobazam or clonazepam or clorazepate dipotassium or diazepam or flunitrazepam or flurizepam or loprazolam or lorazepam or lorazepam or medazepam or midazolam or nitrazepam or oxazepam or temazepam]This register is compiled by systematic searches of major databases, hand searches and conference proceedings (see Group Module). The previous updates were searched for relevant randomised trials by searching several electronic databases (Biological Abstracts, the Cochrane Schizophrenia Group's Register of trials, EMBASE, LILACS, MEDLINE, PsycLIT and SCISEARCH).

1.3 For previous versions of this review

1.3.1 Biological Abstracts (January 1982 to February 2002)

This database was searched using the Cochrane Schizophrenia Group's phrase for randomised controlled trials (see Group search strategy) combined with the phrase:[and (tardive near (dyskine* or diskine*) or (abnormal near movement* near disorder*) or (involuntar* near movement*)] and [benzodiazep* or alprazolam or bromazepam or chlordiazepoxide or clobazam or clonazepam or clorazepate dipotassium or diazepam or flunitrazepam or flurazepam or lorrazepam or lorrazepam or medazepam or midazolam or nitrazepam or oxazepam or temazepam]

1.3.2 Cochrane Schizophrenia Group's Register (February 2002)



This was searched using the phrase:[benzodiazep* or alprazolam or bromazepam or chlordiazepoxide or clobazam or clonazepam or clorazepate dipotassium or diazepam or flunitrazepam or flurazepam or loprazolam or lorazepam or lormetazepam or medazepam or midazolam or nitrazepam or oxazepam or temazepam]

1.3.3 EMBASE (January 1980 to February 2002)

This was searched using the Cochrane Schizophrenia Group's phrase for randomised controlled trials (see Group search strategy) combined with the phrase:[and (tardive dyskinesia in thesaurus -subheadings, prevention, drug therapy, side effect and therapy) or (neuroleptic dyskinesia in thesaurus -all subheadings) or (tardive and dyskines*) or (movement* and disorder*) or (abnormal and movement* and disorder*)] and [benzodiazep* or alprazolam or bromazepam or chlordiazepoxide or clobazam or clonazepam or clorazepam or fluritrazepam or fluritrazepam or lorazepam or lorazepam or medazepam or midazolam or nitrazepam or oxazepam or temazepam]

1.3.4 LILACS (January 1982 to February 2002)

This was searched using the Cochrane Schizophrenia Group's phrase for randomised controlled trials (see Group search strategy) combined with the phrase:[and (tardive and (dyskinesia* or diskinesia*)) or (drug induced movement disorders in thesaurus)] and [benzodiazep* or alprazolam or bromazepam or chlordiazepoxide or clobazam or clonazepam or clorazepate dipotassium or diazepam or flunitrazepam or flurazepam or lorazepam or lorazepam or medazepam or midazolam or nitrazepam or oxazepam or temazepam]

1.3.5 MEDLINE (January 1966 to February 2002)

This was searched using the Cochrane Schizophrenia Group's phrase for randomised controlled trials (see Group search strategy) combined with the phrase:[and (movement-disorders in MeSH / explode all subheadings) or (anti-dyskinesia-agents in MeSH / explode all subheadings) or (dyskinesia-drug-induced in MeSH / explode all subheadings) and (psychosis in MeSH / explode all subheadings) or (schizophrenic disorders in MeSH / explode all subheadings) or (tardive near (dyskine* or diskine*)) or (abnormal* near movement* near disorder*) or (involuntar* near movement*)] and [benzodiazep* or alprazolam or bromazepam or chlordiazepoxide or clobazam or clonazepam or clorazepate dipotassium or diazepam or fluritrazepam or fluritrazepam or loprazolam or lorazepam or lormetazepam or medazepam or midazolam or nitrazepam or oxazepam or temazepam]

1.3.6 PsycLIT (January 1974 to February 2002)

This was searched using the Cochrane Schizophrenia Group's phrase for randomised controlled trials (see Group search strategy) combined with the phrase:[and (explode movement-disorders in DE) or (explode tardive-dyskinesia in DE) or (tardive near (dyskine* or diskine*) or (abnormal* near movement* near disorder*) or (involuntar* near movement*)] and [benzodiazep* or alprazolam or bromazepam or chlordiazepoxide or clobazam or clonazepam or clorazepate dipotassium or diazepam or flunitrazepam or flurazepam or loprazolam or lorazepam or lorazepam or medazepam or midazolam or nitrazepam or oxazepam or temazepam]

1.3.7 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 furth

Selection of studies

For the previous update (July 2004), NS (see Acknowledgements) inspected all abstracts of studies identified as above and identified potentially relevant reports. In addition, to ensure reliability, KSW inspected a random sample of these abstracts, comprising 10% of the total. Where disagreement occurred we resolved this by discussion, or where there was still doubt, acquired the full article for further inspection. We acquired the full articles of relevant reports for reassessment and carefully inspected them for a final decision on inclusion (see Criteria for considering studies for this review). Once we obtained the full articles, NS and KSW in turn inspected all full reports and independently decided whether they met inclusion criteria. NS and KSW were not blinded to the names of the authors, institutions or journal of publication. Where difficulties or disputes arose, we asked author JM for help and if it was impossible to decide, added these studies to those awaiting assessment and contacted the authors of the papers for clarification. For the current update (July 2010) AS and RA independently inspected each report identified by the search to identify relevant studies.

Data extraction and management

1. Extraction

For the update (July 2004), NS extracted data from all included studies. In addition, to ensure reliability, KSW independently extracted data from a random sample of these studies, comprising 10% of the total. Again, we discussed any disagreement, documented decisions and, if necessary, contacted authors of studies for clarification. With remaining problems JM helped clarify issues, and we documented those final decisions. We extracted data presented only in graphs and figures whenever possible, but included these only if two authors 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. Where possible, we extracted data relevant to each component centre of multi-centre studies separately. For the update (July 2010) AS and RA (see Acknowledgements) independently inspected each report identified by the search, and discussed any doubts with LY and MH.



2. Management

2.1 Forms

We extracted data onto standard, simple forms.

2.2 Scale-derived data

We included continuous data from rating scales only if:

- a. the psychometric properties of the measuring instrument had been described in a peer-reviewed journal (Marshall 2000);
- b. the measuring instrument was not written or modified by one of the trialists for that particular trial; and
- c. the measuring instrument is either i. a self-report or ii. completed by an independent rater or relative (not the therapist).

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 used mean differences rather than standardised mean differences throughout (Higgins 2008, Chapter 9.4.5.2).

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 aim to apply the following standards to all data before inclusion.

- a) Standard deviations and means are reported in the paper or obtainable from the authors.
- b) When a scale starts from the finite number zero, the standard deviation, when multiplied by two, is less than the mean (as otherwise the mean is unlikely to be an appropriate measure of the centre of the distribution (Altman 1996).
- c) If a scale started from a positive value (such as the Positive and Negative Syndrome Scale (PANSS), which can have values from 30 to 210), we 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. Endpoint scores on scales often have a finite start and end point and these rules can be applied. 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. We entered skewed data from studies of less than 200 participants in additional tables rather than into an analysis. Skewed data pose less of a problem when looking at means if the sample size is large and were entered into syntheses.

2.5 Common measure

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

2.6 Conversion of continuous to binary

Where possible, we made efforts to convert outcome measures to dichotomous data. This could be done by identifying cut-off points on rating scales and dividing participants accordingly into 'clinically improved' or 'not clinically improved'. We generally assumed that if there had been 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), we could consider this as a clinically significant response (Leucht 2005a; Leucht 2005). 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 indicates a favourable outcome for intensive case management.

2.8 Studies with multiple treatment groups

Where a study involved more than two treatment arms, if relevant, we presented the additional treatment arms in comparisons. Where the additional treatment arms were not relevant, we did not reproduce these data.

2.9 'Summary of findings' table

We anticipated including the following short- or medium-term outcomes in a 'Summary of findings' table. (NS was not biased by being familiar with the data.)

1. Tardive dyskinesia

- 1.1 Not improved to an important extent
- 1.2 Not improved
- 1.3 Deteriorated



2. Adverse effect

- 2.1 Any adverse event
- 2.2 Specific adverse event

3. Quality of life

3.1 Not improved to an important extent

Assessment of risk of bias in included studies

We assessed the risk of bias using criteria described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008) to assess trial quality. 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.

The categories are defined below.

- Yes low risk of bias
- NO high risk of bias
- UNCLEAR uncertain risk of bias

For example, if the sequence generation process within the trial was by quasi-random means, such as by hospital record numbers, we noted this and gave the study a "No - high risk of bias" rating. If data from such studies did not differ from the results of higher grade trials, we have presented these. We have not included trials with high risk of bias (defined as at least three out of five domains categorized as 'No') in the meta-analysis. 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 are provided, we contacted authors of the studies in order to obtain further information. We have reported non-concurrence in quality assessment, but if disputes arose as to which category a trial had to be allocated, again, we achieved resolution by discussion.

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 (Boissel 1999) than odds ratios and that odds ratios tend to be interpreted as RR by clinicians (Deeks 2000). For statistically significant results we had planned to calculate the number needed to treat to provide benefit/to induce harm statistic (NNTB/H), and its 95% confidence interval (CI) using Visual Rx (http://www.nntonline.net/) taking account of the event rate in the control group. This, however, was superseded by 'Summary of findings' table 1 and the calculations therein.

2. Continuous data

2.1 Summary statistic

For continuous outcomes we estimated mean difference (MD) between groups. We preferred not to calculate effect size measures (standardised mean difference SMD). However, had scales of very considerable similarity been used, we would have presumed there was a small difference in measurement, and we would have 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 poses problems. Firstly, 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).

Where clustering is not accounted for in primary studies, we presented 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 (ICC) for their clustered data and to adjust for this by using accepted methods (Gulliford 1999). Where clustering had been incorporated into the analysis of primary studies, we present these data as if from a non-cluster randomised study, but adjusted 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 ICC (Design effect=1+(m-1)*ICC) (Donner 2002). If the ICC was not reported we assumed it to be 0.1 (Ukoumunne 1999).

If cluster studies has been appropriately analysed taking into account ICC and relevant data documented in the report, synthesis with other studies would have been 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 (e.g. 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 use data of the first phase of cross-over studies.

Dealing with missing data

1. Overall loss of credibility

At some degree of loss of follow-up data must lose credibility (Xia 2007). For any particular outcome, should more than 50% of data be unaccounted for, we did 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 marked such data with (*) to indicate that such a result may well be prone to bias.

2. Binary

In the case where attrition for a binary outcome is between 0 and 50% and where these data were not clearly described, we have presented data on a 'once-randomised-always-analyse' basis (an intention-to-treat (ITT) analysis). Those leaving the study early were all assumed to have the same rates of negative outcome as those who completed, with the exception of the outcome of death. We undertook a sensitivity analysis testing how prone the primary outcomes were to change when 'completed' data only were compared to the ITT analysis using the above assumption.

3. Continuous

3.1 Attrition

In the case where attrition for a continuous outcome is between 0 and 50% and completer-only data were reported, we have reproduced these.

3.2 Standard deviations

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 interval (CI) were available for group means, and either 'P' value or 'T' value were available for differences in mean, we calculated them according to the rules described in the *Cochrane Handbook* (Higgins 2008). When only the standard error (SE) is reported, standard deviations (SDs) are calculated by the formula SD=SE * square root (n). Chapters 7.7.3 and 16.1.3 of the *Cochrane Handbook* (Higgins 2008) present detailed formula for estimating SDs from P values, T or F values, CIs, ranges or other statistics. If these formula do 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 Last observation carried forward

We anticipated that in some studies the method of last observation carried forward (LOCF) would be employed within the study report. As with all methods of imputation to deal with missing data, LOCF introduces uncertainty about the reliability of the results. Therefore, where LOCF data have been used in the trial, if less than 50% of the data had been assumed, we reproduced these data and indicated that they are the product of LOCF assumptions.

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 situations or people which we had not predicted would arise. When such situations or participant groups arose, we discussed these fully.

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. When such methodological outliers arose, we fully discussed these.

3. Statistical heterogeneity

3.1 Visual inspection

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



3.2 Employing the I² statistic

We investigated heterogeneity between studies by considering the I² method alongside the Chi² P value. The I² provides an estimate of the percentage of inconsistency thought to be due to chance (Higgins 2003). The importance of the observed value of I² depends on i. magnitude and direction of effects and ii. strength of evidence for heterogeneity (e.g. P value from Chi² test, or a CI for I²). We interpreted I² estimate greater than or equal to 50% accompanied by a statistically significant Chi² statistic as evidence of substantial levels of heterogeneity (Section 9.5.2 - Higgins 2008). When we found substantial levels of heterogeneity in the primary outcome, we explored reasons for heterogeneity (Subgroup analysis and investigation of heterogeneity).

Assessment of reporting biases

Reporting biases arise when the dissemination of research findings is influenced by the nature and direction of results (Egger 1997). These are described in Section 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008). We tried to locate protocols of included trials. If the protocol was available, we compared outcomes in the protocol and in the published report. If the protocol was not available, we compared outcomes listed in the methods section of the trial report with actually reported results. In addition a funnel plot (included trial effect size versus included trial size) may be useful in investigating publication biases but are of limited power to detect small-study effects. We did not use funnel plots for outcomes where there were 10 or fewer studies, or where all studies were of similar sizes. In other cases, where funnel plots were possible, we sought statistical advice in their interpretation.

Data synthesis

We understand that there is no closed argument for preference for use of fixed-effect or random-effects models. The random-effects method incorporates an assumption that the different studies are estimating different, yet related, intervention effects. This often seems to be true to us and the random-effects model takes into account differences between studies even if there is no statistically significant heterogeneity. There is, however, a disadvantage to the random-effects model. It puts added weight onto small studies which often are the most biased ones. Depending on the direction of effect these studies can either inflate or deflate the effect size. Therefore, we chose the fixed-effect model for all analyses. The reader is, however, able to choose to inspect the data using the random model.

Subgroup analysis and investigation of heterogeneity

1. Subgroup analyses

We anticipated one subgroup analyses to test the hypothesis that the use of GABA agonist drugs are most effective for a younger age group (less than 40 years old). We had hoped to present data for this subgroup for the primary outcomes.

2. Investigation of heterogeneity

If inconsistency was high, we reported this. First, we investigated whether data had been entered correctly. Second, if data had been correct, we visually inspected the graph and successively removed studies outside of the company of the rest to see if heterogeneity was restored. Should this occur with no more than 10% of the data being excluded, we presented data. If not, we did not pool data and discussed issues.

Should unanticipated clinical or methodological heterogeneity be obvious, we simply stated hypotheses regarding these for future reviews or versions of this review. We did not anticipate undertaking analyses relating to these.

Sensitivity analysis

1. Implication of randomisation

We aimed to include trials in a sensitivity analysis if they were described in some way as to imply randomisation. For the primary outcomes we included these studies and if there was no substantive difference when the implied randomised studies were added to those with better description of randomisation, then we employed all data from these studies.

2. Assumptions for lost binary data

Where we had to make assumptions 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 results and discuss them but continue to employ our assumption.

Where assumptions had 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 complete data only. A sensitivity analysis was undertaken testing how prone results were to change when 'complete' data only were compared to the imputed data using the above assumption. If there was a substantial difference, we reported results and discuss them but continue to employ our assumption.

WHAT'S NEW



Date	Event	Description
1 November 2017	New citation required but conclusions have not changed	New data added do not substantially change previous conclusions.
26 April 2017	New search has been performed	Title updated, three new included studies added from 2015 searching (Glazer 1985; Mei 2008; Yin 2004), outcomes list updated due to patient consultation, PRISMA study flow chart added, conclusions not substantially changed. Update search run 26 April, 2017. Eight records found and assessed by editorial base Cochrane Schizophrenia, no new studies relevant to this review found. The 8 records were added to Studies awaiting classification of Miscellaneous treatments for antipsychotic-induced tardive dyskinesia (see also Results of the search).

HISTORY

Review first published: Issue 1, 2000

Date	Event	Description
2 March 2011	New citation required but conclusions have not changed	Authorship change and new studies added but conclusions not changed
7 August 2010	New search has been performed	Converted to new review format.
27 July 2010	New search has been performed	Substantial update: results of 2010 search added, six studies added to Characteristics of excluded studies table.
14 April 2010	Amended	Contact details updated.
5 August 2009	Amended	Contact details updated.
25 April 2008	Amended	Converted to new review format.
3 July 2004	New citation required and conclusions have changed	Substantive amendment
18 September 2003	New search has been performed	Search strategy was run again, no new studies were found for inclusion.

CONTRIBUTIONS OF AUTHORS

1. Original review

Karla Soares-Weiser - protocol writing, searching, trial selection, data extraction and assimilation, report writing.

John Rathbone - update - trial selection, data extraction and assimilation, report writing.

Jon Deeks - data extraction and assimilation, statistical support, report writing.

2. 2010 update

Youssef Latifeh, Husam Aldeen Mohammad - trial selection. Samer Alabed - update - trial selection, protocol update, report update.



3. 2017 update

Hanna Bergman - trial selection, data extraction and assimilation, report update.

DECLARATIONS OF INTEREST

Samer Alabed - None known. Youssef Latifeh - None known.

Husam Aldeen Mohammad - None known.

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. Hanna Bergman now has a consultancy contract with Cochrane Response, an evidence services unit operated by the Cochrane Collaboration, to carry out systematic reviews on various topics.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have substantially reformatted this review in light of changes to software (RevMan 5). We add a 'Summary of findings' table, which was prepared using Grade Pro 3.2, and a PRISMA study flow chart. We have also updated the title from 'Gamma-aminobutyric acid agonists for neuroleptic-induced tardive dyskinesia' to Gamma-aminobutyric acid agonists for antipsychotic-induced tardive dyskinesia, and updated the list of outcomes following consultation with consumers.

The previous methods are reproduced in Appendix 1.

INDEX TERMS

Medical Subject Headings (MeSH)

Antipsychotic Agents [adverse effects]; Baclofen [therapeutic use]; Dyskinesia, Drug-Induced [*drug therapy] [etiology]; GABA Agonists [adverse effects] [*therapeutic use]; Isoxazoles [therapeutic use]; Placebos [therapeutic use]; Randomized Controlled Trials as Topic; Valproic Acid [therapeutic use]; gamma-Aminobutyric Acid [analogs & derivatives] [therapeutic use]

MeSH check words

Humans