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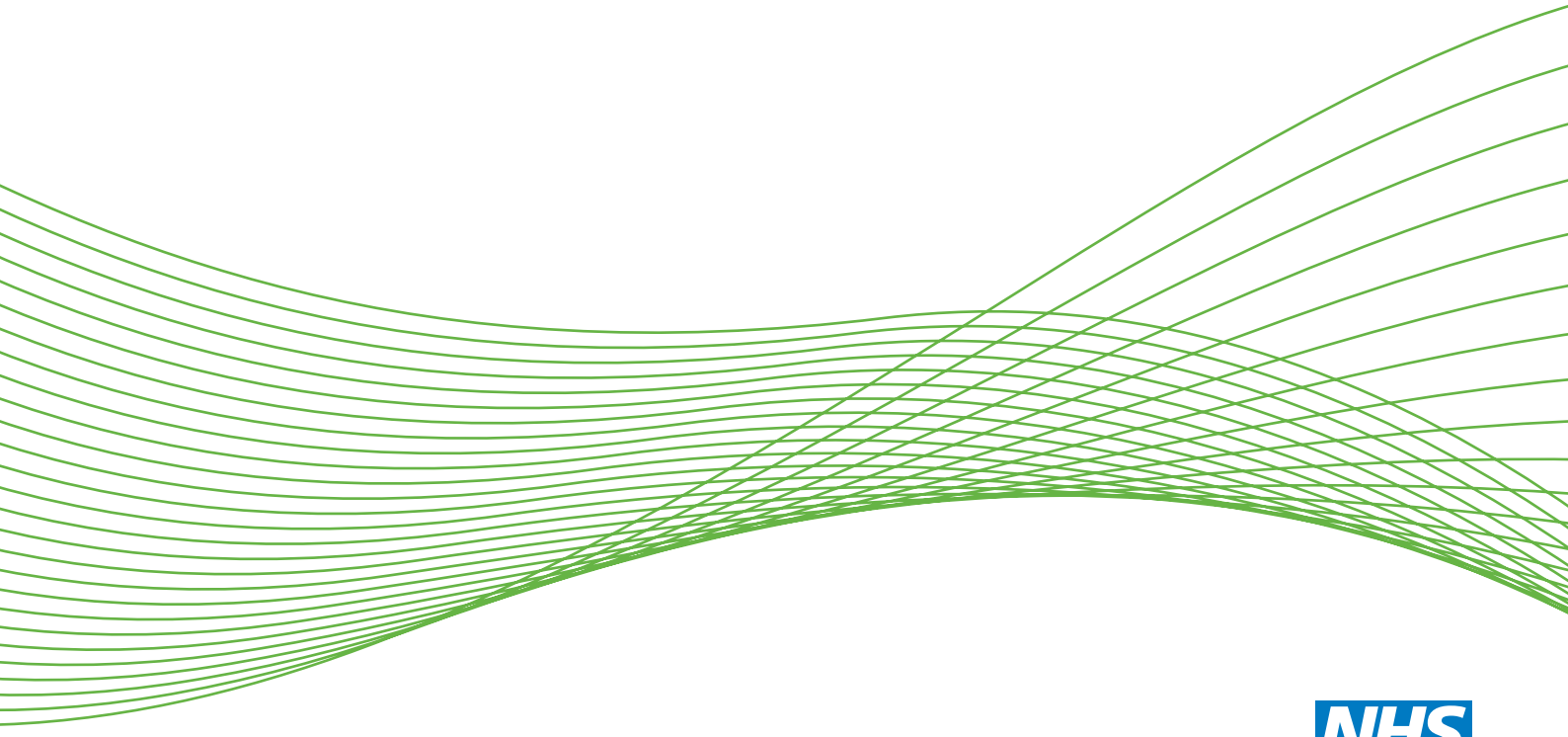

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Systematic review of interventions for treating or preventing antipsychotic-induced tardive dyskinesia

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Abstract

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

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Background: Antipsychotic medication can cause tardive dyskinesia (TD) – late-onset, involuntary, repetitive movements, often involving the face and tongue. TD occurs in > 20% of adults taking antipsychotic medication (first-generation antipsychotics for > 3 months), with this proportion increasing by 5% per year among those who continue to use these drugs. The incidence of TD among those taking newer antipsychotics is not different from the rate in people who have used older-generation drugs in moderate doses. Studies of TD have previously been found to be limited, with no treatment approach shown to be effective.

Objectives: To summarise the clinical effectiveness and safety of treatments for TD by updating past Cochrane reviews with new evidence and improved methods; to undertake public consultation to gauge the importance of the topic for people living with TD/the risk of TD; and to make available all data from relevant trials.

Data sources: All relevant randomised controlled trials (RCTs) and observational studies.

Review methods: Cochrane review methods, network meta-analysis (NMA).

Design: Systematic reviews, patient and public involvement consultation and NMA.

Setting: Any setting, inpatient or outpatient.

Participants: For systematic reviews, adults with TD who have been taking a stable antipsychotic drug dose for > 3 months.

Interventions: Any, with emphasis on those relevant to UK NHS practice.

Main outcome measures: Any measure of TD, global assessments and adverse effects/events.

Results: We included 112 studies (nine Cochrane reviews). Overall, risk of bias showed little sign of improvement over two decades. Taking the outcome of 'TD symptoms improved to a clinically important extent', we identified two trials investigating reduction of antipsychotic dose [$n = 17$, risk ratio (RR) 0.42, 95% confidence interval (CI) 0.17 to 1.04; very low quality]. Switching was investigated twice in trials that could not be combined (switching to risperidone vs. antipsychotic withdrawal: one RCT, $n = 42$, RR 0.45, 95% CI 0.23 to 0.89; low quality; switching to quetiapine vs. haloperidol: one RCT, $n = 45$, RR 0.80, 95% CI 0.52 to 1.22; low quality). In addition to RCTs, six observational studies compared antipsychotic discontinuation with decreased or increased dosage, and there was no clear evidence that any of these

strategies had a beneficial effect on TD symptoms (very low-quality evidence). We evaluated the addition to standard antipsychotic care of several treatments, but not anticholinergic treatments, for which we identified no trials. We found no clear effect of the addition of either benzodiazepines (two RCTs, $n = 32$, RR 1.12, 95% CI 0.6 to 2.09; very low quality) or vitamin E (six RCTs, $n = 264$, RR 0.95, 95% CI 0.89 to 1.01; low quality). Buspirone as an adjunctive treatment did have some effect in one small study ($n = 42$, RR 0.53, 95% CI 0.33 to 0.84; low quality), as did hypnosis and relaxation (one RCT, $n = 15$, RR 0.45, 95% CI 0.21 to 0.94; very low quality). We identified no studies focusing on TD in people with dementia. The NMA model found indirect estimates to be imprecise and failed to produce useful summaries on relative effects of interventions or interpretable results for decision-making. Consultation with people with/at risk of TD highlighted that management of TD remains a concern, and found that people are deeply disappointed at the length of time it has taken researchers to address the issue.

Limitations: Most studies remain small and poorly reported.

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

Future work: TD reviews have data from current trials extracted, tabulated and traceable to source. The NMA highlights one context in which support for this technique is ill advised. All relevant trials, even if not primarily addressing the issue of TD, should report appropriate binary outcomes on groups of people with this problem. Randomised trials of treatments for people with established TD are indicated. These should be large (> 800 participants), necessitating accrual through accurate local/national registers, including an intervention with acceptable treatments and recording outcomes used in clinical practice.

Study registration: This study is registered as PROSPERO CRD4201502045.

Funding: The National Institute for Health Research Health Technology Assessment programme.

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List of abbreviations

AIMS	Abnormal Involuntary Movement Scale
BPRS	Brief Psychiatric Rating Scale
CI	confidence interval
ESRS	Extrapyramidal Symptom Rating Scale
FGA	first-generation antipsychotic
GABA	gamma-aminobutyric acid
GRADE	Grading of Recommendations, Assessment Development and Evaluation
MAO	monoamine oxidase
MD	mean difference
NIHR	National Institute for Health Research
NMA	network meta-analysis
OR	odds ratio
PPI	patient and public involvement
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	randomised controlled trial
RR	risk ratio
SAS	Simpson–Angus Scale
SGA	second-generation antipsychotic
TAU	treatment as usual
TD	tardive dyskinesia
UKU	Udvalg for Kliniske Undersøgelser

Plain English summary

Antipsychotic medication can cause involuntary, repetitive body movements, frequently involving the face and tongue. This condition is known as tardive (because it is a side effect that usually does not appear until after you have been taking medication for a while) dyskinesia (meaning abnormal or unusual movements), or TD.

It has been estimated that TD occurs in about one-fifth of people using antipsychotics. Other studies have found that closer to 1% find it sufficiently severe or persistent to change antipsychotics as a result. Management varies and is particularly problematic where discontinuation or change of treatment is not desired or easily achieved. This work updates past reviews with new evidence and methods. There is frequently an advantage in revisiting old work to see if information that was previously impossible to use can now be employed in building a more complete picture. In recent years, newer methods of presenting and analysing the information in reviews has helped make reviews more accessible and useful.

Although there are many new relevant studies, it appears that little has been learnt from past work. The conduct, analysis and reporting of trials of these treatments continue to be of such poor quality that it is impossible to really trust the results.

This work found that:

- researchers continue to do trials, but take little heed of calls for increased quality and relevance to everyday care
- some new methods used within sophisticated reviews of care really do not work if the building blocks of the reviews (the trials) are of very limited quality
- people with TD feel disappointed and angry at the length of time it has taken for researchers to address the issue of how to treat TD
- we still do not know how to treat people with/at risk of TD effectively.

All information from the reports of past trials, reliably and painstakingly extracted, is fully, freely accessible to anyone online.

Scientific summary

Background

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

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

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

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

Objectives (list of research questions)

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

Methods

Data sources

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

Study selection (inclusion criteria)

Methods
Randomised controlled trials (RCTs).

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

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

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

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

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

Data extraction (and assessment of validity)

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

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

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

Data synthesis

Study level

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

Meta-analyses

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

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

Quality assessment

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

Network meta-analysis

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

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

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

Results

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

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

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

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

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

Reducing antipsychotic dose

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

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

Switching antipsychotic drug

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

Adjunctive treatments in addition to antipsychotic drugs

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

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

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

Conclusions

Implications for health care

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

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

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

Recommendations for research (in order of priority)

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

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

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

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

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

Study registration

This study is registered as PROSPERO CRD4201502045.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Chapter 1 Background

Since the 1950s, antipsychotic medication has been used extensively to control psychotic symptoms and to reduce the harm caused by the symptoms of chronic mental illness, including schizophrenia, bipolar disorder and dementia. Other illnesses that necessitate long-term antipsychotic treatment include autism, Tourette syndrome and other behavioural disturbances. Antipsychotic drugs are associated with a wide range of adverse effects, including tardive dyskinesia (TD), the late onset of involuntary, repetitive body movements, often involving the face and tongue. Critical problems associated with severe TD include difficulty swallowing, locomotion difficulties, involvement of respiratory muscles and speech being rendered unintelligible. TD can be extremely disfiguring, compounds stigma and is associated with poor compliance to treatment.[1]

Tardive dyskinesia occurs in > 20% of people who use first-generation antipsychotic (FGA) drugs continually for > 3 months,[1] and every year 4–5% of those who continually use these drugs begin to show signs of TD.[1] When second-generation antipsychotic (SGA) drugs were introduced in the 1990s, many hoped that they would not cause TD.[2,3] Although the risks of developing TD with SGA drugs do seem to be reduced, they have not been eliminated.[1,3] There is some evidence to indicate that rates of TD do not differ at all between first- and second-generation antipsychotic drugs, making the distinction between the two 'generations' of drugs increasingly redundant.[2] Recent assessments of the incidence and prevalence of TD range from 5% to 60% of patients taking antipsychotic medication for long periods.[4] For example, one recent, well-conducted survey from the Netherlands found that, of 209 people with chronic severe mental illness receiving antipsychotic medication, 28% had TD (yearly incidence rate of TD 19.6%).[5,6] Furthermore, the study reconfirmed that TD was positively associated with age [hazard ratio per year exposure 1.04, 95% confidence interval (CI) 1.02 to 1.06].[5,6]

The large, definitive US randomised trial of antipsychotic treatments for schizophrenia [Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE)], with a 4-year period of follow-up, obtained an incidence rate of TD of around 17% and found no significant difference in rates between first- and second-generation (olanzapine, quetiapine, risperidone, ziprasidone) antipsychotics.[7] A prospective cohort study of 352 psychiatric outpatients confirmed this,[8] but a meta-analysis of nine other studies carried out by the same study authors showed that the yearly TD incidence rate for FGAs was significantly higher than for SGAs; however, many of these studies were not predesigned to detect TD.[8] Another, later, prospective cohort study found no significant difference in TD incidence rates between risperidone and olanzapine in 207 elderly psychiatric in- and outpatients.[9]

As a result of widespread use of SGA drugs, increased off-label use and an ageing population, the frequency of TD is likely to be higher than thought,[10,11] and increasing. The problem will be considerably greater for people in countries in which the use of newer drugs is less prevalent.[12,13]

Given this high incidence and prevalence, the need for prevention or treatment is clear; unfortunately, there has been sparse evidence to guide clinicians.[14,15] Although many treatments have been tested, no one intervention has been shown clearly to be effective.

Although antipsychotic reduction and/or cessation would seem to be a logical first step in the management of antipsychotic-induced TD, this is not always possible in the clinical setting because of the over-riding need to manage current psychotic symptoms and/or reduce the risk of relapse. Changes in several antipsychotic medications have been produced in the last few decades that claim to cause less or no TD.[16] 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 more TD than with newer treatments.[17] In the search for ways to manage antipsychotic-induced TD, certain antipsychotic medications have themselves been proposed as specific treatments for the condition.[18] The usual rationale for such trials relates to variations in the receptor-blocking profile that distinguishes the compound of interest from antipsychotics in general. As for TD, treatment

options for other movement disorders also include antipsychotic dose reduction or the switch to a newer antipsychotic.[19–21] Tetrabenazine is the only Food and Drug Administration-approved drug to specifically treat a movement disorder, Huntington's chorea;[20,22] consequently, and because of the lack of viable treatment options for TD, tetrabenazine has been suggested as a treatment for TD as well.[23]

Drugs that reduce the activity of the cholinergic cells (anticholinergic drugs) are widely used to help treat other antipsychotic-induced movement disorders, such as Parkinsonism and dystonia. It is hypothesised that alterations in striatal cholinergic neurons could serve as pathophysiological basis for TD[24] and, therefore, patients would benefit from cholinergic drugs. Benzodiazepines, the most widely used gamma-aminobutyric acid (GABA) agonists, have also been suggested as potential interventions for TD. Chronic blockade of dopamine receptors in TD leads to inactivity in another set of cells that employ GABA.[25] Also, there is evidence from animal experiments suggesting that GABA dysfunction may be associated with movement disorders.[26] Benzodiazepines have been included as a candidate treatment for TD in several practice guidelines[27–29] and are also used to treat other movement disorders.[19,21,30]

Vitamin E (tocopherol) is a lipid-soluble antioxidant that acts as a free radical scavenger and has also been proposed as a treatment for antipsychotic-induced TD.[31] There has been some suggestion that the chronic use of antipsychotics may cause abnormal production of highly active atoms and chemical groups (cytotoxic free radicals), which may damage specific cells in the brain. This, in turn, could be responsible for the appearance of TD.[32] Vitamin E may assist in minimising damage caused by cytotoxic free radical overproduction, and may prevent or decrease the severity of TD, particularly among those in whom onset occurred in the preceding 5 years.[33,34]

Another agent under investigation for treatment of TD is buspirone, an anxiolytic drug acting as a partial agonist for the serotonin 5-HT_{1A} (5-hydroxytryptamine subtype 1A) receptors, with additional low affinity as an antagonist for the dopamine D2 autoreceptors. A number of studies on TD animal models have found that buspirone ameliorated symptoms.[35,36]

Other, non-pharmacological, treatments should also be examined in the context of TD. 'Mind–body' interventions, including both relaxation techniques and hypnosis, are reported to benefit patients with a number of neurological disorders.[37] The use of different relaxation techniques[38,39] and hypnosis[40] has also been examined in tic disorders and in Parkinson's disease, with some positive preliminary findings; however, their effectiveness in movement disorders and TD specifically has yet to be systematically investigated.

We are aware that TD is not exclusive to people with schizophrenia, but, to illustrate the point regarding the disparate nature of evidence, a comprehensive database with more than 500 controlled trials comparing 101 different interventions used to improve or prevent deterioration of symptoms of antipsychotic-induced TD in schizophrenia was published in 1996.[41,42] The studies in this database were, largely, very small and poorly reported.[41,42] After categorisation according to treatment groups, nine Cochrane reviews were performed (first published in 1995–6 and periodically updated since).[18,23,43–49] An overview of all published Cochrane reviews was published in 1999.[50] These reviews reported a lack of information on the efficacy of most interventions, in particular the logical – but often impractical – step of stopping antipsychotic treatment.[18] Many with TD are faced with a lifetime of suffering from this disfiguring adverse effect.

This is a good time to revisit this difficult area for several reasons:

1. The research community has recognised that TD is not a problem of the past and may be an increasing problem of the future.
2. Widening the inclusion criteria to well beyond people with schizophrenia may lead to a broader appreciation of the research landscape, with opportunities for cross-fertilisation of ideas for prevention/treatment.
3. New approaches have been tested.[51]

4. Methods in systematic reviewing have become considerably more sophisticated, with new techniques to employ evidence from, for example, network meta-analysis (NMA).[52]
5. Dissemination of information is warranted, and methods for dissemination are much wider than has previously been the case, potentially generating further impact for this neglected area of research.

There may not be definitive answers available for the best way to prevent or treat TD, but this work will use all the best available evidence, highlight if there is good evidence for a specific treatment path, and provide high-quality evidence for choice of treatments and techniques for future testing.

Chapter 2 Hypotheses tested in the review (research questions)

To summarise evidence from clinical trials and observational studies of interventions used for treating or preventing deterioration of symptoms of antipsychotic-induced TD by performing an overview of systematic reviews, including updating Cochrane reviews, and NMA.

Specific objectives

1. To identify all relevant evaluative studies.
2. To produce a broad-brush overview of the evaluative research in this area and prioritise the top 10 candidate treatments for head-to-head comparisons.
3. To extract all relevant useful quantitative data on evaluations of the treatments, and to ensure that the source of these data is entirely transparent and made available for future researchers.
4. To produce reviews by:

    i. updating nine existing relevant Cochrane reviews for different groups of interventions comparing TD with placebo
    ii. adding head-to-head comparisons reporting for the treatment and prevention of deterioration of symptoms of antipsychotic-induced TD to all Cochrane reviews in:

        – adults with schizophrenia
        – adults with dementia

    iii. ranking identified interventions according to relevance for the NHS and selecting the potentially relevant ones for NMA
    iv. performing a NMA.

5. To work collaboratively to tailor this evidence to clinical, research and public needs using dissemination techniques appropriate for all three.

Chapter 3 Methods

Part A: methods for patient and public involvement

This project brought together expertise from a range of fields to plan and deliver the review. The main part was review work. In order to assess if current research met the needs of people with experience of TD, a small consultation was planned, taking results from the reviews and exploring whether or not the assessed outcomes matched service user priorities for managing TD. The consultation was advertised by e-mail via the McPin Foundation's large circulation list of people who are interested in being involved. It was also advertised on their website. Interested people were asked to contact the McPin Foundation to book a place to attend. Reimbursement for time and out-of-pocket expenses was offered.

A lay overview of the previously published version of a Cochrane review evaluating the effects of vitamin E in TD[47] gave the foundation for the discussions. All of the researchers involved in the consultation were extremely experienced in involving patients and the public. The session was planned to provide time to reflect on current research on TD and to consider gaps in knowledge.

The discussion was audio-taped and the service users were invited to write comments on Post-it® (3M, Bracknell, UK) notes and paper tablecloths, which were then collected and reviewed. The researchers listened to the recordings after the session and noted any points relevant to the above-mentioned questions that would have an impact on the funded systematic review. Full transcription and formal analyses were not appropriate in this case, as the consultation was not a piece of empirical qualitative work. Furthermore, two of the consultation facilitators had extensive experience in involving patients and the public in research and expert knowledge in this paradigm, including hosting focus groups (or, in this case, a consultation).

Informed by the results of the consultation, we updated outcomes for the summary-of-findings table for the systematic reviews. See *Appendix 1* for the full report.

Part B: methods for systematic review

Please see *Appendix 2* for differences between the project protocol and the review.

Interventions being assessed

We aimed to evaluate any intervention used for treating or preventing deterioration of symptoms of antipsychotic-induced TD. There is a vast array of strategies to deal with TD – one review identified over 100.[50] Based on our experience with Cochrane reviews in this research area, we grouped the interventions as follows:

1. vitamins
2. GABA agonists
3. benzodiazepines
4. anticholinergics
5. cholinergics
6. calcium channel blockers
7. non-antipsychotic dopaminergics and noradrenergics
8. specific antipsychotic drugs
9. antipsychotic reduction or cessation including intermittent therapy
10. other interventions, including botulin toxin, insulin or lithium, among others.

We compared interventions with other interventions used to treat or prevent deterioration of symptoms of antipsychotic-induced TD of relevance to people in the NHS, placebo or no intervention.

Prioritisation of interventions for the NHS

From the included studies we listed all interventions, regardless of the primary condition, in order to map research activity. From this mapping, we chose to target, for this report, the top 10 interventions that seem to have demonstrated some efficacy and that are relevant for clinical practice and the NHS.

Measurement of outcomes

The following outcomes were included in the overview:

- clinical improvement of TD symptoms
- deterioration of TD symptoms
- adverse events – extrapyramidal symptoms
- adverse events – all
- mental state
- acceptability of the treatment – leaving the study early
- social confidence, social inclusion, social networks, or personalised quality-of-life measures [this outcome was designated as important to patients, informed by the results of the patient and public involvement (PPI) consultation].

The Cochrane reviews included several more outcomes.

Design and theoretical/conceptual framework

We included randomised or quasi-randomised controlled trials containing data related to antipsychotic-induced TD, irrespective of language or place of publication. We also considered observational studies for inclusion with the following designs: (1) non-randomised controlled trials, (2) prospective cohort studies with a control group and (3) case–control studies. The systematic reviews and the overview of reviews follow Cochrane design and methodology.[53]

Target population

We included studies of adults with a diagnosis of antipsychotic-induced TD (according to any criteria), regardless of the primary condition.

Inclusion/exclusion criteria

We excluded studies in which participants had used antipsychotic drugs for < 3 months or in which the antipsychotic doses had not been stable for at least 1 month[4] (except in analyses of antipsychotic switch, withdrawal or reduction). In addition, we excluded studies evaluating children and adolescents, or studies evaluating interventions that are not relevant to the NHS.

We also excluded studies that were > 10 years old that otherwise qualified for inclusion, but reported no useable data and in which:

- we contacted study authors requesting data, but received no reply
- we were unable to contact any of the study authors.

Setting/context

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

Search strategy

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

We searched Cochrane Schizophrenia Group's Study-Based Register of Trials on 16 July 2015 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 Allied and Complementary Medicine Database (AMED), Bioscience Information Service, Cumulative Index to Nursing and Allied Health Literature (CINAHL), EMBASE, MEDLINE, PsycINFO and PubMed, and registries of clinical trials including CT.Gov, International Standard Randomised Controlled Trial Number (ISRCTN) and the World Health Organization's International Clinical Trials Registry Platform registries] and their monthly updates, hand-searches, grey literature and conference proceedings (see Group's Module: http://onlinelibrary.wiley.com/o/cochrane/clabout/articles/SCHIZ/frame.html). There are no language, date, document type or publication status limitations for inclusion of records into the register.

We also searched the Cochrane Dementia and Cognitive Improvement Group's Register of Trials via the Cochrane Register of Studies Online (CRSO; http://crso.cochrane.org/) on 21 July 2015 using the following string:

DEMENTIA:CC AND (*Tardive* OR *Dyskinesia*):TI,AB,KY.

For more information about this register, see the register's page (www.medicine.ox.ac.uk/alois/content/about-alois).

Finally, we searched EMBASE, MEDLINE, and PsycINFO for observational studies on 9 January 2017, and details of the search strategy can be found in *Appendix 3*.

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

As some of the Cochrane reviews have not been updated during the past decade, and systematic reviews methods have changed considerably during this period of time, we also cross-checked all included, awaiting assessment, ongoing and excluded studies in the suite of nine Cochrane reviews on antipsychotic-induced TD.

Selection of studies

We uploaded search results into a web-based system (DistillerSR®, Evidence Partners, Ottawa, ON, Canada; www.systematic-review.ca). At least two reviewers (out of Antonio Grande, Rosie Asher, Hanna Bergman and Karla Soares-Weiser) independently screened all citations and abstracts identified by the search. Two reviewers (Hanna Bergman and Karla Soares-Weiser) inspected all studies from the nine Cochrane reviews on TD. We obtained full reports for potentially eligible studies and these were independently screened by two review authors (Antonio Grande and Rosie Asher). Disagreements were resolved through discussion with reviewers (Hanna Bergman and Karla Soares-Weiser). We documented justifications for excluding studies from the review.

Data extraction and management

Reviewer Rosie Asher extracted data from all included studies. These were cross-checked by Antonio Grande, and further validated by Hanna Bergman. Any disagreements about data extraction were documented and resolved by consensus. Any potential differences or data entry problems were discussed and decisions documented.

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

We attempted to contact authors in order to obtain missing information or for clarification whenever necessary.

We extracted data into tabular format, with an 'address' to each point in the document from which each data element had been taken. This allows future researchers to verify extraction and avoid duplication of effort. All data extracted in this way are fully available to researchers.[54]

We extracted data from graphs in GetData Graph Digitizer software version 2.26 (GetData Graph Digitizer, S Federov, Moscow, Russia).

Some specific outcomes

No clinically important improvement in tardive dyskinesia

'No clinically important improvement' was defined as < 50% improvement on any scale measuring TD, or as defined by triallists of the individual studies. For this outcome we assumed that participants with missing data did not improve.

We have shown details of the scales that provided usable data below.

Brief Psychiatric Rating Scale

The Brief Psychiatric Rating Scale (BPRS) is an 18-item scale measuring positive symptoms, general psychopathology and affective symptoms.[55] The original scale has 16 items, although a revised 18-item scale is commonly used. Total scores can range from 0 to 126. Each item is rated on a seven-point scale, with high scores indicating more severe symptoms.

Extrapyramidal Symptom Rating Scale

The Extrapyramidal Symptom Rating Scale (ESRS) was developed to assess four types of drug-induced movement disorders: Parkinsonism, akathisia, dystonia and TD.[56] The score for TD, ranging from 0 to 42, is based on the sum of all seven items in the TD objective examination.

Simpson–Angus Scale

The Simpson–Angus Scale (SAS)[57] is a 10-item scale, with a scoring system of 0–4 for each item, measuring drug-induced Parkinsonism, a short-term drug-induced movement disorder. A low score indicates low levels of Parkinsonism.

Udvalg for Kliniske Undersøgelser Side-Effect Rating Scale

The Udvalg for Kliniske Undersøgelser (UKU) was developed to provide a comprehensive side-effect rating scale with well-defined and operationalised items to assess the side effects of psychopharmacological medications.[58] The scoring sheet includes 48 items, with higher scores indicating more side effects.

Assessment of risk of bias of the included studies

Rosie Asher classified and Hanna Bergman cross-checked studies as being at low, unclear or high risk of bias, based on domain-specific assessments of risk of bias done using the Cochrane Collaboration's existing risk-of-bias tool.[53] 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.

We incorporated these judgements in assessing limitations in study design for outcomes in the summary-of-findings table (see *Table 2*).

Risk-of-bias assessment for observational studies was performed by a senior systematic reviewer (Artemisia Kakourou) using a tool that is currently being tested by Cochrane.[59] The following domains were assessed: (1) confounding and selection bias (including confounders measured and addressed, use of matching and methods of adjustment), (2) performance bias (including any considerations of co-intervention), (3) missing data, (4) detection (for cohort studies) or recall bias (for case–control studies) and (5) selective reporting bias.

Data analysis

Analyses of single studies

Dichotomous data

For each study, the risk ratio (RR) and 95% CI were derived for people receiving the intervention compared with the control.

Continuous data

We included continuous data from rating scales only if:

- the psychometric properties of the measuring instrument had been described in a peer-reviewed journal[60]
- the measuring instrument was not written or modified by only one of the authors of the particular study from which the data were taken, but had also received independent validation.

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

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

Crossover trials

A major concern of crossover trials is the carry-over effect. This 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 washout phase. For the same reason, crossover trials are not appropriate if the condition of interest is unstable.[61] As both effects are very likely in severe mental illness, we used only data of the first phase of crossover studies.

Meta-analyses

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

We understand that there is no closed argument for preference for use of fixed- 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-effects model for all analyses.

Observational studies

We provided an overview of evidence from observational studies. Study characteristics, results and conclusions were tabulated and summarised.

Variation in efficacy according to characteristics of individuals and studies

Visual inspection of the forest plots was used to evaluate the potential statistical heterogeneity (differences between the true intervention effects in the different studies). Heterogeneity was quantified by estimating the between-study variance τ^2- and the I^2-statistics,[62,63] which measures the percentage of observed variation that can be attributed to true differences between the studies.[62] In forest plots and meta-analyses, τ^2 was estimated using the restricted maximum likelihood estimator,[64] whereas its 95% CIs were estimated by the Q-profile method.[65]

Summarising and interpreting results

We used the Grading of Recommendations, Assessment Development and Evaluation (GRADE) approach[66–68] to assess the evidence of the various interventions. For all NHS-prioritised interventions and outcomes, we have presented a summary-of-findings table (see *Table 2*) based on the GRADE results.

Investigation of heterogeneity

We considered a degree of heterogeneity inevitable, and hence we planned to explore only important heterogeneity ($I^2 \geq 75\%$) using metaregression or subgroup analyses for the effect modifiers: (1) risk of bias in the different study designs; (2) length of antipsychotic use; (3) underlying disease (dementia or schizophrenia); (4) sex/age; (4) type of treatment use, specifically first- or second-generation antipsychotics; and (5) whether or not other concomitant drug interventions were used. Analyses were homogeneous with no important heterogeneity ($I^2 \geq 75\%$).

Sensitivity analyses

To ensure that our imputations did not bias our results, we planned to restrict the analyses to studies considered to be at low, and low or unclear risk of selection and detection bias. However, all studies were at unclear risk of selection and detection bias, and we did not carry out this restricted analysis.

Planning of future studies

To judge the sufficiency of the evidence for the comparison of switching to any FGAs versus any SGAs, we calculated the conditional power of an updated meta-analysis for the particular comparison as described in Sutton *et al.*[69] We further investigated whether or not hypothetical future studies are likely to alter the meta-analysis results using extended funnel plots.[70] Given the small number of studies available, a fixed-effect inverse-variance meta-analysis model was assumed for this analysis.

Power of an updated meta-analysis based on simulations of new studies

We estimated the power of an updated meta-analysis through the simulation of (sufficiently similar) hypothetical 'new' studies and calculating the proportion of times that the meta-analysis result would be statistically significant.[69] The event rate was assumed to be equal to that observed, and the number of simulations on which we estimated power was 1000.

Extended funnel plots

We further assessed whether or not future studies are likely to alter the meta-analysis result via extended funnel plots.[70] A colour code appended in conventional funnel plots illustrates where the result of an updated meta-analysis would lie, depending on the effect estimate and the standard error of a hypothetical new study to be added to the evidence base.

Part C: methods for network meta-analysis

In order to facilitate clinical decision-making and a plan of future research, we planned to conduct a NMA as we expected that few studies reported trials with head-to-head comparisons of different interventions.

We carried out an exploratory NMA, and the results are presented in *Appendix 4*. The main reasons for the decision of only presenting the results in the appendix are (1) there were few data, (2) there was a median of one study per comparison, ranging up to 11 for cholinergic drugs and 13 for vitamin E, (3) there were no differences between pairwise meta-analyses and NMA and (4) there were no sufficiently connected networks.

Chapter 4 Part A: results of patient and public involvement

Dawn-Marie Walker worked with the McPin Foundation to organise an event to which a group of service users ($n = 6$) were invited and at which there was the opportunity to discuss the review's results. All of the service users had TD or were at risk of developing it. All attendees recognised TD as a serious condition: 'TD can be as debilitating as the psychosis itself'. They recognised that TD could increase stigma, as one could not hide it, which in turn would have a negative impact on one's self-esteem. Indeed, there were suggestions for a therapeutic intervention to help people with TD learn coping mechanisms. The attendees argued that prevention was better than cure, and wondered how much psychiatrists knew about TD and, in turn, how much patients knew prior to taking a medication. With regard to the outcomes of the trial, they thought that the review placed too much emphasis on pharmaceutical interventions and were concerned that an adverse effect of medication was being treated by other medications. Owing to the lack of definite findings about a treatment for TD, one commented: 'I'm appalled by the poverty of this evidence base given how debilitating TD is' (*Figure 1*).

One of the questions participants posed was whether or not research could be done to try to identify those who are at risk of TD. There was also some debate about the similarities in presentation between Tourette syndrome and TD, with a number of public awareness campaigns helping reduce the stigma of Tourette syndrome, and some participants asked if a similar approach would work for TD. When the outcome measures cited in the review were discussed, the attendees thought all of them were important; however, they felt that some relating to empowerment and autonomy, such as knowledge of TD (health-care practitioner, patient and public) or a social integration scale (see *Appendix 1*), were missing.

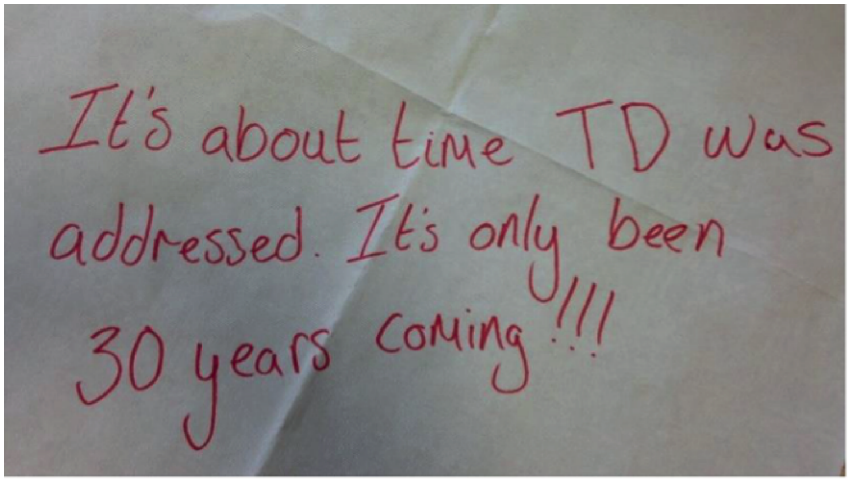

FIGURE 1 Message from one of the participants of the PPI consultation of service user perspectives on TD research.

Chapter 5 Part B: results of systematic reviews

Search and screening

The update search retrieved 704 references from the Cochrane Schizophrenia Group's Register and 29 references from the Cochrane Dementia and Cognitive Improvement Group's Register. Four duplicate reports included in both these registers were removed. In addition, as we aimed to code all studies, we independently re-extracted the data of all included and excluded studies in the published TD Cochrane reviews and cross-checked all references; 222 additional records were found in the reference lists of previously published Cochrane reviews. In total, we screened 947 records. After excluding irrelevant references when screening the titles and abstracts, we identified 565 potentially relevant full-text articles that were assessed for eligibility. We excluded 398 full-text articles (grouped into 329 studies) with documented reasons for exclusion (see *Appendix 5*). We included 112 studies (167 references) in the nine Cochrane reviews (see *Appendix 6*), including two studies awaiting classification and 11 ongoing studies.

We did not identify any included studies for people with dementia and antipsychotic-induced TD. See *Figure 2* for the screening and study selection process.

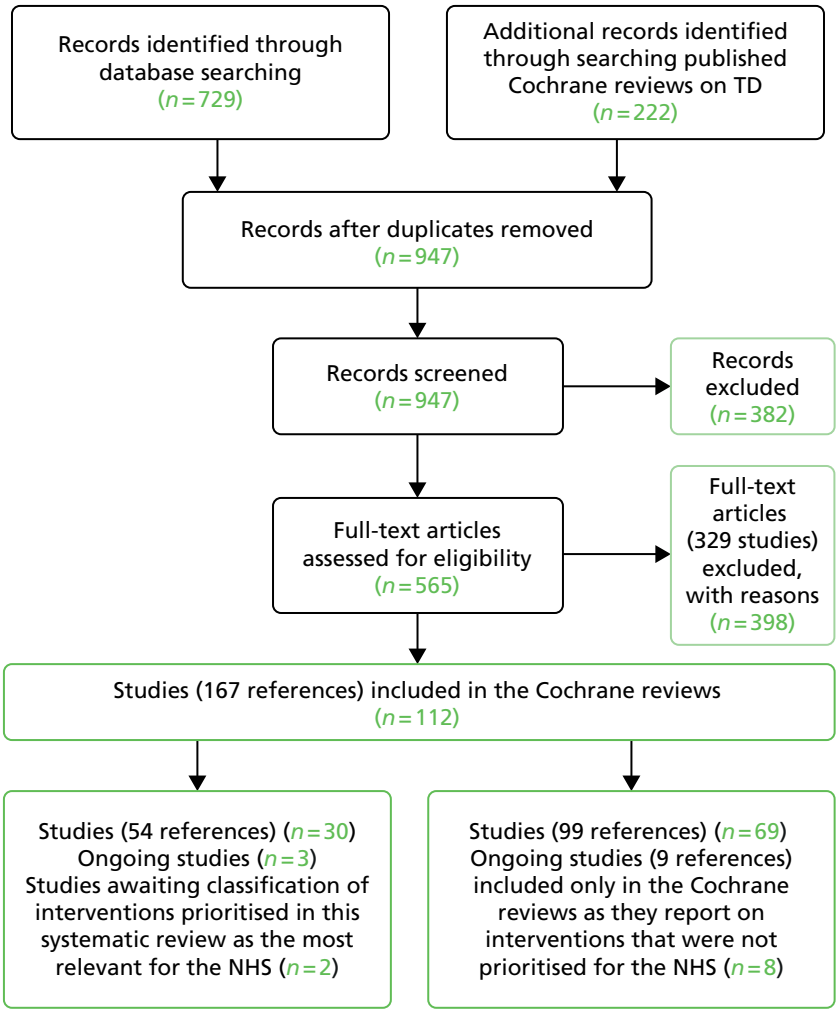

FIGURE 2 The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

Studies were assessed in Chinese, Danish, French, German, Japanese, Korean, Persian, Portuguese, Spanish and English. There were 10 included studies in Chinese,[71–80] three in German,[81–83] three in Japanese,[84–86] and one each in Persian[87] and in Portuguese.[88]

The observational studies search retrieved 3312 references. After de-duplication, 2702 references were screened. A total of 2261 titles and abstracts were excluded, and 41 full texts were retrieved and screened. Thirty studies (31 references) were excluded and eight studies (10 references) were included [see *Figure 11* in *Appendix 3* for the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram].

Prioritisation of interventions

In consultation with a NHS consultant psychiatrist (Clive E Adams), we identified the 10 interventions that are mostly relevant for the NHS, and these interventions (30 unique studies) were included in the current report. The 10 were chosen for 'local' accessibility, breadth of approach and practicality. We realise that opinions could differ on which choice should have been made, but it was directed by having available trials and also being accessible in the UK's NHS. The 10 interventions prioritised as the most relevant for the NHS were anticholinergics, antipsychotics, antipsychotic reduction, antipsychotic withdrawal, benzodiazepines, buspirone, hypnosis and relaxation, placebo, treatment as usual (TAU) and vitamin E. These 10 interventions are included in the pairwise comparisons of this report and in the NMA.

Box 1 lists all interventions from eligible randomised trials included in the Cochrane reviews, and the interventions prioritised and reported in this overview are highlighted in bold. The full Cochrane reviews should be the point of reference for details of every study and outcome (see *Appendix 6*). This report represents a summary.

Accessible data

Because of copyright it is not possible to share the full text of original papers, but all data have been extracted and tabulated, and the exact location of every piece of data is recorded in these tables. Pairing these tables with the original report allows tracking of data back to full text. These extracted data are freely available on Cochrane Schizophrenia Group's website via ResearchGate (ResearchGate GmbH, Berlin, Germany).[54] Also, the extracted data beside the linked full-text reports are available to be used for research purposes in Cochrane Schizophrenia Group's Study-Based Register of Trials.

Description of studies

Studies included in overview

Randomised controlled trials

We included 30 unique clinical trials (54 articles published between 1973 and 2011[75,78,89–139]) reporting results for the effects of the prioritised interventions on clinical improvement and deterioration of TD symptoms, mental state, adverse events and acceptability of treatment. None of the included studies reported on quality of life. All studies were described as being randomised controlled. Seven of the 30 studies used a crossover design with two periods[89–95] and, as planned, we used only data from before the first crossover (see *Appendix 2*, *Unit of analysis issues*). Studies were conducted in North America (15 studies[89,92,93,96,97,101,104,117,120,121,123,128,129,137,139]), Asia (10 studies[75,78,90,91,94,108,112,115,127,138]), Europe (four studies[95,98,119,130]) and Africa (one study[110]), with a total of 1255 participants included. Studies included both men and women of mostly wide age ranges, but participants were mainly men in their fifties, with mean ages ranging from 32 to 68 years.

BOX 1 Prioritised interventions for treatment of TD from eligible randomised trials (those in bold are prioritised interventions)

- **Anticholinergic: procyclidine**[a].
- **Anticholinergic continuation: biperiden**.
- **Anticholinergic withdrawal: biperiden**.
- **Antipsychotic continuation**.
- **Antipsychotic reduction**.
- **Antipsychotic withdrawal (with placebo)**.
- **Benzodiazepine: clonazepam**.
- **Benzodiazepine: diazepam**.
- Calcium channel blocker: diltiazem hydrochloride.
- Calcium channel blocker: diltiazem hydrochloride.
- Calcium channel blocker: nifedipine.
- Cholinergic medication: deanol.
- Cholinergic medication high dose: deanol, 2 g.
- Cholinergic medication low dose: deanol, 1 g.
- Cholinergic medication: galantamine.
- Cholinergic medication: lecithin.
- Cholinergic medication: meclofenoxate hydrochloride.
- Cholinergic medication: rivastigmine.
- GABA agonist: baclofen.
- GABA agonist: GABA.
- GABA agonist: progabide.
- GABA agonist: sodium valproate.
- GABA agonist: THIP.
- Miscellaneous: L-stepholidine.
- Miscellaneous: branched-chain amino acids.
- **Miscellaneous: buspirone**.
- Miscellaneous: ceruletide.
- Miscellaneous: cyproheptadine.
- Miscellaneous: dihydrogenated ergot alkaloids/co-dergocrine mesylate.
- Miscellaneous: oestrogen.
- Miscellaneous: gamma-linolenic acid supplementation (oil of evening primrose).
- Miscellaneous: *Ginkgo biloba* standardised extract (EGb-761).
- **Miscellaneous: hypnosis or relaxation**.
- Miscellaneous: insulin.
- Miscellaneous: levetiracetam.
- Miscellaneous: lithium.
- Miscellaneous: MAO inhibitors (isocarboxazid, selegiline).
- Miscellaneous: melatonin.
- Miscellaneous: omega-3 fatty acid (ethyl-eicosapentaenoic acid).
- Miscellaneous: papaverine.
- Miscellaneous: pemoline.
- Miscellaneous: phenylalanine.
- Miscellaneous: piracetam.
- Miscellaneous: promethazine.
- Miscellaneous: ritanserin.
- Miscellaneous: VMAT2 inhibitor (NBI-98854).
- Non-neuroleptic catecholaminergic: amantadine.
- Non-neuroleptic catecholaminergic: bromocriptine.
- Non-neuroleptic catecholaminergic: carbidodopa/levodopa.

BOX 1 Prioritised interventions for treatment of TD from eligible randomised trials (those in bold are prioritised interventions) (*continued*)

- Non-neuroleptic catecholaminergic: L-DOPA.
- Non-neuroleptic catecholaminergic: oxypertine.
- Non-neuroleptic catecholaminergic: reserpine.
- Non-neuroleptic catecholaminergic: tiapride.
- Non-neuroleptic catecholaminergic: tetrabenazine.
- Non-neuroleptic catecholaminergic: celiprolol.
- Non-neuroleptic catecholaminergic: methyldopa.
- Phenobarbital (as active placebo).
- **Placebo**.
- **Switch to a different FGA**.
- **Switch to a different FGA (not specified)**.
- **Switch to a different FGA (haloperidol)**.
- **Switch to a different FGA [molindone (Moban®; Endo Pharmaceuticals Inc., Malvern, PA, USA)]**[b].
- **Switch to a different FGA (thiopropazate)**[b].
- **Switch to a different FGA (zuclopentixol)**[b].
- **Switch to SGA**.
- **Switch to SGA (amisulpride)**.
- **Switch to SGA (clozapine)**.
- **Switch to SGA (olanzapine)**.
- **Switch to SGA (quetiapine)**.
- **Switch to SGA (risperidone)**.
- **Switch to SGA (ziprasidone)**.
- **TAU**.
- Vitamin B_6 (pyridoxal 5′-phosphate).
- **Vitamin E**.

L-DOPA, L-3,4-dihydroxyphenylalanine; MAO, monoamine oxidase; THIP, 4,5,6,7-tetrahydroisoxazolo[5,4-c] pyridin-3-ol; VMAT2, vesicular monoamine transporter 2.

a Not used (in a head-to-head comparison with isocarboxazid).

b Not used (in a head-to-head comparison with another FGA).

An overview of characteristics of the included studies contributing data for this report are presented in *Table 1* and full details of study characteristics are available in *Appendix 7*.

In addition to the included studies:

1. We have requested details on participants from study authors to determine the eligibility for one study comparing dexetimide and benzhexol.[140]
2. One study described as a double-blind, randomised study on vitamin E could not be identified after exploring numerous sources.[141]
3. The full text of a randomised controlled trial (RCT), published in 1992, comparing buspirone and placebo could not be identified.[142]
4. The full text of a RCT described in a trial registry comparing quetiapine with risperidone could not be identified[143]
5. One study comparing cannabidiol extract with vitamin E is ongoing.[144]

Full details of characteristics for ongoing trials and studies awaiting classification are available in *Appendix 8*.

Observational studies

We included eight unique observational studies (10 articles published between 1983 and 2016[145–154]) reporting results for the effects of the prioritised interventions on clinical improvement and deterioration of TD symptoms and mental state. None of the included studies reported on quality of life, adverse events or acceptability of the intervention. Two studies (three references) were described as non-randomised controlled[145–147] and six (seven references) were described as prospective cohorts.[148–154] Studies were conducted in North America (four studies[145,149,151,153]), Asia (two studies[150,152]) and Europe (two studies[146,148]). A total of 200 participants were included. Studies included adults, both men and women of mostly wide age ranges, with mean ages ranging from 26 to 84 years.

An overview of characteristics of the included observational studies contributing data to this report is presented in *Appendix 3* (see *Table 4*).

Studies excluded from this review

Randomised controlled trials

Sixty-nine studies (99 articles) did not investigate prioritised comparisons and were not included in this report. These studies investigated calcium channel blockers (three studies), cholinergic medication (14 studies), GABA antagonists (11 studies), non-antipsychotic dopaminergic or noradrenergic medication (nine studies), FGAs versus other FGAs (three studies), anticholinergic versus monoamine oxidase (MAO) inhibitors (one study) and various miscellaneous, experimental treatments, such as lithium, melatonin and insulin (28 studies). Full details of these studies and results of comparisons are available in the Cochrane reviews and an overview is available in *Appendix 9*.

Observational studies

Please see *Appendix 3* (see *Table 5*) for details of references excluded at full-text screening. In addition, one of the included observational studies was not prioritised for this report because it investigated deep-brain stimulation, not one of the NHS-relevant interventions.[146,147]

Risk-of-bias assessments

Randomised controlled trials

Detailed risk-of-bias assessments of all included studies are in *Appendix 7*.

Overall risk of bias for the included studies was rated as being high to unclear. It is astonishing to note that only one of the studies was rated as being free from risk of selection bias.[137] The remaining trials reported inadequately on randomisation and allocation concealment. Furthermore, seven studies were rated as being at high risk of performance bias and 13 were rated as being of unclear risk. This was mainly a result of trials being open label, or poor reporting of blinding. One study was rated as being at high risk of detection bias and 18 were rated as being of unclear risk; this is mainly because of poor reporting. Ten studies were rated as being at high risk of attrition bias (because of high or imbalanced dropout rates) and two at unclear risk. Thirteen studies were rated as being at high risk of reporting bias as a result of selective reporting of outcome measures, and 12 were rated at an unclear risk. We sought information from study authors where risk of bias was rated as being unclear.

As a post hoc comparison, we evaluated risk of bias in studies published within the past 20 years (1997–2011) compared with older studies published until 1996 (*Figure 3*). We found that methodological quality had improved only marginally over time on most risk-of-bias categories (selection, performance, attrition and reporting biases). There was no change for detection bias, and other bias had improved over time.

TABLE 1 Overview of included RCTs characteristics

Included studies (first author and year of publication)	Study characteristic									
	Methods				Participants				Interventions	
	Randomised	Double blind	Design	Duration (weeks)	Diagnosis	*n*	Age (years)	Sex	Group 1 intervention	Dose
Antipsychotic drugs										
Kazamatsuri *et al.*, 1973[96]	✗	✗	Parallel	24	Chronic SCZ and TD	13	Mean 55.8	F and M	Haloperidol (after 4-week washout)	4 mg b.i.d. (weeks 15–24 16 mg/day)
Kane *et al.*, 1983[97]	✗	✗	Parallel	48	SCZ/ schizoaffective and TD	8	17–60	Unknown	Fluphenazine	Low dose (1.25–5 mg every 2 weeks)
Cookson, 1987[98]	✗	✗	Parallel	44	SCZ	18	Mean 44.5	F and M	Flupentixol decanoate	50% reduction from original dose
Chouinard and Arnott, 1992,[99,100] 1993;[102] Chouinard *et al.*, 1993;[103] Chouinard, 1995[101]	✗	✗	Parallel	8	SCZ	135	Mean 39	F and M	Risperidone	2 mg per day ($n = 8$), 6 mg per day ($n = 6$), 10 mg per day ($n = 6$), 16 mg per day ($n = 11$)
Tamminga *et al.*, 1994[104]	✗	✗	Parallel	52	SCZ and TD	32	Mean 35.57	F and M	Clozapine and placebo	293.8 mg per day
Bai *et al.*, 2002,[105] 2003,[108] 2005;[106] Pai *et al.*, 2002,[107] 2001[109]	✗	✗	Parallel	12	SCZ and TD	42	Mean 50.2	F and M	Risperidone (after 2-week washout)	2 mg per day increased to 6 mg per day (6 weeks) and maintenance (12 weeks)
Emsley *et al.*, 2004[110,111]	✗		Parallel	50	SCZ and TD	45	Mean 49.2	F and M	Quetiapine (after 2-week washout)	100 mg per day increased to 400 mg per day
Bai *et al.*, 2005[112–114]	✗		Parallel	24	SCZ and TD	80	Mean 50.2	F and M	Olanzapine	Unknown
Chan *et al.*, 2010[115,116]	✗		Parallel	24	SCZ/ schizoaffective and TD	60	Mean 45.3	F and M	Risperidone (after 3–7 days washout)	1.9 mg per day increased to 4.1 mg per day
Caroff *et al.*, 2011;[117] Miller *et al.*, 2005[118]	✗	✗	Parallel	78	SCZ and TD	200	Mean 47.2	F and M	Olanzapine	7.5 mg q.d./b.i.d./ t.i.d./q.i.d.
Anticholinergic drugs										
Greil *et al.*, 1984[119]	✗	✗	Parallel	7	SCZ and TD	10	Mean 56.6	F and M	Biperiden	Dose stopped after 4 weeks and placebo was then given for 3 weeks

				Outcomes				
Group 2 intervention	Dose	Other groups	Other medications allowed	TD symptoms	Study discontinued	QoL measures	Mental state	Adverse events
Tetrabenazine (after 4-week washout)	50 mg b.i.d. (weeks 15–24 200 mg/day)		Antidiabetics and anticonvulsants	✗	✗			
Fluphenazine maintenance	Standard dose 12.5–50 mg/2 weeks)		Procyclidine/ flurazepam/ diazepam	✗	✗			
Flupentixol maintenance	Standard dose		Procyclidine/ haloperidol/ zuclopentixol decanoate/ amitriptyline	✗				✗
Haloperidol	20 mg per day	Placebo	Benzodiazepines/ biperiden or procyclidine					✗
Haloperidol and benztropine	28.5 mg/day		N/A		✗			
Placebo	2 mg per day increased to 6 mg per day (6 weeks) and maintenance (12 weeks)		Benzodiazepines/ antiparkinson medications	✗			✗	✗
Haloperidol (after 2-week washout)	5 mg per day increased to 10 mg per day		Benzodiazepines/ anticholinergic agents	✗	✗		✗	
Amisulpride	Unknown	FGA (unknown dose)	N/A	✗	✗		✗	✗
Olanzapine	8.1 mg per day increased to 12.6 mg per day		N/A	✗			✗	✗
Quetiapine	200 mg/q.d./ b.i.d./t.i.d./q.i.d.	Risperidone 1.5 mg/q.d./ b.i.d./t.i.d./q.i.d. or ziprasidone 40 mg/q.d./ b.i.d./t.i.d./q.i.d.	N/A		✗			
Biperiden	Dose stopped after 1 week and placebo given for 6 weeks		Antipsychotic medications		✗			

TABLE 1 Overview of included RCTs characteristics (*continued*)

Included studies (first author and year of publication)	Study characteristic									
	Methods				Participants				Interventions	
	Randomised	Double blind	Design	Duration (weeks)	Diagnosis	*n*	Age (years)	Sex	Group 1 intervention	Dose
Benzodiazepines										
Bobruff *et al.*, 1981[120]	✗	✗	Parallel	2	Psychiatry patients and TD	21	Mean 51.6	F and M	Clonazepam	3.9 mg per day
Weber *et al.*, 1983[89]	✗		Cross over	24	SCZ/brain syndrome/ unknown and TD	15	Mean 57.4	F and M	Standard care and diazepam	6–25 mg per day
Csernansky *et al.*, 1988[121,122]	✗	✗	Parallel	5–6	SCZ and TD	17	Unknown	Unknown	Diazepam	7.2 mg per day
Xiang and Zhen, 1997[75]	✗	✗	Parallel	8	SCZ and TD	24	Mean 39.4	F and M	Standard care and clonazepam	4–6 mg per day
Vitamin E										
Elkashef *et al.*, 1990[93]	✗	✗	Cross over	10	SCZ/ schizoaffective and TD	10	Mean 56.6	F and M	Vitamin E	400 IU per day (1 week), 400 IU b.i.d. (1 week), 400 IU t.i.d. (2 weeks)
Schmidt *et al.*, 1991[95]	✗	✗	Cross over	4	SCZ/ schizoaffective/ depression and TD	23	Mean 45	F and M	Vitamin E	1200 IU per day
Egan *et al.*, 1992[92]	✗	✗	Cross over	12	SCZ/ schizoaffective/ depression/BD and TD	21	Mean 43.9	F and M	Vitamin E	Week 1: 400 IU per day; week 2: 800 IU per day; week 3: 1200 IU per day; weeks 4–6: 1600 IU per day
Adler *et al.*, 1992,[124] 1993,[125,126] 1998[123]	✗	✗	Parallel	36	SCZ/ depression and TD	40	Mean 58	F and M	Vitamin E	Dose increasing to 1600 IU per day
Akhtar *et al.*, 1993[127]	✗	✗	Parallel	4	Psychiatry patients and TD	32	Mean 53	F and M	Vitamin E	600 mg per day increased to 1200 mg per day
Dabiri *et al.*, 1994[128]	✗	✗	Parallel	12	Psychiatry patients and TD	12	Mean 51	F and M	Vitamin E	Week 1: 400 IU per day; week 2: 800 IU per day; weeks 3–12: 1200 IU per day
Lam *et al.*, 1994[94]	✗	✗	Cross over	16	SCZ and TD	16	Mean 61.8	F and M	Vitamin E	Week 1: 400 IU per day; week 2: 400 IU b.i.d.; weeks 3–6: 400 IU t.i.d.
Lohr and Calgiuri, 1996[129]	✗	✗	Parallel	8	SCZ/ depression/BD and TD	55	Mean 48.9	F and M	Vitamin E	1600 IU per day

				Outcomes				
Group 2 intervention	Dose	Other groups	Other medications allowed	TD symptoms	Study discontinued	QoL measures	Mental state	Adverse events
Phenobarbital (as active placebo)	88.6 mg per day		Antipsychotics	✗	✗			✗
Standard care	Unknown		Antipsychotic and anticholinergic medications	✗	✗		✗	
Placebo	48.3 mg per day	Alprazolam	Anticholinergics	✗	✗			
Standard care and placebo	Unknown		Antipsychotic and anticholinergic medications	✗	✗			
Placebo	Unknown		Antipsychotics	✗	✗			✗
Placebo	Unknown		Antipsychotics	✗	✗			✗
Placebo	Unknown		Antipsychotics	✗	✗			✗
Placebo	Unknown		Antipsychotics	✗	✗			
Placebo	Unknown		Antipsychotics	✗	✗		✗	✗
Placebo	Unknown		Antipsychotics	✗	✗			✗
Placebo	Unknown		Antipsychotics	✗	✗			
Placebo	Unknown		Antipsychotics	✗	✗		✗	

TABLE 1 Overview of included RCTs characteristics (*continued*)

Included studies (first author and year of publication)	Study characteristic									
	Methods				Participants				Interventions	
	Randomised	Double blind	Design	Duration (weeks)	Diagnosis	*n*	Age (years)	Sex	Group 1 intervention	Dose
Dorevitch *et al.*, 1997[91]	✗	✗	Cross over	20	SCZ and TD	10	Mean 63.1	F and M	Vitamin E	Dose increasing to 1600 IU per day
Dorevitch *et al.*, 1997[90]	✗	✗	Cross over	20	SCZ/ schizoaffective and TD	40	Mean 64.4	F and M	Vitamin E	Week 1: 400 IU per day; week 2: 800 IU per day; week 3: 1200 IU per day; weeks 4–8: 1600 IU
Sajjad, 1998[130]	✗	✗	Parallel	28	TD	20	Mean 68	F and M	Vitamin E	400 mg per day increased to 1600 mg per day
Tracy *et al.*, 1997;[131] Lohr and Lavori, 1998;[132] Edson *et al.*, 1997;[133] Caligiuri *et al.*, 1997;[134] Adler *et al.*, 1994,[135] 1999;[137] Brindler, 2001[136]	✗	✗	Parallel	52	SCZ/ schizoaffective and TD	158	Mean 50	F and M	Vitamin E	1600 IU per day
Zhang *et al.*, 2004[138]	✗	✗	Parallel	12	SCZ and TD	41	Mean 54.5	F and M	Vitamin E	Week 1: 800 IU per day; weeks 2–12: 1200 IU per day
Buspirone										
Zeng, 1995[78]	✗	✗	Parallel	6	TD	42	Mean 32.5	F and M	Buspirone	Dose management (1–12 capsules per day)
Hypnosis and relaxation										
Glover, 1980[139]	✗		Parallel	8 sessions	SCZ and TD	15	Mean 34.9	F and M	Hypnosis or relaxation	8 sessions

BD, bipolar disorder; b.i.d., twice per day; F, female; M, male; N/A, not applicable; q.d., one per day; q.i.d., four times per day; QoL, quality of life; RCT, randomised controlled trial; SCZ, schizophrenia; t.i.d., three times per day.

				Outcomes				
Group 2 intervention	Dose	Other groups	Other medications allowed	TD symptoms	Study discontinued	QoL measures	Mental state	Adverse events
Placebo	Unknown		Chlorpromazine		✗			✗
Placebo	Unknown		Antipsychotics	✗	✗			✗
Placebo	Unknown		Antipsychotics	✗	✗			✗
Placebo	Unknown		Antipsychotics	✗	✗		✗	✗
Placebo	Unknown		Antipsychotics	✗	✗			
Placebo	Dose management (1–12 capsules per day)		Antipsychotic and anticholinergic medications	✗				✗
TAU	8 sessions		Psychotropics		✗			

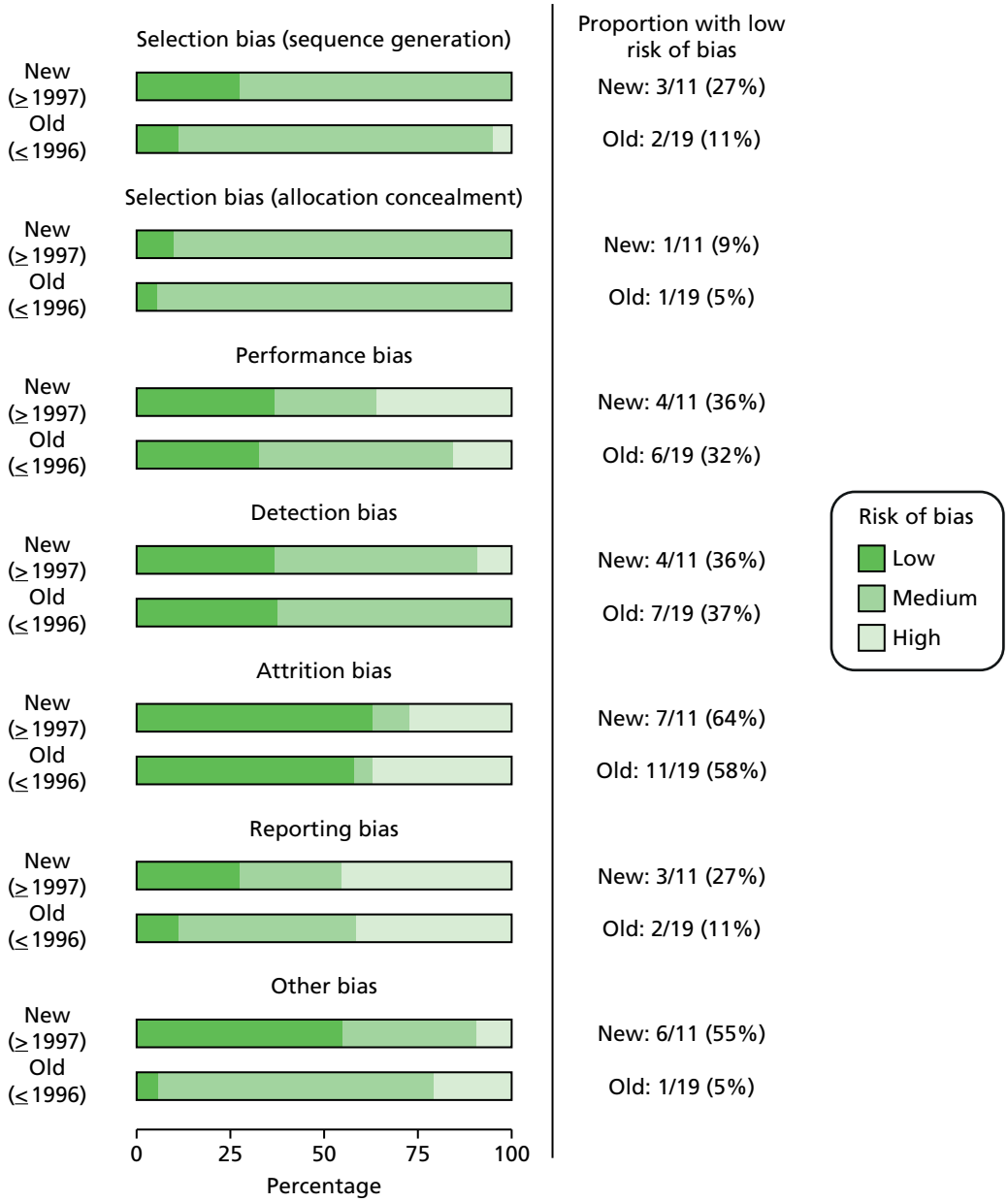

FIGURE 3 Old (1973–96) vs. new (1997–2011) studies risk of bias.

Observational studies

Detailed risk-of-bias assessments of all included studies are in *Appendix 3* (see *Table 4*).

Overall risk of bias for the included observational studies was rated as being high to unclear. None of the observational studies was free from risk of selection bias, one study reported controlling for baseline confounding, and three studies reported a reliable outcome assessment. For the domains of incomplete outcome data and selective outcome reporting, none of the studies reported mechanisms to avoid bias (*Figure 4*).

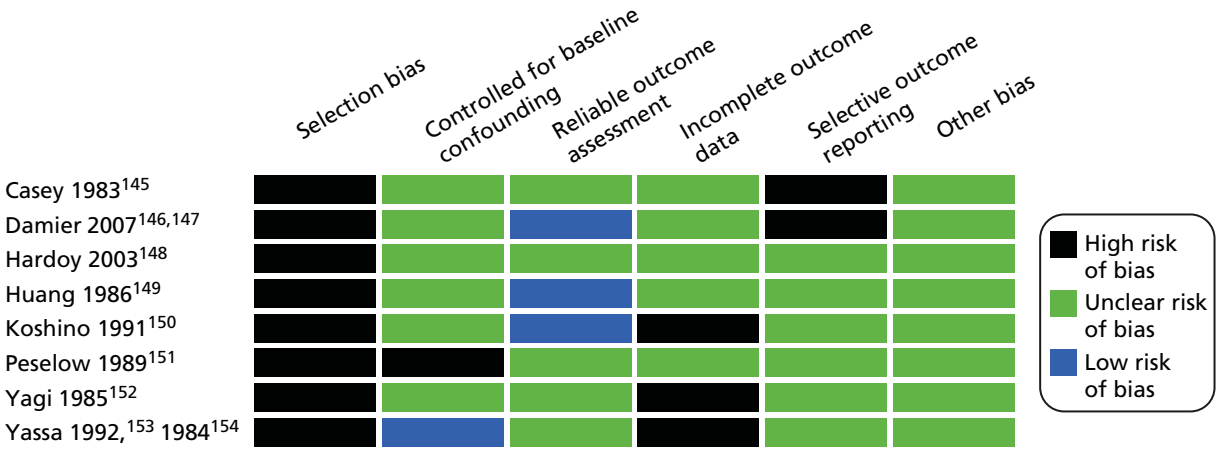

FIGURE 4 Overview of included observational studies risk of bias.

Effects of interventions

Table 2 summarises the results from RCTs for all comparisons. Forest plots for all analyses from RCTs are in *Appendix 10*. An overview of results from observational studies is in *Appendix 3* (see *Table 4*).

Comparison 1: reduced dose of antipsychotics versus continuing antipsychotics

Two very small randomised trials[97,98] conducted with schizophrenia or schizoaffective disorder inpatients and outpatients in the UK and USA reported on reduced doses compared with standard doses of flupentixol and fluphenazine. Evidence was of very low quality (see *Table 2*); therefore, we are uncertain of the results:

- TD symptoms improved to a clinically important extent for significantly more people allocated to antipsychotic reduction than antipsychotic continuation after 44–48 weeks (very low-quality evidence, two RCTs,[97,98] 17 people; RR 0.42, 95% CI 0.17 to 1.04; $I^2 = 0\%$).
- There was no significant difference in deterioration of TD symptoms at 44–48 weeks (very low-quality evidence, two RCTs,[97,98] 17 people; RR 0.61, 95% CI 0.11 to 3.31; $I^2 = 33\%$).
- The number relapsing was not significantly different in the antipsychotic reduction group (1/4) and the antipsychotic maintenance group (0/4) at 44–48 weeks (one RCT,[97] eight people; RR 3.00, 95% CI 0.16 to 57.36).
- The number of people leaving the study early was not significantly different in the antipsychotic reduction group (1/4) and the antipsychotic maintenance group (3/4) (very low-quality evidence, one RCT,[97] eight people; RR 0.33, 95% CI 0.06 to 1.99).

For this comparison there were no studies that reported on adverse events or social confidence, social inclusion, social networks or personalised quality of life.

Observational studies

First-generation antipsychotics: dose discontinuation versus decrease versus increase

Three small observational studies reported on discontinuing antipsychotics compared with a decrease or increase of the antipsychotic doses.[145,150,153,154] The studies were conducted in patients with a serious mental illness, mainly schizophrenia, in Canada, Japan and the USA. Evidence was rated as being of low to very low quality; therefore, we are uncertain of the results:

- Casey and Toenniessen,[145] a small prospective cohort study ($n = 27$), found that psychiatric patients with TD whose antipsychotic medication was reduced or discontinued showed greater improvement in TD symptoms after 5 years of follow-up than patients whose dosage of antipsychotic medication was increased (55–65% vs. 35%). Other outcomes were not reported.

TABLE 2 Summary of findings. Patient or population: psychiatric patients with antipsychotic-induced TD. Setting: inpatients and outpatients in Canada (one study), China (three studies), Germany (one study), Hong Kong (one study), India (one study), Israel (two studies), South Africa (one study), Switzerland (one study), Taiwan (three studies), the UK (two studies) and the USA (14 studies)

Intervention	Comparison	Outcome (follow-up)	Effect estimate (95% CI)	*n*	Quality of the evidence (GRADE)	Rationale for GRADE
Antipsychotic drugs						
Reduced dose of antipsychotics	Continuing antipsychotics	TD: no improvement (44–48 weeks)	RR 0.42 (0.17 to 1.04)	17 (two RCTs)[97,98]	+ – – – (very low) (R1, R2)	• R1: downgraded one level for risk of bias – none of the studies adequately described allocation concealment, one study was a subsample from one site of a RCT and one study's baseline characteristics were not balanced between study groups • R2: downgraded two levels for imprecision – 95% CI includes both no effect and appreciable benefit for antipsychotic reduced dose; very small sample size • R3: downgraded one level for risk of bias – allocation concealment was not adequately described, only a subsample from one site of a RCT qualified for inclusion • R4: downgraded one level for indirectness – leaving the study early can give an indication, but is not a direct measurement, of treatment acceptability
		TD: deterioration (44–48 weeks)	RR 0.61 (0.11 to 3.31)	17 (two RCTs)[97,98]	+ – – – (very low) (R1, R2)	
		Mental state: relapse (44–48 weeks)	RR 3.00 (0.16 to 57.36)	8 (one RCT)[97]	+ – – – (very low) (R2, R3)	
		Leaving the study early (44–48 weeks)	RR 0.33 (0.06 to 1.99)	8 (one RCT)[97]	+ – – – (very low) (R2, R3, R4)	
Switch to different antipsychotic (risperidone/ haloperidol)	Antipsychotic withdrawal (placebo)	TD: no improvement (12 weeks)	RR 0.45 (0.23 to 0.89)	42 (one RCT)[105–109]	+ + – – (low) (R1, R2)	• R1: downgraded one level for risk of bias – generation of random sequence and allocation concealment not adequately described • R2: downgraded one level for imprecision – very small sample size • R3: downgraded two levels for imprecision – 95% CI includes appreciable benefit for both interventions as well as no effect; very small sample size • R4: two comparisons from one study • R5: downgraded one level for indirectness – leaving the study early can give an indication, but it is not a direct measurement, of treatment acceptability
		General mental state (12 weeks)	MD –4.3 (–10.48 to 1.88)	42 (one RCT)[105–109]	+ – – – (very low) (R1, R3)	
		Adverse effects (8–12 weeks)	RR 2.08 (0.74 to 5.86)	48 (one RCT)[99–103]	+ – – – (very low) (R1, R3)	
		Leaving the study early (12 weeks)	RR 0.60 (0.16 to 2.25)	50 (one RCT)[105–109]	+ – – – (very low) (R1, R3, R5)	

Intervention	Comparison	Outcome (follow-up)	Effect estimate (95% CI)	*n*	Quality of the evidence (GRADE)	Rationale for GRADE
Switch to SGA (amisulpride/ clozapine/ olanzapine/ risperidone/ quetiapine)	Switch to different FGA	TD: no improvement (6 months)	RR 0.80 (0.52 to 1.22)	45 (one RCT)[110,111]	+ – – – (very low) (R1, R2)	• R1: downgraded one step for risk of bias – randomisation procedure, allocation concealment and blinding were not adequately described, and the study was at a high risk of attrition bias • R2: downgraded two steps for imprecision – small sample size and 95% CI includes both appreciable benefit and no effect for quetiapine • R3: downgraded one step for risk of bias – randomisation procedure and allocation concealment were not adequately described • R4: downgraded one step for imprecision – small sample size • R5: downgraded two steps for imprecision – small sample size and 95% CI includes appreciable benefit for both intervention arms • R6: downgraded one step for risk of bias – randomisation procedure, allocation concealment or blinding were not adequately described, and two of the studies were at a high risk of attrition bias • R7: downgraded one step for indirectness – leaving the study early can give an indication, but is not a direct measurement, of treatment acceptability • R8: downgraded one step for imprecision – 95% CI includes both no effect and appreciable harm for SGAs
		General mental state (1 year)	RR 1.83 (0.62 to 5.39)	45 (one RCT)[110,111]	+ – – – (very low) (R1, R5)	
		Adverse effects (6 months)	RR 0.52 (0.31 to 0.89)	82 (two RCTs)[99–103,110,111]	+ + – – (low) (R3, R4)	
		Leaving the study early (24–52 weeks)	RR 1.41 (0.74 to 2.67)	168 (three RCTs)[104,110–114]	+ – – – (very low) (R6, R7, R8)	

continued

TABLE 2 Summary of findings. Patient or population: psychiatric patients with antipsychotic-induced TD. Setting: inpatients and outpatients in Canada (one study), China (three studies), Germany (one study), Hong Kong (one study), India (one study), Israel (two studies), South Africa (one study), Switzerland (one study), Taiwan (three studies), the UK (two studies) and the USA (14 studies) (*continued*)

Intervention	Comparison	Outcome (follow-up)	Effect estimate (95% CI)	*n*	Quality of the evidence (GRADE)	Rationale for GRADE
Olanzapine	Amisulpride	Adverse effects (6 months)	MD –0.35 (–2.44 to 1.74)	54 (one RCT)[112–114]	+ – – – (very low) (R1, R2)	• R1: downgraded one step for risk of bias – randomisation procedure and allocation concealment were not adequately described; single-blind study • R2: downgraded two steps for imprecision – small sample size, and 95% CI includes appreciable benefit for both interventions, as well as no effect • R3: downgraded one step for indirectness – leaving the study early can give an indication, but is not a direct measurement, of treatment acceptability
		General mental state (6 months)	MD 1.32 (–1.94 to 4.58)	54 (one RCT)[112–114]	+ – – – (very low) (R1, R2)	
		Leaving the study early (6 months)	RR 1.93 (0.19 to 20.12)	57 (one RCT)[112–114]	+ – – – (very low) (R1, R2, R3)	
Olanzapine	Risperidone	TD: no improvement (6 months)	RR 1.25 (0.82 to 1.90)	60 (one RCT)[115,116]	+ – – – (very low) (R1, R2)	• R1: downgraded one step for risk of bias – allocation concealment was not adequately described, participants and personnel were not blinded • R2: downgraded two steps for imprecision – small sample size and 95% CI includes both no effect and appreciable benefit for one of the interventions • R3: downgraded one step for imprecision – small sample size • R4: downgraded one step for risk of bias – randomisation procedure and/or allocation concealment was not adequately described, participants and personnel were not blinded in one of the studies, in the other study attrition was high and it was a post hoc analysis of individuals with TD at baseline • R5: downgraded one step for indirectness – leaving the study early can give an indication, but is not a direct measurement, of treatment acceptability
		Adverse effects (6 months)	MD –0.70 (–1.33 to –0.07)	60 (one RCT)[115,116]	+ + – – (low) (R1, R3)	
		General mental state (6 months)	RR 1.00 (0.15 to 6.64)	60 (one RCT)[115,116]	+ – – – (very low) (R1, R2)	
		Leaving the study early (6–18 months)	RR 0.73 (0.57 to 0.95)	170 (two RCTs)[115–118]	+ – – – (very low) (R3, R4, R5)	

Intervention	Comparison	Outcome (follow-up)	Effect estimate (95% CI)	*n*	Quality of the evidence (GRADE)	Rationale for GRADE
Olanzapine	Quetiapine	Leaving the study early (18 months)	RR 0.70 (0.54 to 0.90)	116 one RCT)[117,118]	+ – – – (very low) (R1, R2, R4)	• R1: downgraded one step for risk of bias – randomisation procedure and allocation concealment were not adequately described, attrition was high and this was a post hoc analysis of participants with TD at baseline • R2: downgraded one step for imprecision – small sample size • R3: downgraded two steps for imprecision – small sample size; 95% CI includes no effect and appreciable benefit for one of the interventions • R4: downgraded one step for indirectness – leaving the study early can give an indication, but is not a direct measurement, of treatment acceptability
Olanzapine	Ziprasidone	Leaving the study early (18 months)	RR 0.77 (0.56 to 1.05)	82 (one RCT)[117,118]	+ – – – (very low) (R1, R3, R4)	
Quetiapine	Risperidone	Leaving the study early (18 months)	RR 1.05 (0.88 to 1.25)	118 (one RCT)[117,118]	+ – – – (very low) (R1, R3, R4)	
Quetiapine	Ziprasidone	Leaving the study early (18 months)	RR 1.10 (0.86 to 1.40)	90 (one RCT)[117,118]	+ – – – (very low) (R1, R3, R4)	
Ziprasidone	Risperidone	Leaving the study early (18 months)	RR 0.95 (0.74 to 1.23)	84 (one RCT)[117,118]	+ – – – (very low) (R1, R2, R4)	
Haloperidol	Tetrabenazine	TD: no improvement (18 weeks)	RR 1.07 (0.51 to 2.23)	13 (one RCT)[96]	+ – – – (very low) (R1, R2)	• R1: downgraded one step for risk of bias – randomisation procedure, allocation concealment and blinding were not adequately described • R2: downgraded two steps for imprecision – small sample size and 95% CI includes appreciable benefit for both interventions • R3: downgraded one step for indirectness – leaving the study early can give an indication, but is not a direct measurement, of treatment acceptability
		TD: deterioration (18 weeks)	RR 0.86 (0.07 to 10.96)	13 (one RCT)[96]	+ – – – (very low) (R1, R2)	
		Leaving the study early (18 weeks)	RR 4.38 (0.25 to 76.54)	13 (one RCT)[96]	+ – – – (very low) (R1, R2, R3)	

continued

TABLE 2 Summary of findings. Patient or population: psychiatric patients with antipsychotic-induced TD. Setting: inpatients and outpatients in Canada (one study), China (three studies), Germany (one study), Hong Kong (one study), India (one study), Israel (two studies), South Africa (one study), Switzerland (one study), Taiwan (three studies), the UK (two studies) and the USA (14 studies) (*continued*)

Intervention	Comparison	Outcome (follow-up)	Effect estimate (95% CI)	*n*	Quality of the evidence (GRADE)	Rationale for GRADE
Anticholinergic drugs						
Withdrawal of biperiden (stopping after 1 week) and AP continuation	Continuation of biperiden (stopping after 4 weeks) and AP continuation	Leaving the study early (7 weeks)	RR 2.14 (0.11 to 42.52)	10 (one RCT)[119]	+ – – – (very low) (R1, R2, R3)	• R1: downgraded one level for risk of bias – the included study did not adequately describe randomisation procedure or allocation concealment • R2: downgraded one level for indirectness – leaving the study early can give an indication, but is not a direct measurement, of treatment acceptability. In addition, the continuation of anticholinergic medication group stopped biperiden after 4 weeks, but the results were measured after 7 weeks • R3: downgraded two levels for imprecision – very wide 95% CI that includes appreciable benefit for both groups; very small sample size ($n = 10$)

Intervention	Comparison	Outcome (follow-up)	Effect estimate (95% CI)	*n*	Quality of the evidence (GRADE)	Rationale for GRADE
Benzodiazepines						
Benzodiazepines (clonazepam, diazepam) and AP continuation	AP continuation with/without placebo	TD: no improvement (5–10 weeks)	RR 1.12 (0.60 to 2.09)	32 (two RCTs)[89,121,122]	+ – – – (very low) (R1, R2)	• R1: downgraded one step for risk of bias – none of the studies adequately described randomisation procedure or allocation concealment, one study did not blind participants and personnel, and one study was a post hoc subgroup analysis of participants with TD • R2: downgraded two steps for imprecision – small sample size and 95% CI of effect estimate includes both appreciable benefit and appreciable harm for benzodiazepines • R3: downgraded one step for indirectness – leaving the study early can give an indication, but is not a direct measurement, of treatment acceptability • R4: downgraded one step for risk of bias – the included study did not adequately describe randomisation procedure, allocation concealment or blinding • R5: downgraded two steps for imprecision – only one study with a very small sample size
		TD: deterioration (5–10 weeks)	RR 1.48 (0.22 to 9.82)	30 (two RCTs)[89,121,122]	+ – – – (very low) (R1, R2)	
		Leaving the study early (5–10 weeks)	RR 2.73 (0.15 to 48.04)	56 (three RCTs)[75,89,121,122]	+ – – – (very low) (R1, R2, R3)	
Clonazepam and AP continuation	Phenobarbital (as active placebo) and AP continuation	TD: no improvement (2 weeks)	RR 0.44 (0.20 to 0.96)	21 (one RCT)[120]	+ – – – (very low) (R4, R5)	
		Adverse effects (2 weeks)	RR 1.53 (0.97 to 2.41)	21 (one RCT)[120]	+ – – – (very low) (R4, R5)	
		Leaving the study early (2 weeks)	N/E: no reported events	21 (one RCT)[120]	+ – – – (very low) (R3, R4, R5)	

continued

TABLE 2 Summary of findings. Patient or population: psychiatric patients with antipsychotic-induced TD. Setting: inpatients and outpatients in Canada (one study), China (three studies), Germany (one study), Hong Kong (one study), India (one study), Israel (two studies), South Africa (one study), Switzerland (one study), Taiwan (three studies), the UK (two studies) and the USA (14 studies) (*continued*)

Intervention	Comparison	Outcome (follow-up)	Effect estimate (95% CI)	*n*	Quality of the evidence (GRADE)	Rationale for GRADE
Vitamin E						
Vitamin E and AP continuation	Placebo and AP continuation	TD: no improvement (up to 1 year)	RR 0.95 (0.89 to 1.01)	264 (six RCTs)[93–95,123–126,130–137]	+ + – – (low) (R1, R2)	• R1: downgraded one step for risk of bias – most studies did not adequately describe randomisation procedure, allocation concealment or blinding, and some studies were at rated at being at high risk of attrition bias • R2: downgraded one step for imprecision – few events (< 300) were reported • R3: downgraded two steps for imprecision – small sample size and effect estimate includes both appreciable benefit and appreciable harm for vitamin E • R4: downgraded one step for reporting bias – only one study reported on this common, typically monitored adverse effect • R5: downgraded one step for indirectness – leaving the study early can give an indication, but is not a direct measurement, of treatment acceptability
		TD: deterioration (up to 1 year)	RR 0.23 (0.07 to 0.76)	85 (five RCTs)[93–95,123–126,130]	+ + – – (low) (R1, R2)	
		Adverse effects (up to 1 year)	RR 1.21 (0.35 to 4.15)	205 (nine RCTs)[90–93,95,123–128,130]	+ – – – (very low) (R3, R4)	
		Leaving the study early (up to 1 year)	RR 1.07 (0.64 to 1.80)	232 (eight RCTs)[90–92,94,123–126,128,129,138]	+ – – – (very low) (R2, R3, R5)	

Intervention	Comparison	Outcome (follow-up)	Effect estimate (95% CI)	*n*	Quality of the evidence (GRADE)	Rationale for GRADE
Miscellaneous treatments						
Buspirone and AP continuation	Placebo and AP continuation	TD: no improvement (6 weeks)	RR 0.53 (0.33 to 0.84)	42 (one RCT)[139]	+ + – – (low) (R1, R2)	• R1: downgraded one step for risk of bias – randomisation procedure, allocation concealment and blinding were not adequately described • R2: downgraded one step for imprecision – very small sample size and few events reported
		Leaving the study early (6 weeks)	N/E: no reported events	42 (one RCT)[139]	–	
Hypnosis/relaxation and AP continuation	TAU (AP continuation)	TD: no improvement (eight sessions)	RR 0.45 (0.21 to 0.94)	15 (one RCT)[78]	+ – – – (very low) (R1, R2)	• R1: downgraded two steps for risk of bias – fully randomised sequence generation and blinding was not achieved • R2: downgraded one step for imprecision – very small sample size • R3: downgraded two steps for imprecision – 95% CI includes benefit for both intervention arms; very small sample size
		TD: deterioration (eight sessions)	RR 0.18 (0.01 to 3.81)	15 (one RCT)[78]	+ – – – (very low) (R1, R3)	
		Leaving the study early (eight sessions)	N/E: no reported events	15 (one RCT)[78]	–	

AP, antipsychotic; N/E, not estimable.

Note

GRADE Working Group grades of evidence: high quality (++++) – we are very confident that the true effect lies close to that of the estimate of the effect; moderate quality (+++–) – we are moderately confident in the effect estimate, the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; low quality (++––) – our confidence in the effect estimate is limited, the true effect may be substantially different from the estimate of the effect; and very low quality (+–––) – we have very little confidence in the effect estimate, the true effect is likely to be substantially different from the estimate of effect.

- Koshino *et al.*,[150] a small prospective cohort study ($n = 28$), found that the severity of TD was unchanged in 39.3% of the patients, improved in 17.9%, fluctuated in 21.4% and worsened in 21.4% at 11 years' follow-up. The outcome was not associated with discontinuation, increase or decrease in the dosage of antipsychotics.
- Yassa *et al.*,[153,154] also a small prospective cohort study ($n = 44$), reported that 50% of patients had no change in their TD severity, 20% had an improvement and 30% had a worsening of their TD. Little difference was noted in those patients whose medication was decreased (33% had no change in TD severity, 42% had increased TD severity and 25% had decreased TD severity) and those whose medication remained unchanged (56% had no change in TD severity, 25% had increased TD severity and 19% had decreased TD severity) at 10 years' follow-up.

Comparison 2: switch to a different antipsychotic versus antipsychotic withdrawal (with placebo)

Two small randomised trials[101,108] conducted with schizophrenic inpatients in Canada and Taiwan reported on switching to risperidone or haloperidol compared with placebo and withdrawing antipsychotics. Evidence was rated as being of low to very low quality (see *Table 2*); therefore, we are uncertain of the results:

- TD symptoms improved to a clinically important extent for significantly more people allocated to antipsychotic switch to risperidone than those allocated to placebo at 12 weeks (low-quality evidence, one RCT,[105–109] 42 people; RR 0.45, CI 0.23 to 0.89).
- There was no significant difference in the use of antiparkinsonism drugs between switching to risperidone or haloperidol compared with placebo at 8–12 weeks (two comparisons from one RCT,[99–103] 48 people; RR 2.08, CI 0.74 to 5.86; $I^2 = 0\%$).
- General mental state was measured using the continuous BPRS scale (see *Some specific outcomes*). There was no significant difference between switching to risperidone compared with placebo on the average end-point score of the BPRS at 12 weeks (one RCT,[105–109] 42 people; MD –4.30, CI –10.48 to 1.88).
- Using antipsychotics did not significantly increase the chances of a person leaving the study early at 12 weeks (very low-quality evidence, one RCT,[105–109] 50 people; RR 0.60, CI 0.16 to 2.25).

For this comparison there were no studies that reported on deterioration of TD symptoms or social confidence, social inclusion, social networks or personalised quality of life.

Observational studies

First-generation antipsychotics: dose discontinuation versus maintenance

Three small observational studies reported on discontinuing antipsychotics compared with maintenance of the standard doses.[149,151,152] The studies were conducted in patients with a serious mental illness, mainly schizophrenia, in the USA and Japan. Evidence was rated as being of low to very low quality; therefore, we are uncertain of the results:

- Huang,[149] a very small prospective cohort study ($n = 10$), found that psychiatric patients with TD whose antipsychotic medication was reduced or discontinued showed a greater improvement in TD symptoms after 4 years of follow-up than patients whose dosage of antipsychotic medication remained unchanged (60% vs. 21%). Other outcomes were not reported.
- Peselow *et al.*,[151] a small prospective cohort study ($n = 31$), reported a statistically significant decrease in abnormal movements at 1 year of follow-up; this improvement was offset by the fact that 15 of the 21 (71.4%) patients discontinued from antipsychotic treatment relapsed.
- Yagi and Itoh,[152] also a small prospective cohort study ($n = 20$), reported that, at 10 years' follow-up, 64% (9/14) of patients in whom antipsychotics were discontinued or decreased after the occurrence of TD presented a clinically important improvement in symptoms; this also occurred in 75% (3/4) of those for whom the antipsychotic dose had been maintained. The authors suggested that the outcome of TD was determined by the patient's age at onset rather than by the course of antipsychotic treatment.

Comparison 3a: switch to one antipsychotic versus switch to a different antipsychotic

Six small randomised trials[101,104,110,112,115,117] of inpatients and outpatients with schizophrenia and schizoaffective disorder conducted in in Canada, South Africa, Taiwan and the USA reported on switching to a SGA (amisulpride, clozapine, olanzapine, risperidone, quetiapine, ziprasidone) compared with switching to a different antipsychotic, either a FGA (haloperidol, unspecified FGA) or another SGA. Evidence was rated as being of low to very low quality (see *Table 2*); therefore, we are uncertain of the results:

- There were no significant differences on clinically important improvement in TD symptoms at 6 months between quetiapine and haloperidol (low-quality evidence, one RCT,[110,111] 45 people; RR 0.80, 95% CI 0.52 to 1.22) or between olanzapine and risperidone (very low-quality evidence, one RCT,[115,116] 60 people; RR 1.25, 95% CI 0.82 to 1.90).
- The number of people in need of antiparkinsonism drugs was significantly lower in the group allocated to quetiapine than in the group allocated to haloperidol (one RCT,[110,111] 45 people; RR 0.45, 95% CI 0.21 to 0.96), but there was no significant difference between the groups allocated to risperidone or haloperidol (one RCT,[99–103] 37 people; RR 0.68, 95% CI 0.34 to 1.35).
- Extrapyramidal symptoms at 6 months, as measured by the ESRS, were lower among participants on olanzapine than in those on risperidone (one RCT,[115,116] 60 people; MD –0.70, 95% CI –1.33 to –0.07), but there was no significant difference in extrapyramidal symptoms at 6 months, as measured by on SAS, at 6 months between participants on olanzapine and those receiving amisulpride (one RCT,[112–114] 54 people; MD –0.35, 95% CI –2.44 to 1.74).
- There were no significant differences in general adverse events at 6 months, as measured on the UKU scale, between patients on olanzapine (one RCT,[112–114] 53 people; MD 0.08, 95% CI –1.85 to 2.01) or amisulpride (one RCT,[112–114] 53 people; MD –0.55, 95% CI –2.33 to 1.23) and thos receiving an unspecified FGA, or between those on olanzapine and those on amisulpride (one RCT,[112–114] 54 people; MD 0.63, 95% CI –0.93 to 2.19).
- There were no significant differences in deterioration of mental state at 1 year between patients on quetiapine and those on haloperidol (one RCT,[110,111] 45 people; RR 1.83, 95% CI 0.62 to 5.39), or at 6 months between patients on olanzapine and those on risperidone (one RCT,[115,116] 60 people; RR 1.00, 95% CI 0.15 to 6.64) or at 6 months, measured on the BPRS, between patients on olanzapine and those on amisulpride (one RCT,[112–114] 54 people; MD 1.32, 95% CI –1.94 to 4.58).
- People allocated to olanzapine were less likely to leave the study early, that is after 6–18 months, than those allocated to risperidone (two RCTs,[115–118] 170 people; RR 0.73, 95% CI 0.57 to 0.95; $I^2 = 0\%$) or quetiapine (one RCT,[117,118] 116 people; RR 0.70, 95% CI 0.54 to 0.90).
- There were no significant differences at 6 months to 1 year in acceptability of treatment, defined as not leaving the study early, between patients receiving olanzapine or amisulpride and those receiving an unspecified FGA,[112–114] or between those receiving clozapine or quetiapine and those receiving haloperidol,[104,110,111] or between patients receiving olanzapine and those receiving amisulpride[112–114] or ziprasidone,[117,118] or between those on quetiapine and those on risperidone or ziprasidone,[117,118] or between patients on ziprasidone and those on risperidone.[117,118]

For this comparison there were no studies that reported on deterioration of TD symptoms or social confidence, social inclusion, social networks or personalised quality of life.

Observational studies

First-generation antipsychotics and gabapentin versus second-generation antipsychotics and gabapentin

One small observational study compared first-generation antipsychotics with gabapentin to second-generation antipsychotics with gabapentin in patients with serious mental illness (schizoaffective, bipolar I disorder and schizophrenic patients) and TD, in Italy.[148] This prospective cohort study ($n = 30$) reported that gabapentin treatment reduced TD symptoms with a mean percentage improvement on the Abnormal Involuntary Movement Scale (AIMS) of 47.5% (standard deviation ±18.2%) among all treated patients regardless of the antipsychotic used. Those on SGAs (mean 11.2 patients, standard deviation 4.8 patients;

$n = 18$) reported that symptoms improved slightly more than those on FGAs (mean 18.2 patients, standard deviation 5.5 patients; $n = 4$).

Comparison 3b: specific antipsychotic versus other drug – haloperidol versus tetrabenazine

A very small randomised trial[96] conducted with psychiatric inpatients in the USA compared haloperidol with tetrabenazine. The evidence was rated as being of very low quality (see *Table 2*); therefore, we are uncertain of the results:

- There was no significant difference in clinically important improvement in TD symptoms at 18 weeks between patients receiving haloperidol and those receiving tetrabenazine (very low-quality evidence, one RCT,[96] 13 people; RR 1.07, 95% CI 0.51 to 2.23).
- There was no significant difference in deterioration of TD symptoms at 18 weeks between patients receiving haloperidol and those receiving tetrabenazine (very low-quality evidence, one RCT,[96] 13 people; RR 0.86, 95% CI 0.07 to 10.96).
- At 18 weeks there was no significant difference in the proportion of participants who had left the study early between the haloperidol (2/7 participants) and tetrabenazine groups (0/6 participants) (very low-quality evidence, one RCT,[96] 13 people; RR 4.38, 95% CI 0.25 to 76.54).

For this comparison there were no studies that reported on adverse events, mental state or on social confidence, social inclusion, social networks or personalised quality of life.

Comparison 4: withdrawal of anticholinergics versus continuation of anticholinergics

A very small randomised trial[119] conducted in schizophrenia patients in Germany compared stopping biperiden after 1 week or after 4 weeks. The evidence was rated as being of very low quality (see *Table 2*); therefore, we are uncertain of the results:

- There was no significant difference at 7 weeks in the proportion of people leaving the study early between those withdrawn from anticholinergic therapy (1/6 participants) and those who continues (0/4 participants) (very low-quality evidence, one RCT,[119] 10 people; RR 2.14, 95% CI 0.11 to 42.52).

For this comparison there were no studies with useable data on clinically important improvement or deterioration of TD symptoms, adverse events, mental state or on social confidence, social inclusion, social networks or personalised quality of life.

Comparison 5: benzodiazepines versus placebo, treatment as usual or active placebo (with antipsychotic management)

Four small randomised trials[75,89,120,122] conducted with psychiatric inpatients and outpatients in China and the USA compared diazepam or clonazepam and antipsychotic continuation with placebo, TAU or phenobarbital as active placebo and antipsychotic continuation. The evidence was rated as being of very low quality (see *Table 2*); therefore, we are uncertain of the results:

- There was no significant difference in 'no clinically important improvement of TD symptoms' at 5–10 weeks between patients on benzodiazepines and those receiving placebo or no treatment (very low-quality evidence, two RCTs,[89,121,122] 32 people; RR 1.12, 95% CI 0.60 to 2.09; $I^2 = 14\%$). One trial found that clonazepam was more beneficial than phenobarbital (as active placebo) at 2 weeks (very low-quality evidence, one RCT,[120] 21 people; RR 0.44, 95% CI 0.20 to 0.96).
- There was no significant difference in deterioration of TD symptoms at 5–10 weeks (very low-quality evidence, two RCTs,[89,121,122] 30 people; RR 1.48, 95% CI 0.22 to 9.82; $I^2 = 19\%$).
- One study reported on mental state average end-point scores using the BPRS scale and noted no difference between the diazepam and TAU groups at 10 weeks (one RCT,[89] 11 people; MD –0.50, 95% CI –13.83 to 12.83).

- One trial found no significant difference in the number of participants experiencing adverse events after 2 weeks' treatment with clonazepam or phenobarbital (as active placebo) (very low-quality evidence, one RCT,[120] 21 people; RR 1.53, 95% CI 0.97 to 2.41). All participants allocated to clozapine (10) and 7 out of 11 participants allocated to phenobarbital experienced an adverse event.
- Three studies reported that no participants left the study early.[75,120–122] One study reported that 2 out of 33 participants allocated to diazepam, but none (out of 23) allocated to TAU, left the study early and, subsequently, found no significant difference between the two groups at 10 weeks (very low-quality evidence, one RCT,[89] 56 people; RR 2.73, 95% CI 0.15 to 48.04).

For this comparison there were no studies that reported on social confidence, social inclusion, social networks or personalised quality of life.

Comparison 6: vitamin E versus placebo (with antipsychotic management)

Thirteen randomised trials[90–95,123,127–130,137,138] in psychiatric inpatients and outpatients in China (one study[138]), Hong Kong (one study[94]), Israel (two studies[90,91]), India (one study[127]), Switzerland (one study[95]), the UK (one study[130]) and the USA (six studies[92,93,123–126,128,129,131–137]) reported on vitamin E (gamma-tocopherol) and antipsychotic continuation compared with placebo and antipsychotic continuation. The evidence was rated as being of low to very low quality (see *Table 2*); therefore, we are uncertain of the results. After up to 1 year:

- There was no significant difference between the vitamin E and placebo groups in the numbers of patients experiencing no clinically important improvement in TD symptoms (low-quality evidence, six RCTs,[93–95,123–126,130–137] 264 people; RR 0.95, 95% CI 0.89 to 1.01; $I^2 = 0\%$).
- The number of participants who showed deterioration of TD symptoms was significantly lower in the vitamin E group than in the placebo group (low-quality evidence, five RCTs,[93–95,123–126,130] 85 people; RR 0.23, 95% CI 0.07 to 0.76; $I^2 = 0\%$)
- One study[131–137] measured adverse events (extrapyramidal symptoms) using the SAS and found no significant difference between the vitamin E and placebo groups (very low-quality evidence, 104 people; MD 1.10, 95% CI –1.02 to 3.22).
- There was no significant difference in the incidence of any adverse event (very low-quality evidence, nine RCTs,[90–93,95,123–128,130] 205 people; RR 1.21, 95% CI 0.35 to 4.15; $I^2 = 0\%$).
- There was no significant difference in mental state, as measured by the BPRS, between vitamin E and placebo groups (three RCTs,[127,129,131–137] 165 people; MD –0.20, 95% CI –3.21 to 2.82; $I^2 = 38\%$).
- There was no significant difference in acceptability of treatment (leaving the study early) [very low-quality evidence, medium term (overall ≈20% loss to follow-up), eight RCTs,[90–92,94,123–126,128,129,138] 232 people; RR 1.07, 95% CI 0.64 to 1.80; $I^2 = 0\%$].

For this comparison there were no studies that reported on social inclusion, social networks or personalised quality of life.

Comparison 7: buspirone versus placebo (with antipsychotic management)

One small randomised trial,[78] conducted with psychiatric inpatients in China, reported on buspirone and antipsychotic continuation compared with placebo and antipsychotic continuation. Evidence was rated as being of low quality (see *Table 2*); therefore, we are uncertain of the results:

- The number of participants reporting clinically important improvement in TD symptoms after 6 weeks was signficicantly higher in the buspirone group than in the placebo group (low-quality evidence, one RCT,[78] 42 people; RR 0.53, 95% CI 0.33 to 0.84).
- Acceptability of treatment, measured by the number of participants leaving the study early, could not be estimated, as the included study did not report any events.

For this comparison there were no studies that reported on deterioration of TD symptoms, adverse events, mental state or on social confidence, social inclusion, social networks or personalised quality of life.

Comparison 8: hypnosis and relaxation versus treatment as usual (with antipsychotic management)

One very small randomised trial,[139] conducted with psychiatric inpatients in the USA, reported on hypnosis or relaxation and antipsychotic continuation compared with TAU and antipsychotic continuation. The evidence was rated as being of very low quality (see *Table 2*); therefore, we are uncertain of the results:

- Clinically important improvement in TD symptoms after eight sessions was reported by significantly more participants in the hypnosis or relaxation group than in the TAU group (very low-quality evidence, one RCT,[139] 15 people; RR 0.45, 95% CI 0.21 to 0.94).
- There was no significant difference in deterioration of TD symptoms after eight sessions between the hypnosis or relaxation group and the TAU group (very low-quality evidence, one RCT,[139] 15 people; RR 0.18, 95% CI 0.01 to 3.81).
- Acceptability of treatment (leaving the study early) could not be estimated, as the included study reported no events.

For this comparison there were no studies that reported on adverse events, mental state or on social confidence, social inclusion, social networks or personalised quality of life.

Analysis of the robustness of the results (sensitivity analyses)

Risk of bias

We planned to restrict the analyses to studies considered to be at low, and low or unclear, risk of selection and detection bias. None of the included studies was rated as being at a low risk of both selection and detection bias. Studies were rated as being either at an unclear risk of bias or at a low and unclear risk (see *Appendix 7*, *Table 13*), except Glover,[139] which was the only study rated as being at high risk of selection bias. Glover[139] was the only study that investigated hypnosis and relaxation.

Imputed values

We would have undertaken a sensitivity analysis to assess the effects of including data from cluster randomised trials in which we used imputed values for the intracluster correlation coefficient in calculating the design effect. However, we identified no cluster randomised trials for inclusion.

Planning future studies

No clinical improvement of tardive dyskinesia symptoms

Only one study[110] comparing 'switch to FGA' with 'switch to SGA' reported the outcome 'no clinical improvement'. The odds ratio (OR) comparing these two treatments was 1.96 (95% CI 0.56 to 6.92), indicating an insignificant advantage of 'switch to SGA' compared with 'switch to FGA'. The wide CI surrounding the effect estimate suggests that the existing evidence might not be adequate to conclude which of the two interventions is more effective. The power curve in *Figure 5* shows the power of an updated meta-analysis considering that a new study with sample size indicated in the horizontal axis is added to the evidence base. The power of a meta-analysis including a new study with a small sample size would remain low (e.g. we would achieve a power of $< 40\%$ randomising 100 more patients). To achieve a power of 80% for the meta-analysis, a new study with a total sample size of 800 patients would need to be designed and included in the meta-analysis model. The extended funnel plot could not be drawn given the availability of a single study.

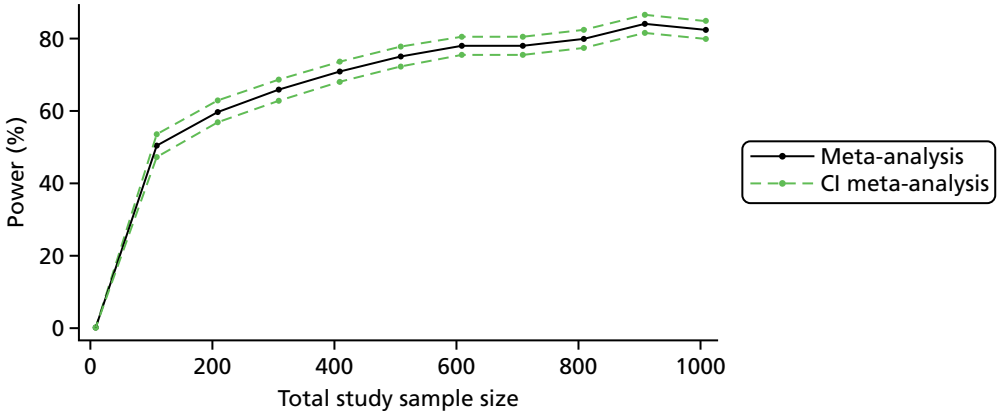

FIGURE 5 Power curves with 95% CIs for the outcome 'no clinical improvement of TD symptoms' for the comparison 'switch to FGA' vs. 'switch to SGA'.

Total discontinuation rates

Three studies comparing 'switch to FGA' to 'switch to SGA' and reporting 'total discontinuation rates' were available. The resulting OR was 0.54 (95% CI 0.21 to 1.42) in favour of a 'switch to FGA' using the fixed-effect inverse-variance meta-analysis model. For a new study to make an important contribution to the existing evidence by rendering the power of the meta-analysis 80%, it would have to have a total sample size of ≥ 1000 patients (*Figure 6*). The implications of including a hypothetical new study in the meta-analysis are illustrated in the extended funnel plot of *Figure 7*. The inclusion of an additional study lying in the left-hand light-green region of *Figure 7* would result in the updated meta-analysis showing a significant result in favour of a 'switch to FGA'. As none of the existing studies lies in this region, it is considered unlikely that a new trial will change meta-analysis conclusions. The possibility that a meta-analysis would change the inference in favour of a 'switch to SGA' is even smaller, as it would require the inclusion of a study with a very small standard error (smaller than 0.1) demonstrating a favoured outcome for the particular treatment. Thus, despite the fact that meta-analysis is inconclusive, it is not likely that a new study would change its conclusions given that its sample size is not substantially large.

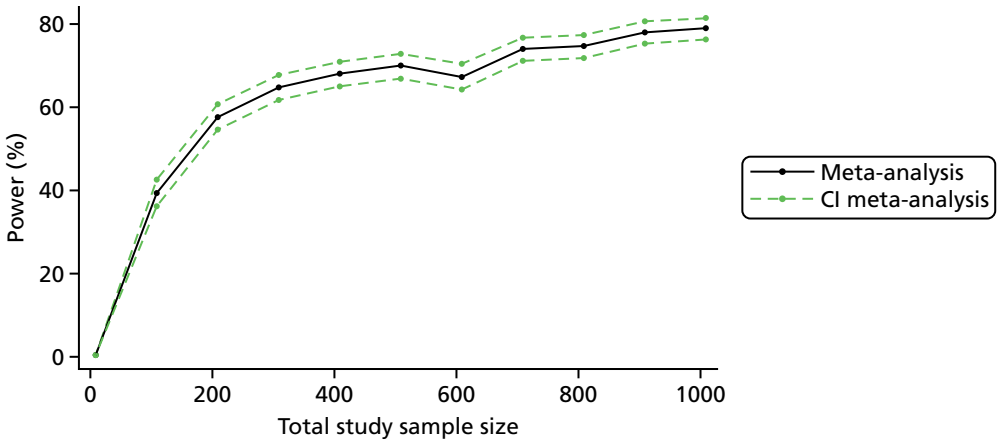

FIGURE 6 Power curves with 95% CIs for the outcome 'total discontinuation rates' for the comparison 'switch to FGA' vs. 'switch to SGA'.

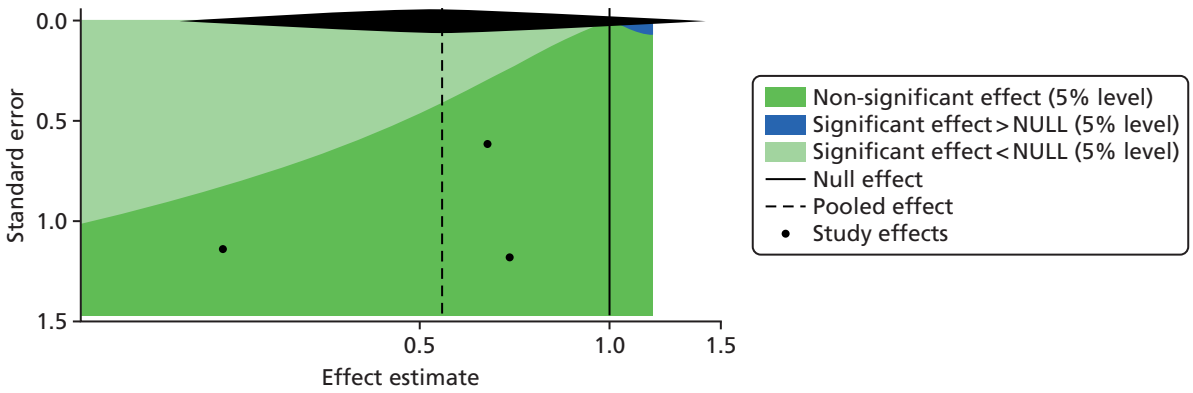

FIGURE 7 Extended funnel plot for the outcome 'total discontinuation rates' for the comparison 'switch to FGA' vs. 'switch to SGA': contours for impact of a new study.

Chapter 6 Part C: results of the network meta-analysis

We intended to synthesise available evidence from treatment options of interest using a NMA model.[155–157] However, the sparseness of the existing evidence imposed important barriers in the analysis rendering the presentation of NMA results as our main analysis impractical. In particular, comparisons were typically informed by very few studies, and many studies had few or even zero events. Analysing and interpreting few data can be particularly challenging, and simulation studies have shown that many of the most commonly used meta-analytic methods produce biased estimates and misleading conclusions when events are rare.[158,159] Challenges in the analysis of few data include the difficulty of justifying the use of distributional approximations to statistics of interest and the potential risk of small studies including unrepresentative populations.[159,160]

Use of NMA can benefit the evidence synthesis of few data by borrowing strength across treatment comparisons and gaining information through the contribution of indirect evidence. Moreover, sharing parameters across the entire network can provide information on their inference; here, we assumed a common heterogeneity parameter across all treatment comparisons. Although the assumption of a common heterogeneity is expected to hold in this setting, formal investigation of between-study variations is limited by the sparseness of the data. Despite efforts to strengthen the evidence body and sharing parameters across networks, analysing and interpreting NMA results under sparseness was challenging; results of NMA for the outcomes 'no clinical improvement of TD symptoms' and 'total discontinuation rates' are presented in *Appendix 4*. Network effects were almost identical to their pairwise meta-analysis counterparts when direct evidence existed; any differences are attributed to the estimation of heterogeneity. When direct evidence was absent, indirect estimates were highly imprecise, failing to produce useful summaries on the relative effectiveness of the interventions of interest and consequently to provide interpretable results to be used for decision-making. Moreover, no closed loops of evidence were formed in the network for the primary outcome and only one existed for total discontinuation rates, making it impossible to evaluate the validity of the consistency assumption. The interventions of interest that were set to be on the priority list did not form a connected network that could be analysed at once; this further limited the value of performing NMA and precluded us from presenting it as our main analysis.

Despite the barriers that lack of sufficient research data may impose, decisions often need to rely on few data. Thus, exploration of possible ways in which inferences could be made based on a limited evidence base would be useful. Use of external evidence, both eliciting expert opinions and using observational data, has been considered elsewhere.[160] The presence of few data, along with the associated highly imprecise NMA effects, highlights the uncertainty surrounding the relative effectiveness between alternative treatment options for TD and underlines the need for further research to be conducted. Future studies should be planned (see *Chapter 8*, *Recommendations for research*) to enrich the existing evidence base and, by making the synthesis of data in a NMA model sensible, to enlighten the relative effectiveness between available treatment options.

Several methods, tailored to outcomes with very low frequency, have been developed.[161–163] Rücker *et al.*[161] proposed the arcsine difference as an alternative effect size measure that enables such studies to be included in a meta-analysis. Despite its advantages, the arcsine method provides an effect size that is difficult to interpret and is poorly understood by clinicians.

Chapter 7 Discussion

Summary of main results

The search

This area of research does not seem to be active. We have identified additional data, but most trials pre-date the year 2000, with only six studies (of prioritised interventions) published between 2000 and 2011. Possible explanations for this include lack of concern with TD in the research community, discouragement regarding the possibility of identifying effective treatments, or, more positively, decreased emergence of the problem in research-active communities because of more thoughtful use of antipsychotic drugs.

In addition to RCTs, we identified eight small prospective cohort studies that reported on efficacy of interventions (mostly antipsychotics) for the treatment of TD.

Few data

The great majority of studies testing treatments for people with TD are short and very small. This whole review of many comparisons shows that only hundreds, not thousands, of people have been randomised, and no one with dementia and TD. Any effect of treatment is likely to be subtle and so substantial sample sizes are needed to show differences with acceptable confidence. This also applies to observational studies, in which eight prospective studies reported on 200 patients with TD.

Many outcomes were not measured at all by included studies. We may have been overambitious in hoping for some of these outcomes in TD trials, but simple reporting of social impact and quality of life does not seem unreasonable, and is of particular interest to patients and carers.

Outcomes

Tardive dyskinesia symptoms

We found low-quality evidence of clinically important improvement in TD symptoms after 12 weeks for switching antipsychotic to risperidone compared with withdrawing antipsychotics (with placebo) (one study, 42 people; RR 0.45, 95% CI 0.23 to 0.89), and after 6 weeks for buspirone compared with placebo while continuing antipsychotics as usual (one study, 42 people; RR 0.53, 95% CI 0.33 to 0.84). We also found low-quality evidence that use of vitamin E could prevent deterioration of TD symptoms compared with placebo while continuing antipsychotics as usual after 1 year (five studies, 85 people; RR 0.23, 95% CI 0.07 to 0.76). Because the quality of evidence is low, we have limited confidence in the effect estimates and CIs; the true effects may be substantially different.

Furthermore, we found very low-quality evidence of clinically important improvement in TD symptoms after 1 year for antipsychotic reduction compared with antipsychotic continuation (two studies, 17 people; RR 0.42, 95% CI 0.17 to 1.04), after 2 weeks for clonazepam compared with phenobarbital as active placebo while continuing antipsychotics as usual (one study, 21 people; RR 0.44, 95% CI 0.20 to 0.96) or for hypnosis or relaxation compared with placebo while continuing antipsychotics as usual for eight sessions (one study, 15 people; RR 0.45, 95% CI 0.21 to 0.94). Because the quality of evidence is very low, we have very little confidence in the effect estimates and CIs; the true effects are likely to be substantially different.

There was very low-quality evidence from observational studies of an improvement in TD symptoms when antipsychotics were discontinued or decreased; on average, these studies were very small, had an unbalanced number of participants in each group and selective outcome reporting bias.

For the remaining comparisons we found low- to very low-quality evidence of little or no difference between groups, but, again, our confidence in these results is limited.

Adverse effects

There was low-quality evidence that fewer people taking SGAs than taking FGAs needed antiparkinsonism medication because of extrapyramidal side effects after 1 year (two studies, 82 people; RR 0.52, 95% CI 0.31 to 0.89). There was also low-quality evidence that after 6 months extrapyramidal symptoms, as measured on the ESRS, were less common in the olanzapine group than in the risperidone group (one study, 60 people; MD –0.70, 95% CI –1.33 to –0.07). Finally, there was very low-quality evidence that after 2 weeks fewer people on phenobarbital as an active placebo than on clonazepam had experienced any adverse events (one study, 21 people; RR 1.53, 95% CI 0.97 to 2.41).

None of the observational studies reported on adverse events for the interventions.

As a result of the low to very low quality of this evidence, our confidence in these results is limited.

For the remaining comparisons, we found low- to very low-quality evidence of little or no difference between groups, but, again, our confidence in these results is limited.

Mental state

We found low- to very low-quality evidence of little or no difference between groups of all comparisons, but, again, our confidence in these results is limited.

Acceptability of treatment: leaving the study early

It is always unclear what leaving a study early means for the participant. It could be related to the participant rejecting treatment for a series of reasons, or attributable to participants finding the trial intolerable. It also could be a function of a trial design in which participants, although willing to continue, are asked to leave because of some degree of protocol violation. In any event, for most of the interventions the numbers of participants leaving the study early were not different for those allocated to either group. Fewer participants allocated to olanzapine than to risperidone (two studies, 170 people; RR 0.73, 95% CI 0.57 to 0.95) or to quetiapine (one study, 116 people; RR 0.70, 95% CI 0.54 to 0.90) left the study early after 6–18 months. Evidence was of very low quality for both comparisons; therefore, we have very little confidence in the effect estimates and CIs; the true effects are likely to be substantially different.

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

Completeness

We excluded 22 studies of prioritised interventions published between 1971 and 2004 because they did not report data that could be used in the review. We contacted the study authors wherever possible, but no further information was available.

As part of this work, the service user consultation participants highlighted their preferred outcomes (*Box 2*). These largely correlated with the perspectives of the clinicians and reviewers – listing clear, clinically meaningful effects on TD, adverse effects or leaving the study early – as being of importance. The consultation added the outcome of some measure of social confidence/inclusion/networks and/or quality of life. There were no data for the measure of social confidence/inclusion/networks and/or quality of life, but in reality all others were incomplete – perhaps with the exception of vitamin E. The large trials – or enough small trials on the same topic – have just not been undertaken. The difficulty of carrying out randomised studies in this area

BOX 2 Outcomes suggested by PPI consultation and implemented within summary-of-findings tables

1. Tardive dyskinesia

1.1 Improved to a clinically important extent.

1.2 Deteriorated.

2. Mental state

3. Adverse effects

3.1 Any adverse event.

3.2 Adverse effects: no clinically significant extrapyramidal adverse effects.

4. Acceptability of treatment

4.1 Leaving the study early.

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

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

should not be underestimated. However, time and time again pioneering triallists have proved that it is possible.

Another problem is that there seems to be little evidence of collaboration; no two trials are the same. With collaborative effort we could have enough people randomised across time to have answers to some practical issues. Currently, we cannot even be confident that dose reduction really helps. Of course, researchers will always be attracted to try the next compound, but this overview illustrates that there are enough 'loose ends' in the past work regarding entirely practical interventions to encourage some large collaborative efforts in randomisation.

This overview – and the clear incompleteness of the data on this old, well-recognised condition – also, we think, serves to encourage some consideration about trial design. Past work does not serve people with TD particularly well. In the 30 years of, largely, pilot studies, trial methodology within mental health has evolved, with larger pragmatic trials becoming more prevalent. The service user consultation has provided outcomes fitting with a pragmatic randomised trial design (see *Box 2*). This trial, which need not be that expensive, could be undertaken wherever TD is a concern and need not be constrained to the somewhat fragmented services often seen in 'Western' medicine.

Applicability

Most trials in this review were hospital based, but nevertheless featured the type of patients likely to be encountered in everyday care. Many of the interventions are readily accessible. The outcomes pose a greater problem of applicability. Scale-derived findings may be applicable, but even the original measures do not really describe how findings are relevant to day-to-day care. Whenever possible, we have extracted outcomes such as 'improved/not improved to a clinically important extent'. For the degree of importance

of the change, we have to trust the judgement of triallists from a wide variety of backgrounds and care cultures.

Quality of the evidence

Overall, the quality of the evidence is low to very low. This means that we have limited to very little confidence in the effect estimates, and the true effect may be, or is likely to be, substantially different from the estimate of the effect. The main reasons for our low confidence in the evidence were:

1. poor study methodology and reporting of methods, resulting in downgrading evidence for risk of bias
2. very small sample sizes, resulting in downgrading evidence for imprecision
3. wide CIs (often attributable to low event rates) that included appreciable benefit or harm for the intervention as well as no effect, resulting in downgrading evidence for imprecision.

Please see *Table 2* for full details.

Potential biases in the review process

Missing studies

We have made every effort 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 intervention investigated; 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.

Introducing bias

We have tried to be balanced in our appraisal of the evidence, but could have inadvertently introduced bias. We have tried to intentionally add bias towards treatments useful within the NHS, but have found no other innovations that really hold promise. We welcome comments or criticisms. We tried to ensure that searches for trials were wide-ranging, covering as many data sources as possible, but we still could easily have missed studies. We think it unlikely, however, that we would have missed large trials with important outcomes.

It is an unavoidable fact that many of the authors were familiar with this literature for many years before undertaking this full overview. However, the PPI exercise was undertaken, largely, blind to the results of the Cochrane reviews and in time to pre-date (and therefore direct) the construction of the summary-of-findings tables.

Agreements and disagreements with other studies or reviews

The only other relevant quantitative review on this topic we know of is the previous Cochrane review.[50] This update expands and improves this review, but does not substantially change the findings or the conclusions.

Chapter 8 Conclusions

Implications for health care

Clinicians, policy-makers and people with/at risk of TD are little better informed on this issue than they were decades ago. Underpowered randomised trials and observational studies of limited quality have repeatedly failed to provide answers.

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

Current treatments for TD are prescribed in hopes that they will have an impact on TD, but none have a strong base in evidence. It could be argued that these treatments are only ethical within well-designed pragmatic trials aimed at informing clinical practice in people with this debilitating problem.

Recommendations for research

Tardive dyskinesia reviews have data from current trials extracted, tabulated and traceable to source.[54] TD reviews, whether or not those within Cochrane, could use this resource to save time and money. These are reliably extracted data for sharing.

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

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

Our public consultation recognised the importance of TD, and participants reacted to the poor quality of research evidence and lack of progress in addressing TD over time. People attending felt that the current outcomes could be enhanced by addressing core concerns of service users such as social networks, quality of life and employment. Ideas for further research included prevalence studies, addressing social stigma, understanding causal mechanisms, developing psychological therapies to address TD specifically and looking at the role of peer support in managing TD. The full details are reported in *Appendix 1*.

The recommendations of the public consultation for focusing on specific key outcomes in our work were implemented directly into the summary-of-findings tables presented in this work and in the Cochrane reviews. In turn, these form the basis of the outcome list.

This review summarises more than three decades of pioneering work, but also highlights a systemic failure to properly address the ongoing issue of TD for clinicians or patients.

More thoughtful use of antipsychotic medication may reduce its prevalence, but TD nevertheless remains a problem.[5] Most people needing antipsychotic medication live in low- and middle-income countries, where the highest potency antipsychotic drugs may be the only ones available. TD is with us from treatments of the past, and continues to emerge from treatment practices of the present.

We realise that we are applying pragmatic clinical demands on studies that may never have been designed to provide them. Largely, the studies we have identified for inclusion were of short duration and grossly

underpowered. The studies used proxy outcomes, often out of necessity, as sensitive scales may show effects even if they are not pragmatic clinical outcomes. However, even in the syntheses we have been able to do, combining the power of similar studies on any outcome seems unlikely to provide sufficient power to illustrate real effects. We feel that the overview, Cochrane reviews and NMA reported here illustrate the need for not only more well-designed, -conducted and -reported pilot studies, but also much larger pragmatic studies reporting outcomes familiar to clinicians and patients.

Pioneering researchers will probably continue to undertake pilot randomised studies. All such studies should make all data available, including those on outcomes suggested by the public consultation, even if underpowered, to highlight clear differences. Randomised trials of treatments for people with established TD are indicated, with the most obvious recommended outcome for a large study being dose reduction. Such trials should be large (> 800 participants), perhaps with accrual supported through accurate local/national registers. The studies should be of adequate duration (1 year minimum), with test interventions that are acceptable and record outcomes relevant to everyone. Such trials could open opportunities for research in places that may be less well funded but carry the burden of care.

Public consultation in the UK has provided a list of simple, and, we think, universally relevant, practical outcomes for the large trials. These, along with any other routinely collected data, include outcomes that can be used for risk–benefit analyses and economic considerations.

These large trials should take place before another three decades pass.

There are many small, short trials investigating interventions for people with schizophrenia and TD but none for those with dementia and TD. Public consultation highlighted the need for updated prevalence studies of TD in groups of people with schizophrenia, those exposed to antipsychotic medication and, finally, patients with dementia.

Use of crossover design

Triallists find it difficult to identify people with both TD and schizophrenia to participate in trials.[95] Randomised crossover designs are used in the hope of improving the power of the study to find outcomes of interest. In this design, participants are initially randomised to one of the experimental interventions and then, at a prespecified time, cross over to the treatment that they did not receive at first. Conditions with a more stable time course than TD are better suited for crossover studies.[164]

The carry-over effect introduces additional difficulties. Many substances used to treat TD may well persist in the body for long periods after discontinuation; unless crossover studies include a mid-study washout period (which ensure that the participant is free from the inital treatment before starting the next arm of the study), any effect of treatment may continue into the second, placebo, arm of the trial – the 'carry-over effect'. In addition, carry-over may involve the regrowth or retreat of neuroreceptors. This slow rebalancing, if started, could continue long after all traces of intervention drugs are gone, so the physiological half-life of the experimental treatment may not be the only variable to consider when thinking through the issues of carry-over. TD is also an unstable condition, and people with TD may not remain compliant with medication. All these factors make the arguments for not using crossover methodology strong, despite the initial attraction.[164–166]

Planning of future studies

The relative effectiveness and safety of a 'switch to FGA' compared with a 'switch to SGA' is considered to be of great importance in terms of deterioration of symptoms of antipsychotic-induced TD. However, only a handful of studies examined that particular comparison – one and three studies for the outcomes 'no clinical improvement of TD symptoms' and 'total discontinuation rates' were available, respectively. NMA did not offer any additional advantage or further insight on the 'switch to FGA versus switch to SGA' comparison; no indirect evidence feeding this comparison existed and, thus, the network estimates were identical to their pairwise meta-analysis counterparts (see *Appendix 4*).

Figures 6 and *7* imply that, although the meta-analysis can be considered reasonably robust to the addition of new studies with a small sample size, conclusions might change if large studies are added. If further studies are to be designed and conducted, a total sample size of 1000 patients would give a good prospect of reaching a conclusive result for both outcomes. Decisions on whether or not new studies are to be conducted should take into account the feasibility of such a sample size. In any case, informed and evidence-based decisions would require the systematic assessment of existing evidence before embarking into new research.[167,168]

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Contributions of authors

Hanna Bergman (Systematic Reviewer, systematic review methods) co-ordinated updates of the nine Cochrane reviews on which this report is based, co-ordinated traceable data coding, selected studies, extracted, analysed and interpreted data, created summary-of-findings tables and wrote the final report.

Dawn-Marie Walker (Associate Professor, PPI) was one of the researchers who was awarded the grant with Karla Soares-Weiser and Clive E Adams, helped to design the project, oversaw the patient involvement and discussed the findings from the review with them, helped write the PPI section and reviewed the document through iterative drafts.

Adriani Nikolakopoulou (Doctor of Philosophy Student in Biostatistics, evidence synthesis methods) planned and conducted the NMA, and wrote the NMA sections of the report.

Karla Soares-Weiser (Deputy Editor in Chief for Cochrane, until September 2015 was the Managing Director of Enhance Reviews, psychiatry, evidence synthesis) was actively involved in the preparation of the original reviews, helped write the proposal, helped supervise the search and selection, co-ordinated the overall process and wrote the final report.

Clive E Adams (Chairperson of Mental Health Services Research, systematic reviewing, schizophrenia) helped do original reviews, helped supervise the search and selection, co-ordinated the overall process, and helped assimilate and write the final report.

Publications

Currently, only this report is published, but nine Cochrane reviews (see *Appendix 6*) are updated and are going through to full publication.

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Tammenmaa IA, McGrath JJ, Sailas E, Soares-Weiser K. Cholinergic medication for neuroleptic-induced tardive dyskinesia. *Cochrane Database Syst Rev* 2002;**3**:CD000207.

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Essali A, Deirawan H, Soares-Weiser K, Adams CE. Calcium channel blockers for neuroleptic-induced tardive dyskinesia. *Cochrane Database Syst Rev* 2011;**11**:CD000206. http://dx.doi.org/10.1002/14651858.CD000206.pub3

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Data sharing statement

Extracted data are freely available on Cochrane Schizophrenia Group's website via ResearchGate (http://dx.doi.org/10.13140/RG.2.2.28907.95529).

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Appendix 1 Patient and public involvement report: tardive dyskinesia – adding perspectives from personal experience to the research agenda

Introduction

On 15 April 2016, the McPin Foundation hosted a consultation group to gather feedback from people with a lived experience of TD. This endeavour was undertaken by the Cochrane Schizophrenia Group at the University of Nottingham in an effort to inform our systematic review. The consultation was commissioned by a group of researchers who have completed a NIHR-funded systematic review to ascertain effective interventions to treat TD. An integral part of any health research is to gain the service user perspective; therefore, the results of the review were discussed. Another aim of the session was to elicit what people with lived experience thought would be a good research project in this area.

Methods

The consultation was planned to enable the voices of people with personal experience of TD to be heard. The consultation was advertised by e-mail via the McPin Foundation's large circulation list of people who have an expressed interest in being involved, as well as on their website. Interested people were asked to contact the McPin Foundation to book a place to attend. Prior to the meeting, two documents were circulated to attendees: a lay report providing an overview of the review and one of the individual systematic reviews that had been included. These documents gave the foundation for the discussions of the day.

The consultation was held at the McPin Foundation offices in London, UK. Reimbursement for time and out-of-pocket expenses was offered. The consultation was facilitated by Ruth Sayers (Peer Researcher at the McPin Foundation), with support from Megan Rees (Public Involvement in Research Co-ordinator at the McPin Foundation) and Dr Dawn-Marie Walker (Associate Professor at the University of Southampton). All of these researchers have extensive experience in involving patients and the public in research consultation. Furthermore, although this collaboration is not empirical qualitative research per se, both Ruth and Dawn-Marie have expert knowledge in this paradigm, including hosting focus groups (or in this case a collaboration). The session was planned to provide time to reflect on current research on TD and to consider gaps in knowledge.

Following an introduction to the consultation by Ruth Sayers, Dr Dawn-Marie Walker gave an oral overview of the review and the findings.

The group was then shown a video clip from YouTube (YouTube, LLC, San Bruno, CA, USA) showing people with TD. The primary purpose of showing the clip was to give attendees an overview of the effects of TD and to provide a common starting point for the discussion. The YouTube clip shown towards the beginning of the consultation was entitled 'Tardive Dyskinesia'. Uploaded on 12 June 2016, the clip is a training digital versatile disc (DVD) that presents the AIMS exam by showing a range of abnormal involuntary movement-associated conditions in patients, including scoring by an expert medical panel.

The clip can be found at www.youtube.com/watch?v=FUr8ltXh1Pc (accessed 13 June 2017).

Attendees were then asked to consider:

- What is important to people who have experience of managing TD alongside living with severe mental illness?
- Are the outcomes used in current TD research, as reflected in the Cochrane reviews, appropriate from a lived experience perspective?
- What other outcomes might be important to service users and carers for research into TD?
- Ideas for future research in the area.

The consultation included open group discussions and prioritisation of ideas. All discussions were audio-recorded, while the attendees were asked to write down their ideas throughout the day on paper tablecloths and Post-it notes to help keep an accurate record of discussion and in order to encourage everyone to participate (see *Figures 1, 8* and *9*). The researchers listened to the recordings after the session and noted any points relevant to the above mentioned questions that would have impact on the funded systematic review. Full transcription and formal analyses were not appropriate in this case, as the consultation was not a piece of empirical qualitative work.

Group demographics

A total of six people attended the consultation, excluding facilitators. All collaborators were mental health service users and one was a carer. All service users were taking, or had previously taken, antipsychotics. The researchers acknowledge that a larger, diverse group may have presented a wider range of perspectives on the review; however, for the type of involvement we anticipated, a more formal method for recruitment (e.g. purposive sampling) would not have been appropriate.

Findings

Within the relatively open format of the consultation, the group were asked to bear in mind the four consultation questions. A number of attendees, including facilitators, were disturbed by the YouTube clip shown at the session, particularly its sole emphasis on identifying the physical symptoms of TD.

> *That's how others see me! Mad old woman from a 1950s asylum.*

TABLE 3 Demographic details

Category	Participants' details
Sex	Male, $n = 0$; female, $n = 6$
Age group (years)	25–34, $n = 2$; 35–44, $n = 1$; 45–54, $n = 1$; 55–64, $n = 1$; ≥ 65, $n = 1$
Ethnic group	White British, $n = 4$; other, $n = 2$
Service user/carer	Service user, $n = 5$; carer, $n = 1$
Antipsychotic use	Taken in past: olanzapine, quetiapine, thioridazine, haloperidol, risperidone olanzapine, sulpiride, quetiapine, haloperidol
	Currently taking antipsychotics: olanzapine, Depakote® (AbbVie Inc., North Chicago, IL, USA), venlafaxine

The group went on to discuss the debilitating nature of TD. One attendee noted that, unlike symptoms of psychosis such as hearing voices and hallucinations, people with TD are unable to conceal the effects of TD when they are out in public. This, in turn, can have a very negative impact on a person's self-esteem and ability to maintain social networks.

TD can be as debilitating as the psychosis itself.

From group discussions, a key theme that emerged was informed consent and the extent to which service users are made aware of the adverse effects of antipsychotic medication. There was a consensus that, on the whole, people are not given enough information about the adverse effects of antipsychotic medication. This lack of information makes it impossible for people to weigh the pros and cons of taking medications prior to beginning treatment. Informed consent is not only a key principle of treatment, but it also leads to higher levels of 'treatment adherence' and treatment satisfaction. Attendees felt that informed consent was important in both inpatient and outpatient settings.

I think psychiatrists presume that patients are stupid and can't make an informed choice.

Although attendees acknowledged that increasing the level of information provided to people would not directly lead to a lower incidence of TD, it would probably lead to people feeling more empowered and better able to accept the consequences of any treatment. Although we acknowledge that published evidence suggests that clinical efficacy is more important to patients than the side-effect profile of antipsychotics, a clear message that emerged from this consultation was the need for full informed consent obtained by outlining adverse effects in a patient-centred consultation. Only one of the collaborators had heard of TD before, although all had taken antipsychotics at some time.

Key recommendation for research outcomes in TD: measure the extent to which people feel informed about their treatment and the possibility of adverse effects such as TD.

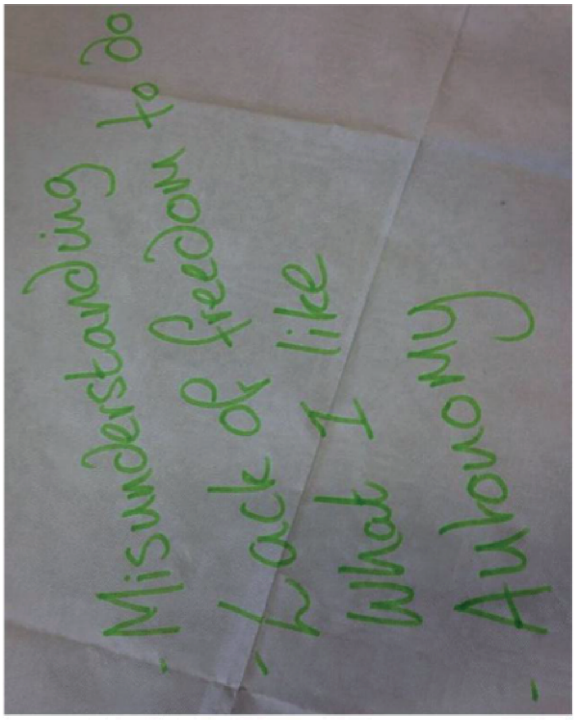
Participants also noted the importance of people having access to quality, evidence-based information about TD. This would make service users less reliant on clinicians for information, and support full informed consent.

Key recommendation for research outcomes in TD: measure service users' access to quality information about TD.

Discussions about informed consent led into a discussion about accountability. Attendees highlighted service users' feelings of anger and impotence that result from experiencing the distressing adverse effects of medication, particularly in cases in which people have not previously been provided with adequate information. In many cases, people have no way of holding the medical profession to account because adverse effects of medication are often similar to defined symptoms of mental illness and, thus, it is difficult for people to prove a direct link with medication. This is not the case with TD, as there is a general consensus that TD results solely from medication consumption. Accountability was an important outcome, particularly for people who have developed lifelong TD as a result of taking medication.

Key recommendation for research outcomes in TD: for people who have developed lifelong TD as a result of taking medication, to what extent do organisations/individuals take responsibility? Are people supported or encouraged to seek accountability?

Prevention was another key theme in the discussion. Attendees were concerned that adverse effects of medication are often treated with more medication and that the research included in the Cochrane review placed an over-reliance on pharmaceutical interventions to treat TD. They wondered, 'Why are all of the approaches pharmacological?'.



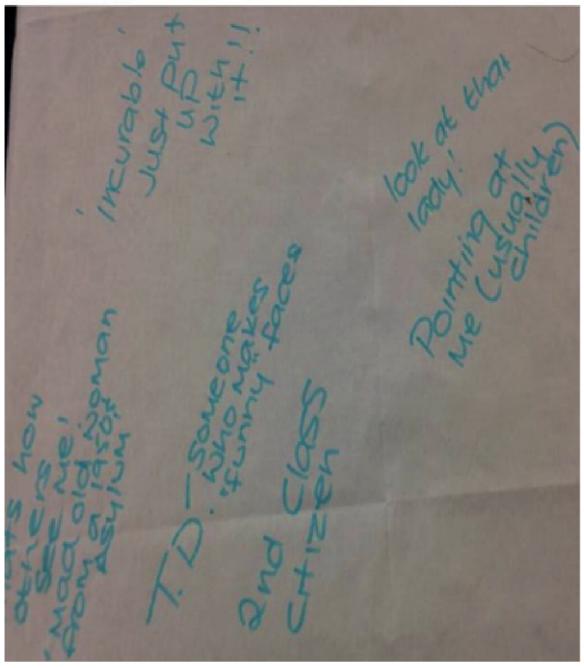


FIGURE 8 Some comments from the consultation.

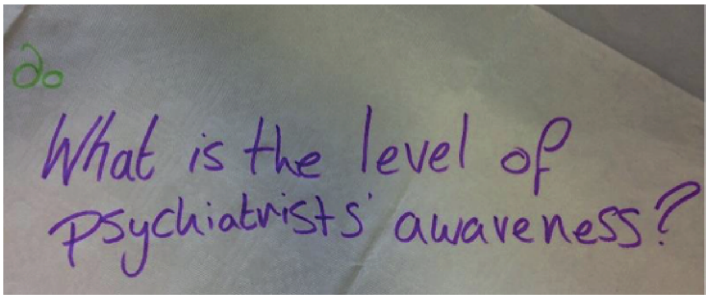


FIGURE 9 A key concern.

Furthermore, in light of the Cochrane review's findings, attendees were not confident that reducing or stopping taking antipsychotic drugs reduces instances of TD.

> *I'm appalled by the poverty of this evidence base given how debilitating tardive dyskinesia is.*

Attendees suggested other avenues that may be worth exploring, including attempting to understand the causal mechanisms behind TD through brain imaging.

Key recommendation for future research in TD: understanding the causal mechanisms that result in TD as well as developing methods to assess individuals' risk of developing TD as a result of medication consumption.

As the group discussed ideas for future research into TD, the issue of prevalence was raised. Is TD a diminishing problem? Prevalence was not addressed in the research compiled by the Cochrane review and the group were not aware of any substantive data to suggest that the prevalence of TD is decreasing. A number of recommendations were made in relation to prevalence.

Key recommendation for future research in TD: understanding the prevalence of medication-related TD.

Key recommendation for research outcomes in TD: measuring clinician awareness of TD as a side effect of psychiatric medications.

Key recommendation for research outcomes in TD: measuring the level of reporting with regard to incidences of TD.

Following the discussion about prevention and prevalence, the group considered the best ways of supporting those already living with TD and the role that research can play. None of the research that has taken place thus far has explored the effectiveness of psychological therapies, peer support and social interventions to help people to cope with the symptoms of TD. Coping mechanisms are very important in the absence of effective treatments, particularly for those who experience these adverse effects long term. Attendees noted that some of the most debilitating aspects of living with TD stem from social stigma and the negative impacts of TD on an individual's confidence:

> *Look at that lady!*
>
> *People point at me, particularly children.*
>
> *Tardive dyskinesia makes you feel vulnerable because it's so obvious.*

The group made a number of suggestions relating to managing the symptoms of TD, as well as measuring the effectiveness of particular treatments in relation to service users' confidence, social inclusion and quality of life.

Key recommendation for future research in TD: what psychological therapies are effective in managing the symptoms of TD?

Key recommendation for future research in TD: is peer support effective in managing the symptoms of TD?

Key recommendation for research outcomes in TD: social confidence, social inclusion, social networks, personalised quality-of-life measures and employment.

The group discussed the parallels between Tourette syndrome and TD. A number of public awareness campaigns have been successful in informing the public about Tourette syndrome, and this in turn has reduced social stigma. The group suggested that similar campaigns would probably be effective in reducing the stigma associated with TD.

Key recommendation for future research in TD: measuring public awareness of TD.

Finally, attendees were asked to review the outcomes that have been used in TD research to date to assess their relevance. As illustrated in the Cochrane review, the outcomes used in research relating to TD are as follows:

1. improvement in TD
2. level of functioning
3. improvement/reduction in psychiatric symptoms
4. deterioration
5. relapse
6. mental state changes
7. acceptability of treatment
8. quality of life
9. satisfaction with care
10. adverse effects
11. hospital admission
12. death
13. dropped out of trial/left the study early.

There was consensus within the group that all of the outcomes used to date have their merits and that their relevance would depend on a large number of factors including the type of treatment being assessed and trial design. However, the list of outcomes included in the Cochrane review has some notable omissions. Outcomes and areas of research that have thus far been underexplored are listed below.

List of key recommendations for outcomes and research in to tardive dyskinesia

Outcomes

- Measure the extent to which service users feel informed about their treatment and the possibility of adverse effects such as TD.
- Measure patients' access to quality information about TD.
- For people who have developed lifelong TD as a result of taking medication, to what extent do organisations/individuals take responsibility? Are service users supported or encouraged to seek accountability?
- Measuring clinician awareness of TD as a side effect of psychiatric medications.
- Measuring the level of reporting with regard to incidences of TD.

- Measuring social confidence, social inclusion, social networks, personalised quality-of-life measures and employment.
- Measuring public awareness of TD (*Figure 10*).

Future research

- Understanding the causal mechanisms that result in TD as well as developing methods to assess individuals' risk of developing TD as a result of medication consumption.
- Understanding the prevalence of medication-related TD.
- What psychological therapies are effective in managing the symptoms of TD?
- Is peer support effective in managing the symptoms of TD?

It is important to note that the above list of recommendations reflects the context within which they were suggested, either as additional outcomes to be considered within future TD research or as future research projects.

However, it was clear that almost all of the recommendations relating to 'outcomes' could equally be important areas of interest for future research in and of themselves. Moreover, some studies that are not solely focused on ascertaining the prevalence of medication-related TD may be improved by including an outcome measure to understand the prevalence of TD among their participant group.

Reflections of the facilitating team

Megan Rees

> *I really enjoyed the session and given I had little prior experience of working in the field of TD, I found the group's discussions very enlightening.*

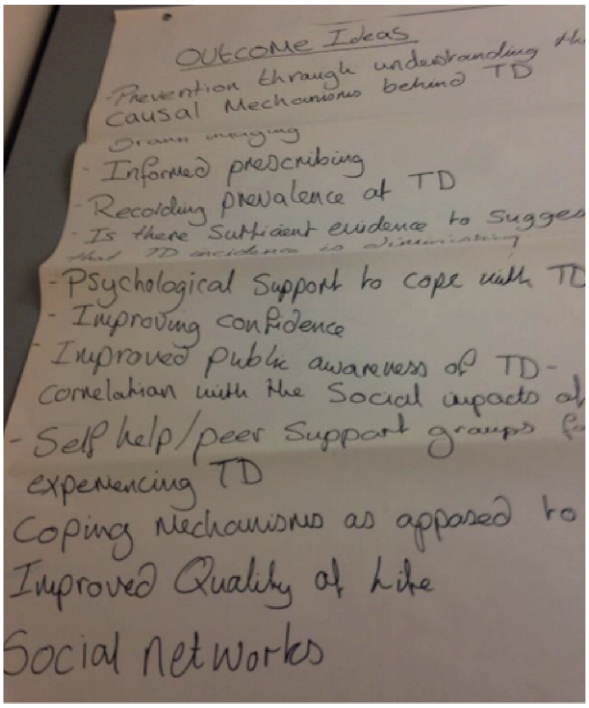


FIGURE 10 Key outcomes of interest.

When it came to the most important outcomes for research, attendees unanimously supported the goals of research included in the Cochrane review. Preventing and treating the symptoms of TD were, for obvious reasons, a key concern of service users. However, attendees were quick to highlight important outcomes that appeared to be missing from the research. One such 'missing' outcome referred to as 'informed prescribing' particularly struck me. After watching a rather graphic video of the effects of TD, there was a palpable sense of injustice. A number of attendees wondered how many people who are prescribed antipsychotics are made aware of such severe side effects and expressed how important it is that service users are given the opportunity to make an informed choice before taking medication. If, as the review found, we are unable to effectively prevent or treat this particular side effect, some emphasis must be placed on giving service users enough information that they are able to essentially own their decisions when it comes to medication. This would at least mitigate against the feeling of powerlessness and subjugation that many people feel when they experience medication side effects that they were not initially made aware of.

The group made a number of highly insightful suggestions throughout the day but it was their focus on outcomes relating to empowerment and autonomy that were so striking given that these outcomes were conspicuous by their absence in the research that has taken place so far.

Dawn Marie-Walker

I really enjoyed the session, and was reassured by the passionate responses from the service users that this research is really worthwhile.

Since being part of this work, one of my PhD [doctor of philosophy] students from Saudi Arabia has had a nephew with severe mental health difficulties. His nephew has been given vast amounts of medication, including anti psychotics, and what has resulted, from the description of my student, as TD.

Although initially my colleagues and I thought TD was a declining problem (due to having far more knowledge about it and medication regimes), it appears that it is still a grave problem internationally. Also in dementia, where antipsychotics are prescribed off licence, it may also be more of a problem.

Ruth Sayers

I appreciated the openness and engagement of the people who attended the workshop. Individual accounts of experiencing TD differed considerably, but all showed clearly the level of distress, vulnerability and stigmatisation that can be associated with tardive dyskinesia. Lack of awareness of TD was compared with the growing awareness of Tourette's, and the efforts being made to de-stigmatise that condition, especially with young people.

Several felt angry that they had not been given sufficient information at the time of prescribing about side effects of antipsychotics to make an informed choice – to enable them to balance the risks for themselves. There were many questions raised about how much was known, and how much doctors know, or reported, about TD, and therefore whether the actual prevalence is known, in the UK or elsewhere. Suggestions about what might help people included greater knowledge and an opportunity to avoid TD, and personal and social support to cope with the stigmatising condition. I hope that the workshop raised some important issues for further exploration.

Conclusion and next steps

It is clear that service users and carers from the consultation thought that research into TD to date has been limited and that further exploration is required. They supported the outcomes used in Cochrane schizophrenia review work on TD, but would recommend that the field is broadened. In addition, a formal recommendation was to put information on the prevalence of TD into the public domain. If data on prevalence do not currently exist, service users and carers recommend that this be sought out urgently. There was acknowledgement that data might include under-reporting, but this was felt to be an important benchmark for understanding.

The ultimate goal of research is to improve service user outcomes. The consultation group felt that there were some key issues that needed to be addressed. First, it was felt that better information about TD was needed, so that service users and their carers can make informed choices about medication. Second, strategies for coping with TD were identified as essential. A greater emphasis needs to be placed on psychological and social interventions for managing the symptoms of TD. For people already living with persistent symptoms of TD, supporting people in the management of the numerous impacts of TD was very important. Third, the consultation group felt that social stigma needed to be addressed as public reactions to people living with TD can be as hard to cope with as the symptoms of underlying mental health problems themselves, such as schizophrenia.

Appendix 2 Differences between protocol and review

Details of difference	Comments
We planned to include evidence from crossover trials. We only included evidence from the first phase of crossover trials	A major concern of crossover trials is the carry-over effect. This 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 washout phase. For the same reason, crossover trials are not appropriate if the condition of interest is unstable.[61] As both effects are very likely in severe mental illness, we used only data of the first phase of crossover studies
The planned outcomes list was reviewed and updated	As a consequence of the PPI session, outcome measures for the review were reviewed to also reflect outcomes important to patients
We planned to rely on evidence from the NMA. We decided not to rely on evidence from the NMA	The complete NMA was performed and it is available in *Appendix 4*. We have very little confidence in the results of the NMA because of (1) few data, (2) few studies in each comparison, (3) no differences between pairwise meta-analyses and NMA, and (4) not sufficiently connected networks. Therefore, we only used the results of the NMA to support planning future studies in this area
We carried out a different search from the protocol-specified search	As the Cochrane Schizophrenia Group maintains a good register that is regularly updated with a variety of databases and grey literature, we believed it was more appropriate to run the searches for all potential RCT TD references in their register. We also searched included and excluded studies of published Cochrane reviews

Appendix 3 Observational studies: additional methods and results

Search strategy and results

See *Figure 11* for the PRISMA diagram of observational study screening and study selection process.

The search strategy and results per database are presented below.

EMBASE

Date searched: 9 January 2017.

Date range searched: 1974 to 2017 week 2.

Number of results: 696.

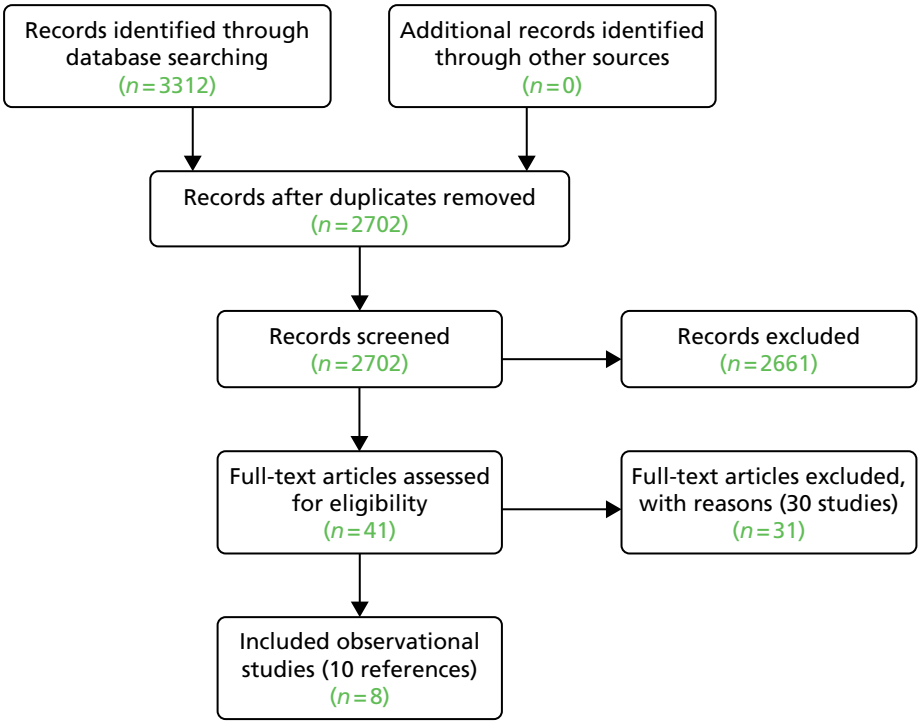


FIGURE 11 The PRISMA diagram of observational study screening and study selection process.

Search strategy

1. exp cohort analysis/ or exp longitudinal study/ or exp prospective study/ or exp case control study/ or exp follow up/ or cohort$.tw. or (case$ and control$).tw.
2. tardive dyskinesia/ or 'tardive dyskinesia?'.mp.
3. 1 and 2
4. Limit 3 to human

Ovid MEDLINE In-Process & Other Non-Indexed Citations and Ovid MEDLINE

Date searched: 9 January 2017.

Date range searched: 1946 to 9 January 2017.

Number of results: 2072.

Search strategy

1. exp cohort studies/ or epidemiologic methods/ or exp case-control studies/ or (case$ and control$).tw. or cohort$.tw.
2. tardive dyskinesia/ or 'tardive dyskinesia?'.mp.
3. 1 and 2
4. Limit 3 to humans

PubMed

Date searched: 9 January 2016.

Date range searched: up to 9 January 2017.

Number of results: 377.

Search strategy

1. Therapy/Broad[filter] AND ('observational study'[Publication Type] OR 'observational studies as topic'[MeSH Terms] OR 'observational studies'[All Fields]).
2. tardive dyskinesia/ or 'tardive dyskinesia?'.mp.
3. 1 and 2
4. Limit 3 to humans

PsycINFO

Date searched: 9 January 2017.

Date range searched: 1806 to January week 1 2017.

Number of results: 167.

Search strategy

1. cohort analysis/ or followup studies/ or exp longitudinal studies/ or (case$ and control$).tw. or cohort$.tw.
2. tardive dyskinesia/ or 'tardive dyskinesia?'.mp.
3. 1 and 2
4. Limit 3 to human

Results

Included studies

TABLE 4 Included observational studies: study characteristics, results, risk-of-bias assessments and conclusions

Study characteristics	Outcomes	Results			Conclusion; risk of bias					
					Selection bias	Controlled for baseline confounding	Reliable outcome assessment	Incomplete outcome data (attrition bias)	Selective outcome reporting	Other bias
Casey and Toenniessen, 1983[145]		Discontinuation of FGAs	Decrease of FGAs	Increase of FGAs	A small NRCT found that psychiatric patients with TD whose antipsychotic medication was reduced or discontinued showed greater improvement in TD symptoms (even resolution of symptoms) after 5 years of follow-up, compared with patients whose dosage of antipsychotic medication was increased or remained unchanged					
5-year NRCT ($n = 27$) of 30- to 77-year-old F and M inpatients with various mental disorders and TD in the USA	Mean (%) improvement in TD symptoms (AIMS)	55	65	35						
	Mental state (relapse) (*n*/*N*)	4/10	8/10	7/7	High	UC	UC	UC	High	UC
Comedications: lithium										
Damier *et al.*, 2007[146]	Mean (%) improvement in TD symptoms (ESRS)	There was a 50% improvement (range 30–66%) ($p = 0.002$) with bilateral globus pallidus deep-brain stimulation compared with no brain stimulation			A very small NRCT found that bilateral globus pallidus deep-brain stimulation seems to offer a greater benefit (50%) in decreasing TD symptoms at 6 months' follow-up compared with no stimulation					
6-month Phase II NRCT ($n = 10$) of 26- to 69-year-old F and M participants with various mental disorders and TD in France					High	UC	Low	UC	High	UC
Comedications: benzodiazepine, mianserin and amitriptyline										

continued

TABLE 4 Included observational studies: study characteristics, results, risk-of-bias assessments and conclusions (*continued*)

Study characteristics	Outcomes	Results		Conclusion; risk of bias					
				Selection bias	Controlled for baseline confounding	Reliable outcome assessment	Incomplete outcome data (attrition bias)	Selective outcome reporting	Other bias
Hardoy *et al.*, 2003[148] 1-year prospective cohort study ($n = 30$) of F and M outpatients with various mental disorders and TD in Italy	TD symptoms scale scores (AIMS mean end point) (low = less severe)	Gabapentin ± typical antipsychotics: 18.2 (SD 5.5); $n = 4$	Gabapentin ± atypical antipsychotics: 11.2 (SD 4.8); $n = 18$	A small prospective cohort study found that gabapentin treatment reduced TD symptoms in schizoaffective, bipolar I disorder and schizophrenic patients with a mean percentage of improvement at AIMS of 47.5% (SD ± 18.2%) in all treated patients. A trend towards improvement was revealed in both the participants taking concurrently atypical antipsychotics and those concurrently on traditional antipsychotics, with those on atypical antipsychotics (mean AIMS score 11.2, SD 4.8; $n = 18$) doing a little better than those on traditional antipsychotics (mean 18.2, SD 5.5; $n = 4$)					
Comedications: antipsycotics and mood stabilisers		Dosage: gabapentin commenced at 300 mg/day, increased after 2 days to 600 mg/day and reached 900–1200 mg/day during the first week. Mean dosage administered: 1170 ± 278 mg/day		High	UC	UC	UC	UC	UC
Huang, 1986[149] 4-year prospective cohort study ($n = 10$) of 50- to 68-year-old F and M inpatients with various mental disorders and TD in the USA Comedications: benztropine	TD symptoms scale scores: mean end point (Kazamatsuri *et al.*[169]) (low = less severe)	Discontinuation or reduced dose of FGAs 1.9; $n = 5$	No change in dose of FGAs 3.3; $n = 5$	A very small prospective cohort study found that psychiatric patients with TD whose antipsychotic medication was reduced or discontinued showed greater improvement in TD symptoms after 4 years of follow-up, compared with patients whose dosage of antipsychotic medication remained unchanged at 4 years' follow-up					
	Mean improvement in TD symptoms	60%; $n = 5$	21%; $n = 5$	High	UC	Low	UC	UC	UC

Study characteristics	Outcomes	Results		Conclusion; risk of bias					
				Selection bias	Controlled for baseline confounding	Reliable outcome assessment	Incomplete outcome data (attrition bias)	Selective outcome reporting	Other bias
Koshino *et al.*, 1991[150] 11-year prospective cohort study ($n = 28$) of 37- to 77-year-old F and M participants with various mental disorders and TD in Japan Comedications: not reported		Decreased dose of FGAs	Increased dose or no change of FGAs	A small prospective cohort study found that the severity of TD was unchanged in 39.3% of the patients, improved in 17.9% of patients, fluctuated in 21.4% of patients and worsened in 21.4% of patients at 11 years' follow-up. The outcome was not associated with patient sex, age, duration of primary illness, dosage of antipsychotics or changes in dosage					
	Improvement in TD symptoms (*n*/*N*)	2/13	3/15						
	No change in TD symptoms (*n*/*N*)	4/13	7/15						
	Worsening of TD symptoms (*n*/*N*)	3/13	3/15						
	Fluctuation of TD symptoms (*n*/*N*)	4/13	2/15						
		Dosage: the mean daily dose of FGAs was 221.4 mg (SD 153.7 mg) of CPZE (average for all groups)		High	UC	Low	High	UC	UC
Peselow *et al.*, 1989[151] 1-year prospective cohort study ($n = 31$) of F and M inpatients with schizophrenia and TD in the USA Comedications: not reported		Discontinuation of fluphenazine decanoate	Maintenance of fluphenazine decanoate	A small prospective cohort study found that, although there was a statistically significant decrease in abnormal movements at 1-year follow-up, this improvement was offset by the fact that 15 of the 21 (71.4%) patients discontinued from antipsychotic treatment relapsed					
	No clinically important improvement in TD symptoms (*n*/*N*)	14/21	9/10						
	TD symptoms scale scores: mean end-point AIMS score	5.76; $n = 21$	7.8; $n = 10$						
	Mental state (relapse) (*n*/*N*)	15/21	1/10	High	High	UC	UC	UC	UC
		Dosage: average 41.93 mg (SD ± 21.9 mg) biweekly							

continued

TABLE 4 Included observational studies: study characteristics, results, risk-of-bias assessments and conclusions (*continued*)

Study characteristics	Outcomes	Results		Conclusion; risk of bias					
				Selection bias	Controlled for baseline confounding	Reliable outcome assessment	Incomplete outcome data (attrition bias)	Selective outcome reporting	Other bias
Yagi and Itoh, 1985[152] 10-year prospective cohort study ($n = 20$) of 35- to 84-year-old F and M participants with various mental disorders and TD in Japan Comedications: antipsychotics		Discontinuation or decreased dose of antipsychotics	Antipsychotic maintenance	A small prospective cohort study found that the long-term outcome (10 years) of TD is determined by the patient's age at onset rather than by the course of antipsychotic treatment (discontinuation, maintenance or decreased dose) after the occurrence of TD					
	No clinically important improvement in TD symptoms (*n*/*N*)	5/14	1/4						
	Disappearance of TD (*n*/*N*)	6/14	2/4						
	Mental state (relapse) (*n*/*N*)	3/14	1/4	High	UC	UC	High	UC	UC
Yassa *et al.*, 1992[153,154] 10-year prospective cohort study ($n = 44$) of 42- to 83-year-old F and M inpatients and outpatients with various mental disorders and TD in Canada Comedications: anticholinergic medication, lithium carbonate, antidepressant		No change in antipsychotic dose (dosage: 357 mg/dl)	Decrease in antipsychotic dose (dosage: 312 mg/dl)	A small prospective cohort study found that the majority (50%) had no change in their TD severity, 20% had an improvement and 30% had a worsening of their TD. Little difference was noted in those patients whose medication was decreased (33% had no change in TD severity, 42% had increased TD severity and 25% had decreased TD severity) and those whose medication remained unchanged (56% had no change in TD severity, 25% had increased TD severity and 19% had decreased TD severity) at 10 years' follow-up					
	TD symptoms scale scores: mean endpoint AIMS score	4.8 (SD 3.8); $n = 32$	6.6 (SD 4.7); $n = 12$						
	No change in TD severity (*n*/*N*)	18/32	4/12						
	Increase in TD severity (*n*/*N*)	8/32	5/12						
	Decrease in TD severity (*n*/*N*)	6/32	3/12	High	Low	UC	High	UC	UC

CPZE, chlorpromazine equivalents; F, female; M, male; NRCT, non-randomised controlled trial; SD, standard deviation; UC, unclear.

Description of excluded studies

Thirty studies (31 references) were excluded at full-text screening. Reasons for exclusion were: not an observational study (seven studies), observational study with no control group (19 studies), study only measuring prevalence (three studies) or no treatment was provided (one study). *Table 5* shows full references and reasons for exclusion per study.

TABLE 5 Studies excluded from the observational studies review search, with reasons for exclusion

Study	Reason for exclusion
Ascher-Svanum H, Zhu B, Faries D, Peng X, Kinon BJ, Tohen M. Tardive dyskinesia and the 3-year course of schizophrenia: results from a large, prospective, naturalistic study. *J Clin Psychiatry* 2008;**69**:1580–8	No treatment provided
Bai YM, Yu SC, Chen JY, Lin CY, Chou P, Lin CC. Risperidone for pre-existing severe tardive dyskinesia: a 48-week prospective follow-up study. *Int Clin Psychopharmacol* 2005;**20**:79–85	48-week open-label follow-up of RCT (12 weeks: risperidone × placebo) with all receiving risperidone
Barron ET, McCreadie RG. One year follow-up of tardive dyskinesia. *Br J Psychiatry* 1983;**143**:423–4	TD prevalence only
Caine ED, Polinsky RJ, Kartzinel R, Ebert MH. The trial use of clozapine for abnormal involuntary movement disorders. *Am J Psychiatry* 1979;**136**:317–20	Already excluded RCT: Tourette syndrome, Huntington disease and drug-induced atypical dyskinesia, no TD symptoms at baseline
Chaplin RH. Risperidone, tardive dyskinesia, and the elderly. *Am J Psychiatry* 2001;**158**:1336–7	Review/commentary/editorial
Chen PH, Liu HC. Rapid improvement of neuroleptic-induced tardive dyskinesia with levetiracetam in an interictal psychotic patient. *J Clin Psychopharmacol* 2010;**30**:205–7	Case series/case report
Chouinard G, Annable L, Mercier P, Ross-Chouinard A. A five year follow-up study of tardive dyskinesia. *Psychopharmacol Bull* 1986;**22**:259–63	TD prevalence only
Cortese L, Caligiuri MP, Williams R, Schieldrop P, Manchanda R, Malla A, Harricharan R. Reduction in neuroleptic-induced movement disorders after a switch to quetiapine in patients with schizophrenia. *J Clin Psychopharmacol* 2008;**28**:69–73	Already excluded RCT; people with schizophrenia, no TD symptoms at baseline
Factor SA. Propranolol therapy for tardive dyskinesia revisited. *Mov Disord* 2012;**27**:1703	Case series/case report
Glazer WM, Moore DC, Schooler NR, Brenner LM, Morgenstern H. Tardive dyskinesia. A discontinuation study. *Arch Gen Psychiatry* 1984;**41**:623–7	No comparison group. Reported probabilities based on regression analyses
Glazer WM, Morgenstern H, Schooler N, Berkman CS, Moore DC. Predictors of improvement in tardive dyskinesia following discontinuation of neuroleptic medication. *Br J Psychiatry* 1990;**157**:585–92	No comparison group. Reported probabilities based on regression analyses
Hatcher-Martin JM, Armstrong KA, Scorr LM, Factor SA. Propranolol therapy for tardive dyskinesia: a retrospective examination. *Parkinsonism Relat Disord* 2016;**32**:124–6	Observational study without a control group (mentioned tetrabenazine as treatment of choice)
Heimburger RF. Dentatectomy in the treatment of dyskinetic disorders. *Confin Neurol* 1967;**29**:101–6	Case series/case report
Kantrowitz JT, Srihari VH, Tek C. Resolution of tardive dyskinesia after addition of aripiprazole to haloperidol depot. *J Clin Psychopharmacol* 2007;**27**:525–6	Case series/case report
Kucerová H. Olanzapine and improvement of tardive dyskinesia. *Eur Psychiatry* 2002;**17**:421–4	Case series/case report

continued

TABLE 5 Studies excluded from the observational studies review search, with reasons for exclusion (*continued*)

Study	Reason for exclusion
Lee JG, Shin BS, Lee YC, Park SW, Kim YH. Clinical effectiveness of the Kampo medicine kamishoyosan for adjunctive treatment of tardive dyskinesia in patients with schizophrenia: a 16-week open trial. *Psych Clin Neurosci* 2007;**61**:509–14	Observational study without a control group
Louzã MR, Bassitt DP. Maintenance treatment of severe tardive dyskinesia with clozapine: 5 years' follow-up. *J Clin Psychopharmacol* 2005;**25**:180–2	Case series/case report
Mendhekar D, Aggarwal A. Olanzapine and trihexyphenidyl-induced tardive dyskinesia. *Indian J Pharmacol* 2005;**37**:263	Case series/case report
Michael N, Sourgens H, Arolt V, Erfurth A. Severe tardive dyskinesia in affective disorders: treatment with vitamin E and C. *Neuropsychobiology* 2002;**46**(Suppl. 1):28–30	Case series/case report
Morgenstern H, Glazer WM, Woods SW. Risperidone and tardive dyskinesia. *Int J Geriatr Psychiatry* 2001;**16**:541–2	Review/commentary/editorial
Naber D, Leppig M, Grohmann R, Hippius H. Efficacy and adverse effects of clozapine in the treatment of schizophrenia and tardive dyskinesia – a retrospective study of 387 patients. *Psychopharmacology* 1989;**99**:S73–6	Retrospective case series
O'Brien CF, Jimenez R, Hauser RA, Factor SA, Burke J, Mandri D, *et al.* NBI-98854, a selective monoamine transport inhibitor for the treatment of tardive dyskinesia: a randomised, double-blind, placebo-controlled study. *Mov Disord* 2015;**30**:1681–7	RCT – included in Cochrane review
Pi EH, Simpson GM. Atypical neuroleptics: clozapine and the benzamides in the prevention and treatment of tardive dyskinesia. *Mod Probl Pharmacopsychiatry* 1983;**21**:80–6	Review/commentary/editorial
Rajarethinam R, Dziuba J, Manji S, Pizzuti A, Lachover L, Keshavan M. Use of aripiprazole in tardive dyskinesia: an open label study of six cases. *World J Biol Psychiatry* 2009;**10**:416–19	Case series/case report
Saltz BL, Kane JM, Woerner MG, Lieberman JA, Alvir JM, Blank K, *et al.* Prospective study of tardive dyskinesia in the elderly. *Psychopharmacol Bull* 1989;**25**:52–6	Only TD prevalence
Sharma A, Ramaswamy S, Dewan VK. Resolution of ziprasidone-related tardive dyskinesia with a switch to aripiprazole. *Prim Care Companion J Clin Psychiatry* 2005;**7**:36	Case series/case report
Singh MM, Becker RE, Pitman RK, Nasrallah HA, Lal H. Sustained improvement in tardive dyskinesia with diazepam: indirect evidence for corticolimbic involvement. *Brain Res Bull* 1983;**11**:179–85	Before-and-after study, irrelevant study design
Thara R. Use of antipsychotics and tardive dyskinesia. *J Postgrad Med* 2004;**50**:172	Review/commentary/editorial
van Harten PN, Hoek HW, Matroos GE, van Os J. Evidence that lithium protects against tardive dyskinesia: the Curaçao Extrapyramidal syndromes study VI. *Eur Neuropsychopharmacol* 2008;**18**:152–5	Observational study without a control group
Viallet F, Gayraud D, Gombert C, Renie L, Martinez-Almoyna L, Di Legge S, *et al.* Utility of tetrabenazine for managing L-Dopa induced dyskinesias in advanced Parkinson's disease: a retrospective observational study on 10 patients. *Mov Disord* 2014;**29**:S149	Observational study without a control group
Yasui-Furukori N, Kikuchi A, Katagai H, Kaneko S. The effects of electroconvulsive therapy on tardive dystonia or dyskinesia induced by psychotropic medication: a retrospective study. *Neuropsychiatr Dis Treat* 2014;**10**:1209–12	Case series/case report

Appendix 4 Network meta-analysis on comparative safety and clinical effectiveness of interventions for antipsychotic-induced tardive dyskinesia: methods and results

Objectives

We aimed to compare the safety and clinical effectiveness of interventions for deterioration of symptoms of antipsychotic-induced TD. We also aimed to generate a clinically meaningful hierarchy of the eligible interventions according to their efficacy and safety.

Methods

Criteria for considering studies for this review

Types of interventions

We included interventions used to treat or prevent deterioration of symptoms of antipsychotic-induced TD of relevance for people in the NHS, indicated as priority interventions: 'switch to SGA (including switch to amisulpride, clozapine, olanzapine, quetiapine, risperidone, ziprasidone)', 'antipsychotic (AP) reduction', 'antipsychotic maintenance/TAU (including AP)', 'antipsychotic withdrawal (with placebo)', 'FGA (any)', 'anticholinergic and AP continuation', 'anticholinergic withdrawal and AP continuation', 'benzodiazepines and AP continuation', 'buspirone and AP continuation', 'hypnosis or relaxation and AP continuation', 'vitamin E and AP continuation' and 'placebo (with AP continuation)'.

We assumed that any patient who met the inclusion criteria was, in principle, equally likely to be randomised to any of the interventions and, thus, the transitivity assumption was likely to hold on the onset.

Types of outcome measures

The following outcomes were measured:

- primary outcome – no clinical improvement of TD symptoms (< 50% improvement on scales)
- secondary outcome – total discontinuation rates.

We intended to analyse all planned outcomes described in the main paper but we were unable to do so because of the limited data available. We estimated the relative ranking of the competing interventions according to both of the above outcomes.

Data collection and analysis

Measures of treatment effect

Relative treatment effects

Odds ratios were employed for dichotomous outcomes. When continuous outcomes were measured, we analysed them using the MD if all studies used the same measure to assess the same outcome. Standardised mean difference, Hedge's adjusted *g*, was used when a different measure was used across studies to assess a common continuous outcome.[170]

Relative treatment ranking

We estimated *p*-scores, which are the most frequent analogues of surface under the cumulative ranking curves (SUCRAs), to obtain a hierarchy of the competing interventions.[171,172]

1. Assessment of clinical and methodological heterogeneity within treatment comparisons.
   We assessed the presence of clinical and methodological heterogeneity within each pairwise comparison by comparing trial and study population characteristics across all eligible trials. Considerable differentiation in synthesised studies in terms of patient, study and intervention characteristics might lead to a lack of usefulness of obtained results.[173]
2. Assessment of transitivity across treatment comparisons
   The assumption underlying NMA implies that one can learn about the relative effectiveness of 'A versus B' via a common comparator, for instance C.[155,174] We were unable to compare the distribution of effect modifiers across comparisons because of the limited data, but we compared the particular study characteristics qualitatively. Moreover, we assessed if the indication of the included interventions varied according to the alternative it is compared against.

Data synthesis

Methods for direct treatment comparisons

Initially, standard pairwise meta-analysis was performed for all pairwise comparisons with at least two studies using the random-effects inverse variance model in Stata.[175]

Methods for indirect and mixed comparisons

Network meta-analysis integrates direct and indirect evidence for each pairwise comparison to derive relative treatment effects between all competing treatments. We intended to perform NMA using the methodology of multivariate meta-analysis in which different treatment comparisons are handled as different outcomes using the 'network' package (which includes the 'mvmeta' command) in Stata.[156,176] As a result of the substantial number of treatment nodes and the version of Stata available, however, analysis using the 'network' package was not feasible and we performed NMA using graph theoretical methods as described in Rücker.[177,178] To this aim, we used the 'netmeta' package in R.[179] We also used available Stata routines to present the evidence base and to illustrate the results.[180] We produced a plot to present jointly the relative ranking of treatments for 'no clinical improvement' and 'total discontinuation rates', and we used a hierarchical cluster analysis to group interventions in meaningful subsets.[180]

Assessment of statistical heterogeneity

Assumptions when estimating the heterogeneity

In pairwise meta-analysis we assumed different heterogeneity variances for each comparison. In NMA, we assumed a common heterogeneity variance across all treatment comparisons in the network.

Measures and tests for heterogeneity

Between-study variance τ^2 was estimated in both pairwise and NMA using the DerSimonian and Laird estimator.[175] We assessed statistical heterogeneity based on the magnitude of the estimated parameter. We also compared the magnitude of τ^2 with empirical distributions derived in Turner *et al.*[181] and Rhodes *et al.*[182]

Assessment of statistical inconsistency

Network meta-analysis assumes consistency between various sources of evidence; that means that direct and indirect evidence is expected to be in agreement. However, it might be that the assumption of consistency is violated either in certain parts or in the entire network. We intended to evaluate statistical inconsistency using both local and global methods. In particular, we intended to evaluate the consistency assumption using the loop-specific approach.[183] Employing this method, we would estimate the disagreement between direct and indirect evidence in each closed loop (inconsistency factors).

Moreover, we intended to evaluate inconsistency in the entire network using the design-by-treatment interaction model.[156,184,185] However, there was only one closed loop in the network for the 'total discontinuation rates' outcome and, thus, we only judged on inconsistency for this loop using the loop-specific approach.

Investigation of heterogeneity and inconsistency

Several metaregression and subgroup analyses were planned in order to assess the impact of potential effect modifiers on the treatment effects. Our intention was to explore the impact of study and population characteristics fitting network metaregression models in a Bayesian environment using the WinBUGS software version 1.4.3 (MRC Biostatistics Unit, Cambridge, UK) and considering vague prior distributions for the covariates. As these analyses are known to have low power,[186,187] their presentation would be of questionable usefulness in the case of very few data.

Sensitivity analysis

We planned to perform the following four sensitivity analyses to ensure the robustness of the NMA results:

1. analysis restricted to studies rated as being at low risk of selection bias
2. analysis restricted to studies rated as being at low or unclear risk of selection bias
3. analysis restricted to studies rated as being at low risk of detection bias
4. analysis restricted to studies rated as being at low or unclear risk of detection bias.

Results

Summary

The primary outcome (no clinical improvement of TD symptoms) was reported in 46 studies (one three-arm study and 45 two-arm studies), including 1560 patients. Total discontinuation rates were reported in 78 studies (one four-arm study, one three-arm study and 76 two-arm studies) with 2965 patients. The number of studies and the number of participants per comparison with available direct data are given in *Table 6*.

Pairwise meta-analysis results

From the available comparisons with direct data described in *Table 6*, we kept data only for those that compared interventions described in *Chapter 5*, *Prioritisation of interventions*. *Table 7* and *Figures 12* and *13* show the available direct estimates for outcomes 'no clinical improvement of TD symptoms' and 'total discontinuation rates' for comparisons including interventions of priority with at least two studies available. Direct evidence suggests that 'switch to olanzapine' appears to be associated with lower discontinuation rates than 'switch to risperidone', whereas no important differences were detected between 'vitamin E and AP continuation' and 'placebo with AP continuation' for the outcome 'total discontinuation rates'. In terms of no clinical improvement of TD symptoms, 'vitamin E and AP continuation' has an insignificant advantage over 'placebo with AP continuation'. The comparison of 'antipsychotic maintenance/TAU (including AP)' versus 'antipsychotic reduction (reduced dose FGA)' is not statistically significant, but the overall treatment effect estimate does not rule out a beneficial effect of the second intervention.

TABLE 6 Number of studies and number of participants per comparison for the outcomes 'no clinical improvement of TD symptoms' and 'total discontinuation rates'

Comparisons	No clinical improvement of TD symptoms		Total discontinuation rates	
	Number of studies	Number of participants	Number of studies	Number of participants
Placebo (with AP continuation) vs.:				
Benzodiazepine (clonazepam, diazepam) and AP continuation	1	17	2	41
Branched-chain amino acids and AP continuation	1	52	1	52
Buspirone and AP continuation	1	42	1	42
Ceruletide and AP continuation	–	–	1	85
Cholinergic medication (deanol, galantamine, lecithin, meclofenoxate hydrochloride) and AP continuation	3	17	11	278
Cyproheptadine and AP continuation	–	–	1	42
Dihydrogenated ergot alkaloids/co-dergocrine mesylate and AP continuation	1	28	2	48
Dopaminergic (amantadine, bromocriptine, carbidopa/levodopa, oxypertine, reserpine, tiapride) and AP continuation	1	20	6	163
GABA agonist (baclofen, GABA, progabide, sodium valproate, THIP) and AP continuation	6	258	6	218
Ginkgo biloba standardised extract (EGb-761) and AP continuation	1	157	1	157
Insulin and AP continuation	1	20	1	20
Levetiracetam and AP continuation	–	–	2	119
Lithium and AP continuation	1	11	1	11
MAO inhibitor (isocarboxazid, selegiline) and AP continuation	1	33	1	33
Melatonin and AP continuation	2	32	3	54
Noradrenergic (celiprolol, methyldopa) and AP continuation	1	20	1	35
Oestrogen and AP continuation	1	12	1	12
Oil of evening primrose and AP continuation	1	16	1	16
Omega-3 fatty acid and AP continuation	–	–	1	84
Pemoline and AP continuation	1	46	1	46
Phenylalanine and AP continuation	–	–	1	18
Piracetam and AP continuation	–	–	1	40
Promethazine and AP continuation	1	34	1	34
Ritanserin and AP continuation	1	10	1	10
VMAT2 inhibitor (NBI-98854) and AP continuation	1	88	1	88
Vitamin B_6 and AP continuation	1	45	–	–
Vitamin E and AP continuation	6	264	13	475
1-Stepholidine and AP continuation	1	57	1	57

TABLE 6 Number of studies and number of participants per comparison for the outcomes 'no clinical improvement of TD symptoms' and 'total discontinuation rates' (*continued*)

Comparisons	No clinical improvement of TD symptoms		Total discontinuation rates	
	Number of studies	Number of participants	Number of studies	Number of participants
MAO inhibitor AP vs. anticholinergic (biperiden, procyclidine) and AP continuation	1	20	1	20
Antipsychotic maintenance/TAU (including AP) vs.:				
Benzodiazepine (clonazepam, diazepam) and AP continuation	1	15	1	15
Hypnosis or relaxation and AP continuation	1	15	–	–
Antipsychotic reduction (reduced dose FGA)	2	17	1	8
Active placebo (phenobarbital) and AP continuation vs. benzodiazepine (clonazepam, diazepam) and AP continuation	1	21	1	21
Switch to haloperidol/unspecified FGA vs.:				
Dopaminergic (tetrabenazine) and AP withdrawal	1	13	–	–
Dopaminergic (amantadine, bromocriptine, carbidopa/levodopa, oxypertine, reserpine, tiapride) and AP continuation	1	13	1	13
Switch to amisulpride	–	–	1	55
Switch to clozapine	–	–	1	39
Switch to molindone (FGA)	–	–	1	18
Switch to olanzapine	–	–	1	56
Switch to quetiapine	1	45	1	45
Switch to thiopropazate (FGA)	1	20	1	20
Switch to zuclopentixol	1	15	–	–
Dopaminergic (amantadine, bromocriptine, carbidopa/levodopa, oxypertine, reserpine, tiapride) and AP continuation vs. noradrenergic (celiprolol, methyldopa) and AP continuation	1	20	–	–
Switch to risperidone vs.:				
Switch to olanzapine	1	60	2	170
Switch to ziprasidone	–	–	1	84
Switch to quetiapine	–	–	1	118
Switch to ziprasidone vs.:				
Switch to olanzapine	–	–	1	82
Switch to quetiapine	–	–	1	90
Switch to amisulpride vs. switch to olanzapine	–	–	1	57
Switch to quetiapine vs. switch to olanzapine	–	–	1	116
Antipsychotic withdrawal (placebo) vs. switch to risperidone	1	50	1	50
Anticholinergic withdrawal (biperiden stopped after 1 week) and AP continuation vs. anticholinergic AP	–	–	1	10

THIP, 4,5,6,7-tetrahydroisoxazolo[5,4-c]pyridin-3-ol; VMAT2, vesicular monoamine transporter 2.

TABLE 7 Summary estimates for the outcomes 'no clinical improvement of TD symptoms' and 'total discontinuation rates' for comparisons with at least two studies available derived from standard pairwise meta-analysis (using a random-effects model and using different heterogeneity parameters across comparisons)

Comparisons	No clinical improvement of TD symptoms		Total discontinuation rates	
	OR (95% CI)	τ	OR (95% CI)	τ
Placebo (with AP continuation) vs.:				
Benzodiazepine (clonazepam, diazepam) and AP continuation	–	–	Excluded	Excluded
Vitamin E and AP continuation	2.28 (0.76 to 6.88)	0	1.02 (0.64 to 1.62)	0
Antipsychotic maintenance/TAU (including AP) vs. antipsychotic reduction (reduced dose FGA)	8.41 (0.91 to 77.72)	0	–	–
Switch to risperidone vs. switch to olanzapine	–	–	**2.17 (1.10 to 4.26)**	0

Notes
Bold results indicate statistical significance.
Heterogeneity was estimated using the method of moments estimator.
ORs > 1 favour the second treatment.

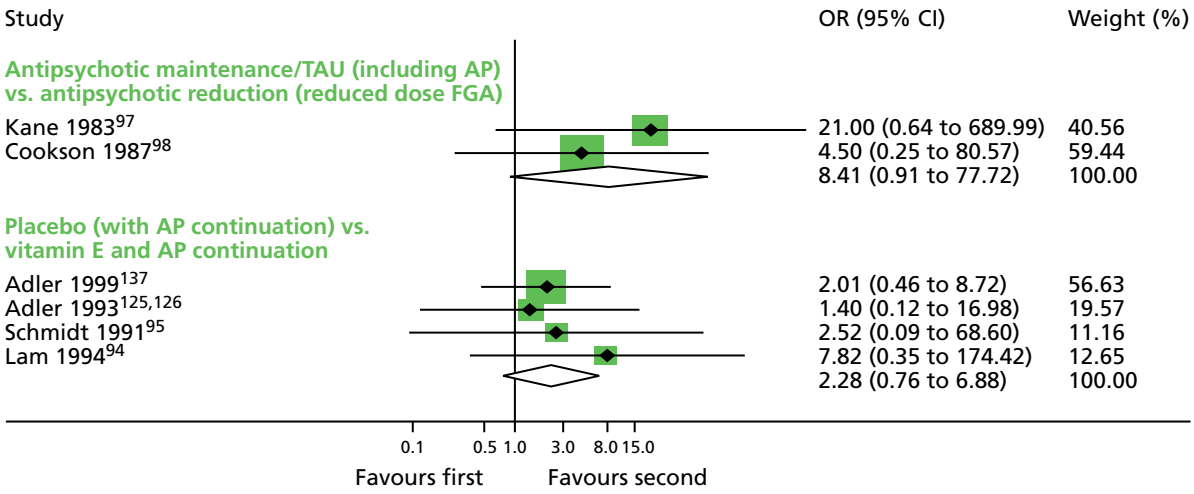


FIGURE 12 Pairwise meta-analysis results for active treatments vs. placebo (with AP continuation) for outcome 'no clinical improvement of TD symptoms' (comparisons with more than two studies, random-effects model, different heterogeneity parameters across comparisons). Heterogeneity was estimated using the method-of-moments estimator.

Network meta-analysis results

No clinical improvement of tardive dyskinesia symptoms

Evidence for the outcome 'no clinical improvement of TD symptoms' formed two disconnected networks that were analysed separately using NMA. The two formed networks for the outcome 'no clinical improvement of TD symptoms' are illustrated in *Figure 14* [included treatments: 'benzodiazepine (clonazepam, diazepam) and AP continuation', 'buspirone and AP continuation', 'MAO inhibitor (isocarboxazid, selengiline) and AP continuation', 'vitamin E and AP continuation', 'anticholinergic (biperiden, procyclidine) and AP continuation', 'antipsychotic maintenance/TAU (including AP)', 'hypnosis or relaxation and AP continuation', 'antipsychotic reduction (reduced dose FGA)'] and *Figure 15* (included treatments: 'switch to haloperidol', 'switch to thiopropazate', 'switch to quetiapine'). Nodes represent available treatments and edges represent available comparisons. Nodes and edges are weighted according

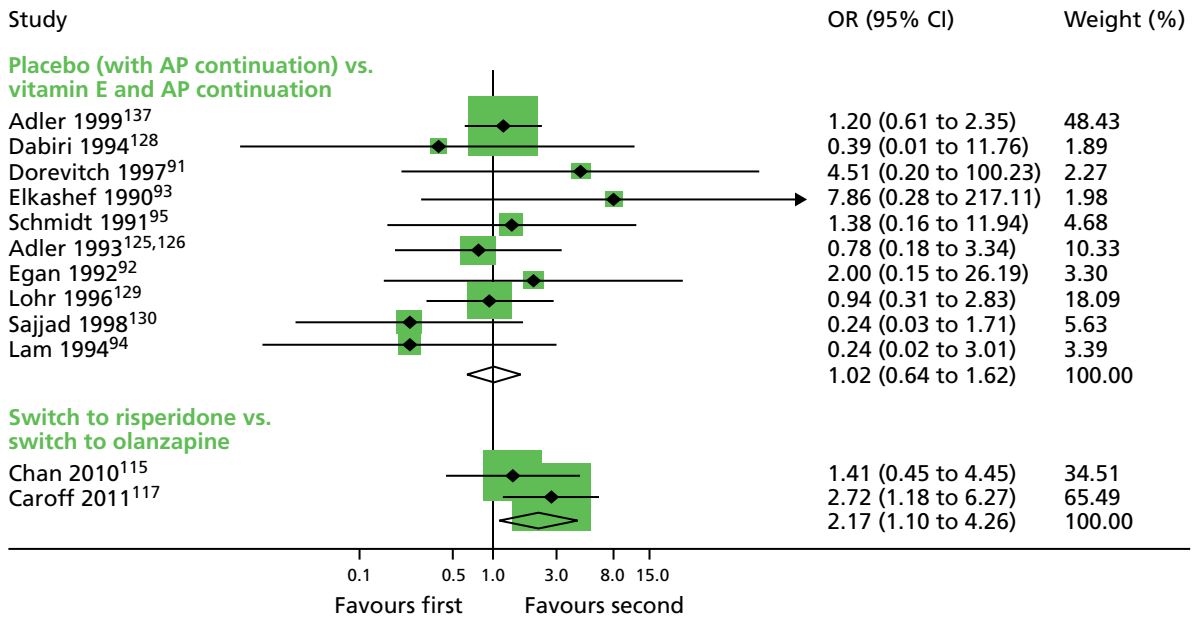


FIGURE 13 Pairwise meta-analysis results for active treatments vs. placebo (with AP continuation) for outcome 'total discontinuation rates' (comparisons with more than two studies, random-effects model, different heterogeneity parameters across comparisons). Heterogeneity was estimated using the method-of-moments estimator.

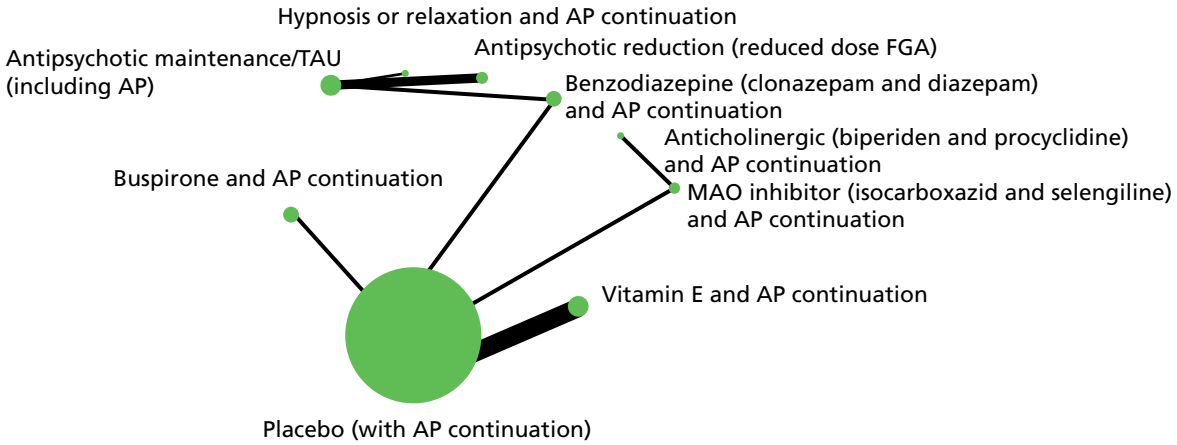


FIGURE 14 Network plot for the first subnetwork for the outcome 'no clinical improvement of TD symptoms'.

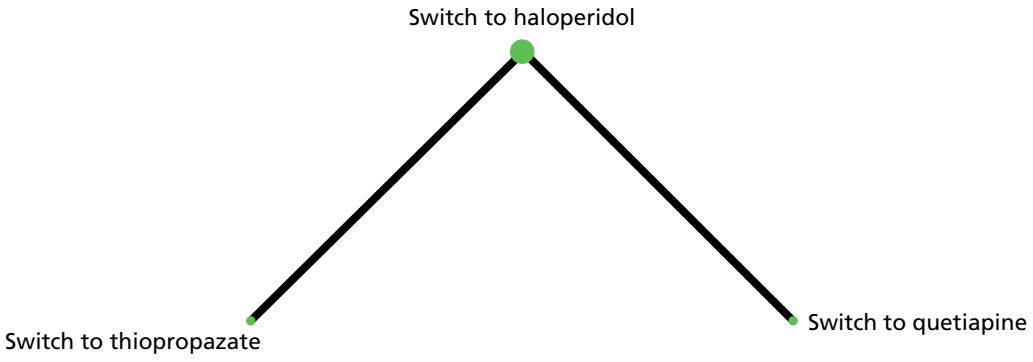


FIGURE 15 Network plot for the second subnetwork for the outcome 'no clinical improvement of TD symptoms'.

to the number of studies involved in each treatment. Two studies[105–109,115,116] compared treatments that were connected to neither of the two networks and, thus, were excluded from the NMA. 'MAO inhibitor (isocarboxazid, selengiline) and AP continuation' is included in the first subnetwork of *Figure 14* despite the fact that it is not in the list of priority interventions as it connects 'placebo (with AP continuation)' to 'anticholinergic (biperiden, procyclidine) and AP continuation', the relative effectiveness of which is of interest.

Table 8 shows the NMA results for the network illustrated in *Figure 14* for the outcome 'no clinical improvement of TD symptoms'. Studies in which all participants were classified as events or non-events in both groups were excluded. The forest plot in *Figure 16* shows the ORs of all treatments versus 'placebo (with AP continuation)' derived from the NMA. According to *Table 8* and *Figure 16*, the NMA suggests that 'hypnosis or relaxation and AP continuation' has the greatest benefit over 'placebo (with AP continuation)', whereas 'buspirone and AP continuation' and 'antipsychotic reduction (reduced dose FGA)' are also more effective than 'placebo (with AP continuation)'. 'Anticholinergic (biperiden and procyclidine) and AP continuation' appears to be less effective than 'placebo (with AP continuation)'. The results are consistent with the corresponding effect estimates derived from pairwise meta-analysis. It should be noted, however, that any judgements on the relative effectiveness of the treatments are mitigated by the high imprecision associated with most network estimates.

The subnetwork corresponding to *Figure 15* is formed by two studies only; a third study that was connected to the network[188] was excluded as all participants were classified as events. Thus, we do not present indirect estimates for the particular network as the value of drawing inferences would be doubtful because of the substantially limited data availability. The only study that compared 'switch to FGA' with 'switch to SGA' for the outcome 'no clinical improvement' was Emsley *et al.*,[110,111] in which an OR of 1.96 (95% CI 0.56 to 6.92) in favour of 'switch to SGA' was calculated. This comparison does not benefit from the NMA as it is not connected with the largest subnetwork of *Figure 14* and there is no indirect evidence that can be used to strengthen evidence on the relative effectiveness of the two interventions.

Total discontinuation rates

Evidence for the outcome 'total discontinuation rates' formed two disconnected networks that were analysed separately using NMA, and are illustrated in *Figures 17* and *18*. Nodes represent available treatments and edges represent available comparisons. Nodes and edges are weighted according to the number of studies involved in each treatment. 'MAO inhibitor (isocarboxazid, selengiline) and AP continuation' is included in the subnetwork of *Figure 17* despite the fact that it is not in the list of priority interventions as it connects 'placebo (with AP continuation)' to 'anticholinergic (biperiden, procyclidine) and AP continuation'.

Studies in which all participants were classified as events or non-events in both groups were excluded. The forest plot in *Figure 19* shows the ORs of all treatments versus 'placebo (with AP continuation)' derived from the NMA corresponding to the network plot of *Figure 17*. *Tables 9* and *10* summarise the network estimates corresponding to the networks of *Figures 17* and *18*, respectively. As is shown in *Tables 9* and *10* and *Figure 19*, most network estimates are highly imprecise (with rather wide CIs), rendering any conclusions on relative treatment effectiveness impractical. No statistically significant differences occur for any treatment versus 'placebo (with AP continuation)' in terms of discontinuation rates.

Sensitivity analysis merging switch to antipsychotics

As a sensitivity analysis, we further conducted a NMA for the subnetwork of *Figure 18* in which all switches to SGAs were merged into a 'switch to SGA (any)' treatment node, and all switches to FGAs were merged into a 'switch to FGA (any)' treatment node. The Caroff *et al.*,[117,118] Chan *et al.*,[115,116] Glazer *et al.*[189,190] and Kazamatzuri *et al.*[169] studies were excluded from this analysis as they examined either second- or first-generation antipsychotics only, and thus were representing a single treatment node. The network plot for this analysis is represented in *Figure 20*. Nodes and edges are weighted according to the number of studies involved in each treatment.

TABLE 8 Network meta-analysis results for the outcome 'no clinical improvement of TD symptoms'

Intervention	OR (95% CI)								
	Anticholinergic (biperiden, procyclidine) and AP continuation	Benzodiazepine (clonazepam, diazepam) and AP continuation	Buspirone and AP continuation	Hypnosis or relaxation and AP continuation	MAO inhibitor (isocarboxazid, selengiline) and AP continuation	Antipsychotic maintenance/TAU (including AP)	Antipsychotic reduction (reduced dose FGA)	Placebo (with AP continuation)	Vitamin E and AP continuation
Anticholinergic (biperiden, procyclidine) and AP continuation	–	**0 (0 to 0.09)**	**0 (0 to 0.01)**	**0 (0 to 0)**	**0.01 (0 to 0.33)**	**0 (0 to 0.03)**	**0 (0 to 0.01)**	**0 (0 to 0.01)**	**0 (0 to 0.05)**
Benzodiazepine (clonazepam, diazepam) and AP continuation	**908.73 (11.22 to 73,567.47)**	–	0.17 (0.01 to 2.33)	**0.01 (0 to 0.67)**	12.73 (0.61 to 267.28)	0.17 (0.01 to 2.56)	**0.02 (0 to 0.67)**	1.75 (0.23 to 13.16)	0.85 (0.09 to 8.22)
Buspirone and AP continuation	**5426.4 (77.13 to 381,770.62)**	5.97 (0.43 to 83)	–	0.06 (0 to 8.6)	**76 (4.45 to 1298.45)**	1 (0.02 to 44.23)	0.12 (0 to 9.62)	**10.45 (1.93 to 56.64)**	5.09 (0.7 to 36.88)
Hypnosis or relaxation and AP continuation	**86,632 (204.27 to 36,740,218.23)**	**95.33 (1.49 to 6100.75)**	15.96 (0.12 to 2190.69)	–	**1213.33 (7.01 to 210,075.5)**	15.89 (0.69 to 365.14)	1.89 (0.04 to 88.25)	**166.38 (1.64 to 16,971.54)**	81.34 (0.71 to 9268.58)
MAO inhibitor (isocarboxazid, selengiline) and AP continuation	**71.4 (3 to 1696.74)**	0.08 (0 to 1.65)	**0.01 (0 to 0.22)**	**0 (0 to 0.14)**	–	**0.01 (0 to 0.78)**	**0 (0 to 0.16)**	0.14 (0.01 to 1.34)	**0.07 (0.01 to 0.82)**
Antipsychotic maintenance/TAU (including AP)	**5452.36 (30.85 to 963,526.55)**	6 (0.39 to 92.28)	1 (0.02 to 44.66)	0.06 (0 to 1.45)	**76.36 (1.28 to 4567.86)**	–	0.12 (0.01 to 1.1)	10.5 (0.35 to 313.68)	5.12 (0.15 to 178.19)
Antipsychotic reduction (reduced dose FGA)	**45,832.92 (164.1 to 12,801,390.75)**	**50.44 (1.49 to 1710.27)**	8.45 (0.1 to 686.61)	0.53 (0.01 to 24.7)	**641.92 (6.1 to 67,591.57)**	8.41 (0.91 to 77.72)	–	**88.26 (1.52 to 5118.87)**	43.03 (0.65 to 2838.5)
Placebo (with AP continuation)	**519.27 (10.48 to 25,740.14)**	0.57 (0.08 to 4.3)	**0.1 (0.02 to 0.52)**	**0.01 (0 to 0.61)**	7.27 (0.74 to 71.11)	0.1 (0 to 2.85)	**0.01 (0 to 0.66)**	–	0.49 (0.17 to 1.37)
Vitamin E and AP continuation	**1065.09 (18.8 to 60,350.44)**	1.17 (0.12 to 11.29)	0.2 (0.03 to 1.42)	0.01 (0 to 1.4)	**14.92 (1.22 to 182.13)**	0.2 (0.01 to 6.8)	0.02 (0 to 1.53)	2.05 (0.73 to 5.75)	–

Notes
ORs > 1 indicate that the treatment specified in the row is better.
Bold results indicate statistical significance.
The overall heterogeneity (τ) is equal to 0 estimated using the methods-of-moment estimator.

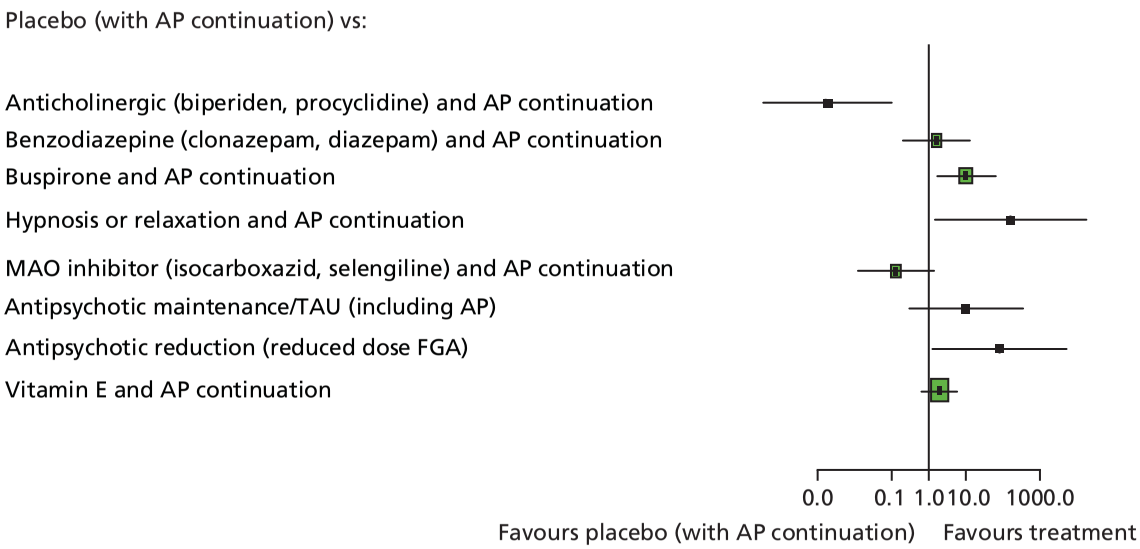


FIGURE 16 Network meta-analysis results for comparisons 'placebo (with AP continuation) vs. active treatments for outcome 'no clinical improvement of TD symptoms' (random-effects model, common heterogeneity parameter across comparisons). Heterogeneity was estimated using the methods-of-moment estimator.

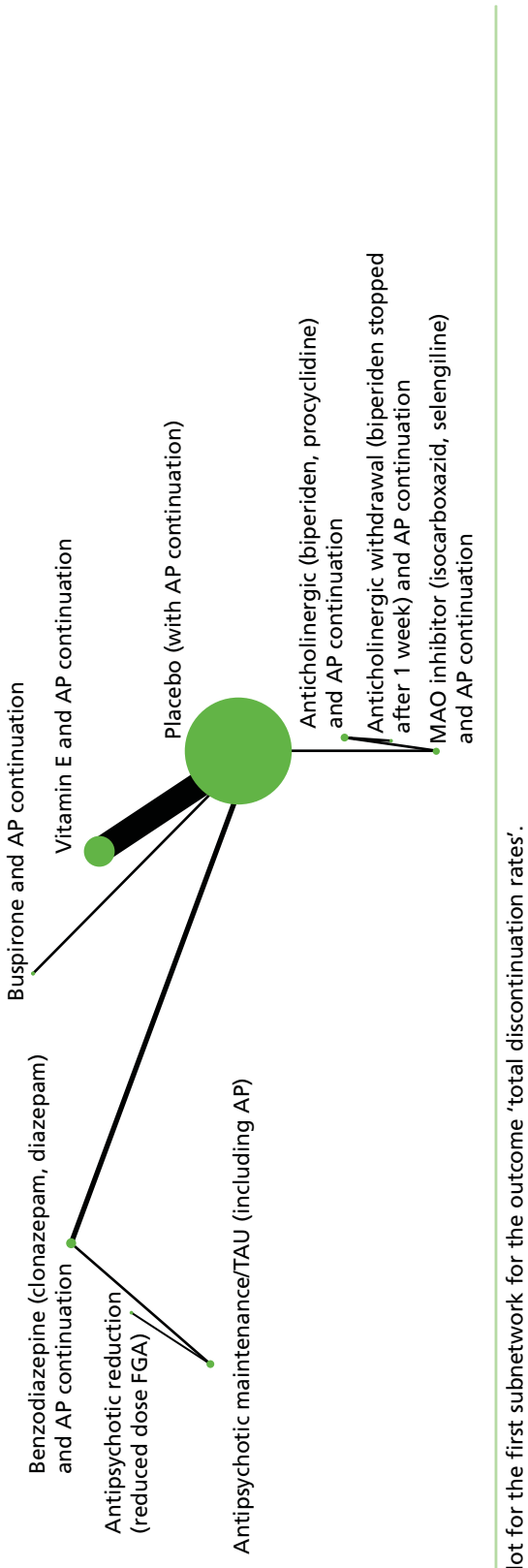


FIGURE 17 Network plot for the first subnetwork for the outcome 'total discontinuation rates'.

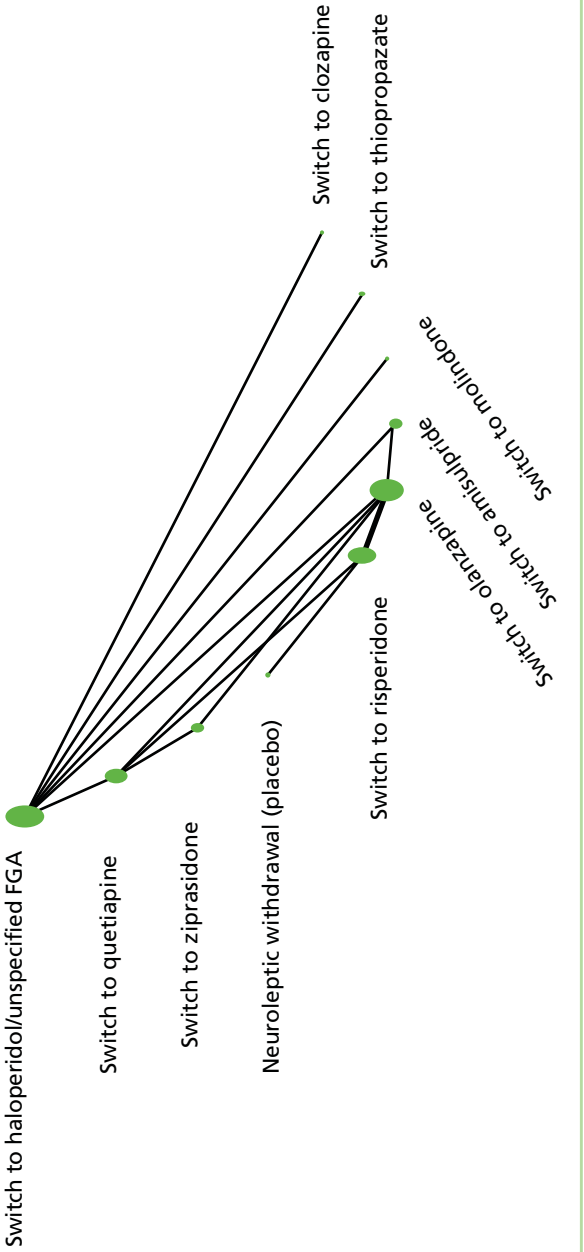


FIGURE 18 Network plot for the second subnetwork for the outcome 'total discontinuation rates'.

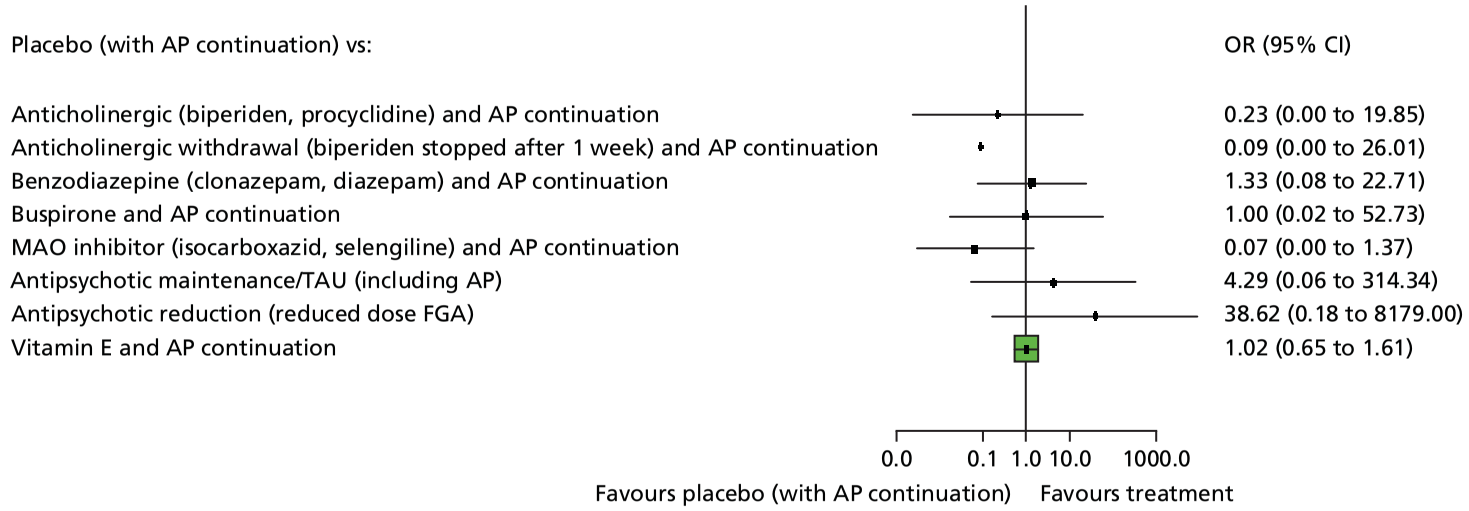


FIGURE 19 Network meta-analysis results for the comparisons of active treatments vs. placebo for the outcome 'total discontinuation rates' (using a random-effects model and using a common heterogeneity parameter across comparisons) corresponding to the subnetwork of *Figure 15*. Heterogeneity was estimated using the methods-of-moment estimator.

TABLE 9 Network meta-analysis results for the outcome 'total discontinuation rates' corresponding to the subnetwork of *Figure 17*

Intervention	OR (95% CI)								
	Anticholinergic (biperiden, procyclidine) and AP continuation	Anticholinergic withdrawal (biperiden stopped after 1 week) and AP continuation	Benzodiazepine (clonazepam, diazepam) and AP continuation	Buspirone and AP continuation	MAO inhibitor (isocarboxazid, selengiline) and AP continuation	Antipsychotic maintenance/ TAU (including AP)	Antipsychotic reduction (reduced dose FGA)	Placebo (with AP continuation)	Vitamin E and AP continuation
Anticholinergic (biperiden, procyclidine) and AP continuation	–	0.41 (0.01 to 12.64)	5.81 (0.03 to 1154.15)	4.38 (0.01 to 1716.99)	0.3 (0.01 to 8.33)	18.79 (0.04 to 9209.95)	169.14 (0.16 to 180,458.34)	4.83 (0.05 to 380.6)	4.47 (0.05 to 397.87)
Anticholinergic withdrawal (biperiden stopped after 1 week) and AP continuation	2.45 (0.08 to 76.13)	–	14.26 (0.03 to 7831.6)	10.75 (0.01 to 10,546.15)	0.74 (0.01 to 87.82)	46.13 (0.04 to 54,962.09)	415.15 (0.17 to 985,782.71)	10.75 (0.04 to 3004.46)	10.98 (0.04 to 3125.61)
Benzodiazepine (clonazepam, diazepam) and AP continuation	0.17 (0 to 34.21)	0.07 (0 to 38.53)	–	0.75 (0.01 to 98.99)	0.05 (0 to 3.2)	3.24 (0.13 to 80.99)	29.12 (0.31 to 2728.71)	0.75 (0.04 to 12.91)	0.77 (0.04 to 13.67)
Buspirone and AP continuation	0.23 (0 to 89.54)	0.09 (0 to 91.28)	1.33 (0.01 to 174.17)	–	0.07 (0 to 9.86)	4.29 (0.01 to 1482.25)	38.62 (0.05 to 30,257.79)	1 (0.02 to 52.73)	1.02 (0.02 to 55.29)
MAO inhibitor (isocarboxazid, selengiline) and AP continuation	3.32 (0.12 to 91.6)	1.35 (0.01 to 160.25)	19.26 (0.31 to 1187.7)	14.52 (0.1 to 2079.47)	–	62.31 (0.33 to 11,645.88)	**560.82 (1.22 to 258,196.52)**	14.52 (0.73 to 287.84)	14.83 (0.72 to 304.38)
Antipsychotic maintenance/TAU (including AP)	0.05 (0 to 26.08)	0.02 (0 to 25.83)	0.31 (0.01 to 7074)	0.23 (0 to 80.48)	0.02 (0 to 3)	–	9 (0.37 to 220.93)	0.23 (0 to 17.07)	0.24 (0 to 17.86)
Antipsychotic reduction (reduced dose FGA)	0.01 (0 to 6.31)	0 (0 to 5.72)	0.03 (0 to 3.22)	0.03 (0 to 20.28)	**0 (0 to 0.82)**	0.11 (0 to 2.73)	–	0.03 (0 to 5.48)	0.03 (0 to 5.71)
Placebo (with AP continuation)	0.23 (0 to 19.85)	0.09 (0 to 26.01)	1.33 (0.08 to 22.71)	1 (0.02 to 52.73)	0.07 (0 to 1.37)	4.29 (0.06 to 314.34)	38.62 (0.18 to 8197)	–	1.02 (0.65 to 1.61)
Vitamin E and AP continuation	0.22 (0 to 19.9)	0.09 (0 to 25.94)	1.3 (0.07 to 23.07)	0.98 (0.02 to 53.02)	0.07 (0 to 1.38)	4.2 (0.06 to 315.42)	37.82 (0.18 to 8167.79)	0.98 (0.62 to 1.55)	–

Notes
ORs > 1 indicate that the treatment specified in the column is better.
Bold results indicate statistical significance.
The overall heterogeneity (τ) is equal to 0, estimated using the restricted maximum likelihood estimator.

TABLE 10 Network meta-analysis results for the outcome 'total discontinuation rates' corresponding to the subnetwork of *Figure 18*

	OR (95% CI)									
Intervention	Antipsychotic withdrawal (placebo)	Switch to amisulpride	Switch to clozapine	Switch to haloperidol/ unspecified FGA	Switch to molindone	Switch to olanzapine	Switch to quetiapine	Switch to risperidone	Switch to thiopropazate	Switch to ziprasidone
Antipsychotic withdrawal (placebo)	–	5.48 (0.31 to 97.6)	0.66 (0.03 to 13.64)	2.73 (0.36 to 20.93)	2.73 (0.03 to 247.59)	3.85 (0.71 to 20.94)	1.38 (0.23 to 8.08)	1.83 (0.39 to 8.67)	13.63 (0.32 to 588.99)	1.98 (0.31 to 12.77)
Switch to amisulpride	0.18 (0.01 to 3.26)	–	0.12 (0 to 3.35)	0.5 (0.04 to 5.8)	0.5 (0 to 55.39)	0.7 (0.07 to 7.38)	0.25 (0.02 to 2.79)	0.33 (0.03 to 3.79)	2.49 (0.05 to 136.84)	0.36 (0.03 to 4.52)
Switch to clozapine	1.51 (0.07 to 30.91)	8.24 (0.3 to 227.37)	–	4.11 (0.44 to 38.23)	4.11 (0.04 to 408.14)	5.8 (0.45 to 74.88)	2.07 (0.17 to 24.8)	2.76 (0.21 to 36.85)	20.53 (0.43 to 987.99)	2.98 (0.21 to 43.25)
Switch to haloperidol/ unspecified FGA	0.37 (0.05 to 2.81)	2.01 (0.17 to 23.37)	0.24 (0.03 to 2.27)	–	1 (0.02 to 55.8)	1.41 (0.4 to 4.94)	0.5 (0.17 to 1.5)	0.67 (0.18 to 2.51)	5 (0.21 to 118.65)	0.73 (0.17 to 3.17)
Switch to molindone	0.37 (0 to 33.29)	2.01 (0.02 to 223.34)	0.24 (0 to 24.22)	1 (0.02 to 55.8)	–	1.41 (0.02 to 95.3)	0.5 (0.01 to 32.53)	0.67 (0.01 to 46.3)	5 (0.03 to 835.73)	0.73 (0.01 to 52.66)
Switch to olanzapine	0.26 (0.05 to 1.41)	1.42 (0.14 to 14.92)	0.17 (0.01 to 2.23)	0.71 (0.2 to 2.48)	0.71 (0.01 to 47.8)	–	**0.36 (0.16 to 0.78)**	**0.48 (0.24 to 0.93)**	3.54 (0.12 to 106.65)	0.51 (0.19 to 1.38)
Switch to quetiapine	0.73 (0.12 to 4.27)	3.98 (0.36 to 44.28)	0.48 (0.04 to 5.78)	1.98 (0.67 to 5.89)	1.98 (0.03 to 127.88)	**2.8 (1.28 to 6.14)**	–	1.33 (0.57 to 3.12)	9.91 (0.35 to 282.22)	1.44 (0.5 to 4.18)
Switch to risperidone	0.55 (0.12 to 2.58)	2.99 (0.26 to 33.77)	0.36 (0.03 to 4.84)	1.49 (0.4 to 5.56)	1.49 (0.02 to 102.44)	**2.1 (1.07 to 4.12)**	0.75 (0.32 to 1.75)	–	7.44 (0.24 to 229.66)	1.08 (0.39 to 3.02)
Switch to thiopropazate	0.07 (0 to 3.17)	0.4 (0.01 to 22.07)	0.05 (0 to 2.34)	0.2 (0.01 to 4.75)	0.2 (0 to 33.43)	0.28 (0.01 to 8.51)	0.1 (0 to 2.87)	0.13 (0 to 4.15)	–	0.15 (0 to 4.78)
Switch to ziprasidone	0.5 (0.08 to 3.25)	2.76 (0.22 to 34.5)	0.34 (0.02 to 4.86)	1.38 (0.32 to 6.01)	1.38 (0.02 to 99.73)	1.94 (0.72 to 5.21)	0.69 (0.24 to 2.01)	0.93 (0.33 to 2.59)	6.88 (0.21 to 226.2)	–

Notes
ORs > 1 indicate that the treatment specified in the column is better.
Bold results indicate statistical significance.
The overall heterogeneity (τ) is equal to 0 estimated using the restricted maximum likelihood estimator.

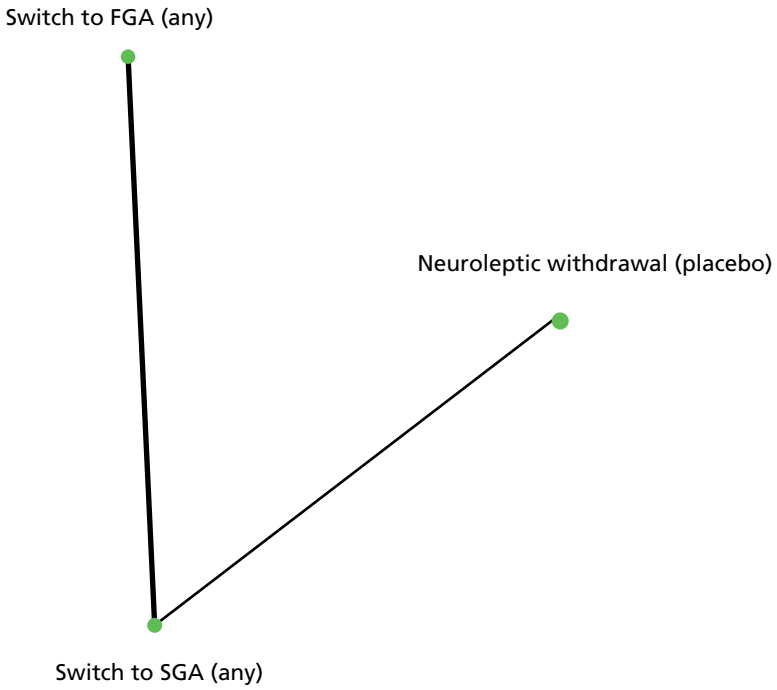


FIGURE 20 Network plot for the second subnetwork of *Figure 18* for the outcome 'total discontinuation rates', in which switch to first- and second-generation antipsychotics have been merged to 'switch to FGA (any)' and 'switch to SGA (any)' treatment nodes, respectively.

As the network presented in *Figure 20* comprised only four trials, we did not perform NMA as the validity of the results of such an analysis would be questionable. The comparison 'switch to FGA (any) versus switch to SGA (any)' was informed by three studies, resulting in a pairwise meta-analysis OR of 0.54 (95% CI 0.21 to 1.42) in favour of 'switch to FGA'. There is no indirect evidence to enrich the available information for this comparison and, thus, the use of NMA does not contribute to the knowledge regarding the relative effectiveness of the two interventions.

Comparison of heterogeneity parameters with empirical distributions

For a binary mental health outcome and a 'non-pharmacological versus any' comparison type, a median value of 0.13 is suggested for τ.[181] The specific value is greater than our estimation of heterogeneity (0) for both outcomes 'no clinical improvement of TD symptoms' and 'total discontinuation rates'.

Evaluation of inconsistency

We intended to evaluate the consistency assumption using the loop-specific approach in Stata using a common heterogeneity within each loop (but different across loops).[180] We also intended to further assess the assumption of consistency in the entire network simultaneously using the design-by-treatment interaction model in Stata.[156,176] However, for the outcome 'no clinical improvement of TD symptoms' all loops were formed by multiarm studies only (consistent by definition) and, thus, consistency could not be evaluated. For the outcome 'total discontinuation rates' only one loop was formed for the subnetwork illustrated in *Figure 18*, 'switch to olanzapine – switch to quetiapine – switch to haloperidol'; the inconsistency factor using the loop-specific approach was estimated at 1.45, with a (truncated) CI (0 to 4.51) indicating a lack of evidence of inconsistency.

Relative ranking of treatments

Table 11 shows the *p*-scores of the treatments involved in the outcomes 'no clinical improvement of TD symptoms' and 'total discontinuation rates' (networks of *Figures 14* and *17*), which are frequent analogues of SUCRAs.[171,172]

TABLE 11 *p*-scores for the outcomes 'no clinical improvement of TD symptoms' and 'total discontinuation rates'

Treatment	No clinical improvement of TD symptoms	Total discontinuation rates
Hypnosis or relaxation and AP continuation	0.89	–
Antipsychotic reduction (reduced dose FGA)	0.85	0.90
Buspirone and AP continuation	0.66	0.56
Antipsychotic maintenance/TAU (including AP)	0.62	0.74
Vitamin E and AP continuation	0.36	0.59
Benzodiazepine (clonazepam, diazepam) and AP continuation	0.35	0.61
Placebo (with AP continuation)	0.24	0.58
MAO inhibitor (isocarboxazid, selengiline) and AP continuation	0.10	0.19
Anticholinergic (biperiden, procyclidine) and AP continuation	0.01	0.38
Anticholinergic withdrawal (biperiden stopped after 1 week) and AP continuation	–	0.29

Note
Treatments are ordered according to the *p*-scores for the outcome 'no clinical improvement of TD symptoms'.

No clinical improvement of tardive dyskinesia symptoms

The *p*-score value of 'hypnosis or relaxation and AP continuation' is 89%, indicating that it is 89% as effective as a treatment that would be ranked always first without uncertainty. 'Anticholinergic (biperiden, procyclidine) and AP continuation' appears to be the worst treatment in terms of 'no clinical improvement of TD symptoms' as it has a *p*-score close to 0. These findings are in agreement with the network effect estimates presented in *Table 8* and *Figure 16*.

Total discontinuation rates

'Antipsychotic reduction (reduced dose FGA)' has the greatest *p*-score (90%) in terms of total discontinuation rates. Uncertainty in treatment effects escalates in uncertainty in treatment ranking resulting in many *p*-scores around 50%.

Clustered ranking plot for the outcomes 'no clinical improvement of tardive dyskinesia symptoms' and 'total discontinuation rates'

In *Figure 21* we have ranked treatments according to the outcomes 'no clinical improvement of TD symptoms' and 'total discontinuation rates'. Hierarchical cluster analysis is performed to group the competing treatments. Different colours represent different groups of treatments considering jointly their relative ranking for two outcomes. Treatments that belong to the same group may be considered as being of comparable performance with respect to both outcomes. According to *Figure 21*, 'antipsychotic reduction (reduced dose FGA)' has the highest performance on both outcomes in terms of ranking for the two considered outcomes. 'Anticholinergic (biperiden, procyclidine) and AP continuation' and 'MAO inhibitor (isocarboxazid, selengiline) and AP continuation' can be considered as the treatments having the worst joint performance for the outcomes 'no clinical improvement of TD symptoms' and 'total discontinuation rates'.

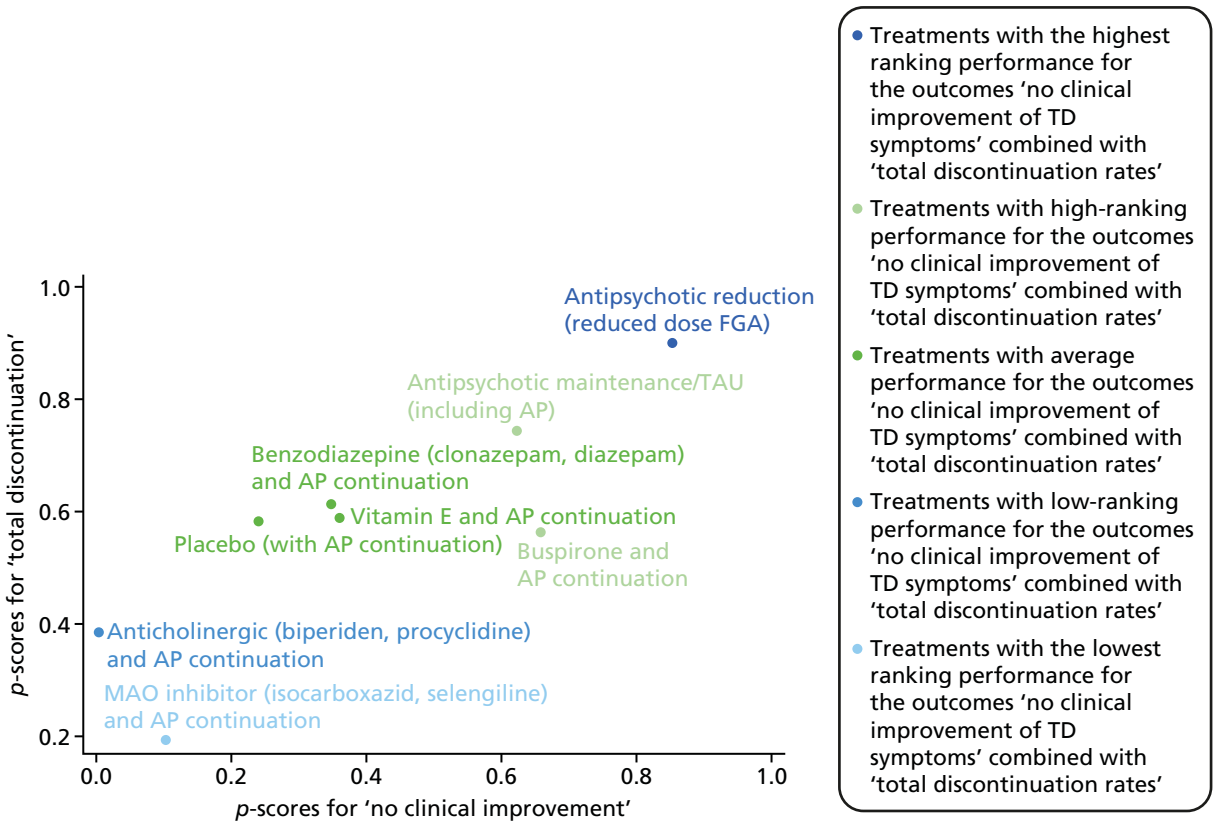


FIGURE 21 Clustered ranking based on *p*-scores for the outcomes 'no clinical improvement of TD symptoms' and 'total discontinuation rates'. Hierarchical cluster analysis is performed to group the competing treatments.

Appendix 5 Studies excluded from the search: reasons for exclusion

Summary

Table 12 summarises the number of studies and references excluded from the review with reasons for exclusion.

References for *Appendix 5* and reasons for exclusion

Not randomised controlled trial or randomised comparison

Adler L, Duncan E, Reiter S, Angrist B, Peselow E, Rotrosen J. Effects of calcium-channel antagonists on tardive dyskinesia and psychosis. *Psychopharmacol Bull* 1988;**24**:421–5.

Albus M, Naber D, Muller-Spahn F, Douillet P, Reinertshofer T, Ackenheil M. Tardive dyskinesia: relation to computer-tomographic, endocrine, and psychopathological variables. *Biol Psychiatry* 1985;**20**:1082–9.

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TABLE 12 Summary of excluded studies with reasons for exclusion

Reason for exclusion	Number of studies (number of references from which studies found)
Not RCT or randomised comparison	170 (201)
Randomised but not TD	88 (103)
Randomised, TD, but not stabilised on antipsychotics	5 (6)
Randomised, TD, no usable data reported – authors contacted to confirm lack of data	15 (19)
Randomised, TD, but no usable data reported – no author contact details, study > 20 years old	8 (12)
Randomised, TD, but no separate data reported on minority with TD – authors contacted to confirm lack of data	3 (3)
Randomised, TD, but crossover trial with no separate data reported for phase before crossing over to second treatment – authors contacted to confirm lack of data	26 (36)
Randomised, TD, but crossover trial with no separate data reported for phase before crossing over to second treatment – no author contact details, study > 20 years old	14 (18)
Total	329 (398)

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Appendix 6 Cochrane reviews on antipsychotic-induced tardive dyskinesia

Published Cochrane reviews on TD are listed below. They can be accessed through The Cochrane Library. All these reviews have been updated and are in the pre-publication process at the time of writing.

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Tammenmaa I, McGrath J, Sailas E, Soares-Weiser K. Cholinergic medication for neuroleptic-induced tardive dyskinesia. *Cochrane Database Syst Rev* 2002;**3**:CD000207.

Soares-Weiser K, Joy C. Miscellaneous treatments for neuroleptic-induced tardive dyskinesia. *Cochrane Database Syst Rev* 2003;**2**:CD000208.

Bhoopathi PS, Soares-Weiser K. Benzodiazepines for neuroleptic-induced tardive dyskinesia. *Cochrane Database Syst Rev* 2006;**3**:CD000205.

El-Sayeh HG, Lyra da Silva JP, Rathbone J, Soares-Weiser K. Non-neuroleptic catecholaminergic drugs for neuroleptic-induced tardive dyskinesia. *Cochrane Database Syst Rev* 2006;**1**:CD000458.

Soares-Weiser K, Rathbone J. Neuroleptic reduction and/or cessation and neuroleptics as specific treatments for tardive dyskinesia. *Cochrane Database Syst Rev* 2006;**1**:CD000459.

Alabed S, Latifeh Y, Mohammad HA, Rifai A. Gamma-aminobutyric acid agonists for neuroleptic-induced tardive dyskinesia. *Cochrane Database Syst Rev* 2011;**4**:CD000203.

Essali A, Deirawan H, Soares-Weiser K, Adams CE. Calcium channel blockers for neuroleptic-induced tardive dyskinesia. *Cochrane Database Syst Rev* 2011;**11**:CD000206.

Soares-Weiser K, Maayan N, McGrath J. Vitamin E for neuroleptic-induced tardive dyskinesia. *Cochrane Database Syst Rev* 2011;**2**:CD000209.

Appendix 7 Detailed study characteristics and risk-of-bias assessments

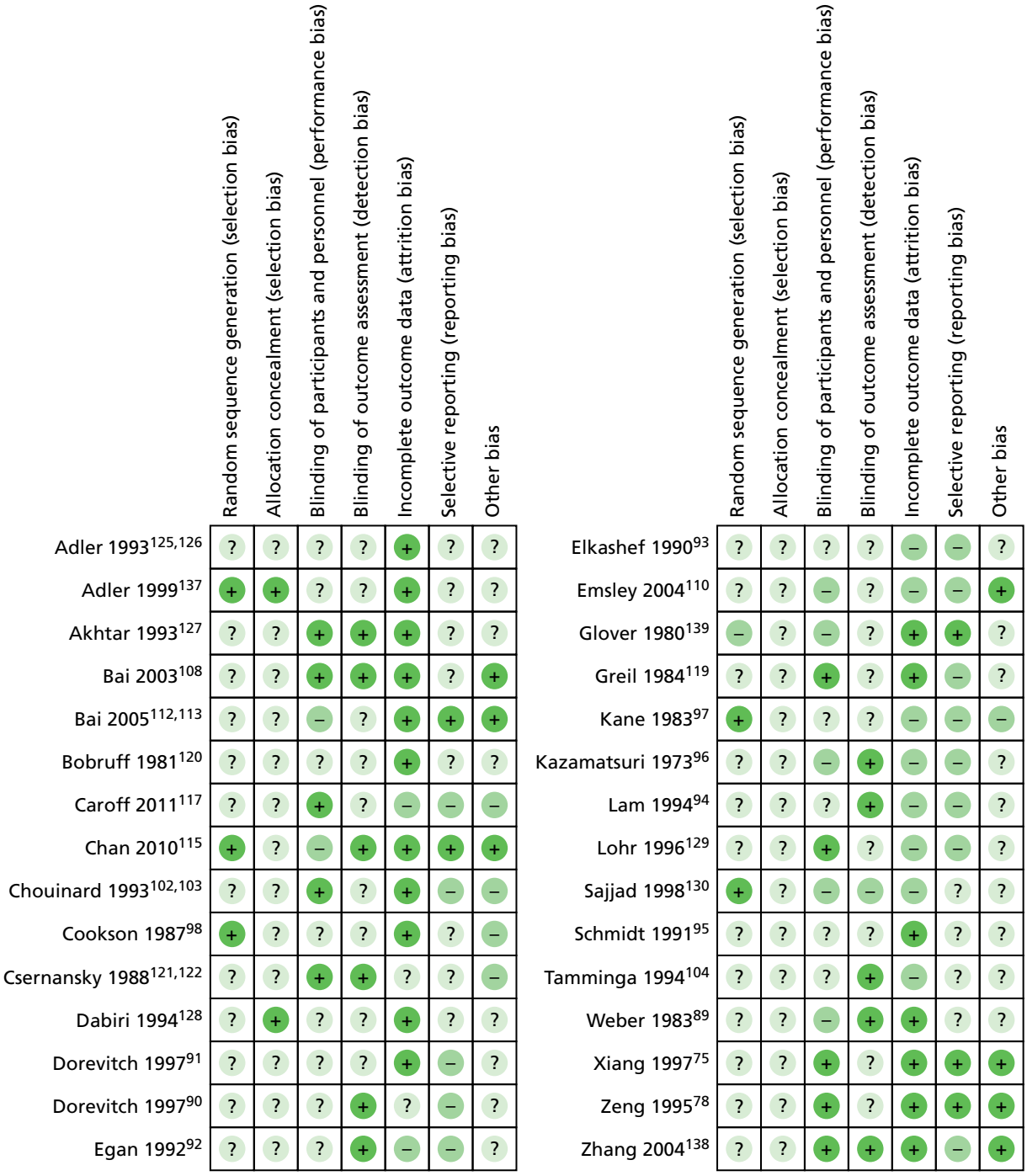

FIGURE 22 Summary of risk-of-bias assessments for included studies. –, high risk of bias; +, low risk of bias; ?, unclear risk of bias.

Antipsychotic drugs

TABLE 13 Characteristics and risk of bias of included studies evaluating antipsychotic drugs as treatment for TD

Included study	Description
***Bai* et al., *2003*[108]**	
Study characteristics	
Characteristic	***Description***
Methods	• Allocation: 'randomly assigned', not described • Blindness: 'double blind', partially described • Design: parallel groups • Setting: inpatients, Taiwan • Duration: 12 weeks
Participants	• Diagnosis: schizophrenia with persistent severe tardive dyskinesia (DSM-IV,[191] Kane criteria). $n = 49$ randomised, 42 completed • Age: 50.2 (SD 9.7) years • Sex: 28 male and 14 female • History: maintenance on conventional antipsychotics for > 1 year with an equivalent dosage of < 200 mg/day of chlorpromazine; duration of TD not reported
Interventions	After a 4-week washout period with all original conventional antipsychotics discontinued: 1. risperidone – started at 2 mg/day and increased, with a 2-mg increase every 2 weeks, to 6 mg/day over 6 weeks, then maintenance dose of 6 mg/day for 12 weeks, $n = 22$ 2. placebo – placebo for 12 weeks, $n = 20$ Concomitant medication included benzodiazepines (86–90%) and antiparkinsonism drugs (50–86%)
Outcomes	• TD symptoms: AIMS • Adverse effects: extrapyramidal symptoms (parkinsonism) (ESRS) • Adverse effects: dystonia (ESRS) • TD symptoms: clinical efficacy (decrease in AIMS of 3 or 4 = responder), BPRS
Notes	Sponsorship source: supported by Janssen-Cilag Taiwan, Johnson & Johnson Taiwan Ltd
Risk of bias	

Bias	***Authors' judgement***	***Support for judgement***
Random sequence generation (selection bias)	Unclear risk	'. . . subjects were randomly assigned to the risperidone or placebo groups', further details not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias)	Low risk	*. . . double-blind . . . A placebo with an identical appearance to the risperidone dose was prescribed for the placebo group using the same dose schedule*
Blinding of outcome assessment (detection bias)	Low risk	*The TD condition was evaluated blindly by a psychiatrist with the Abnormal Involuntary Movement Scale (AIMS) every 2 weeks*
Incomplete outcome data (attrition bias)	Low risk	Seven of 49 participants withdrew: *Four subjects dropped out due to psychotic symptom exacerbation (2 subjects during the washout period: 1 subject in the placebo group and 1 subject in the risperidone group). Another 3 subjects withdrew due to a medical condition (infectious disease, heart condition, and lung carcinoma)*
Selective reporting (reporting bias)	Unclear risk	Unclear if all predefined outcomes have been reported. A protocol is not available for verification
Other bias	Low risk	The study seems to be free of other sources of bias

TABLE 13 Characteristics and risk of bias of included studies evaluating antipsychotic drugs as treatment for TD (*continued*)

Included study	Description	
***Bai* et al., *2005*[112,113]**		
Study characteristics		
Characteristic	***Description***	
Methods	• Allocation: 'randomised', not described • Blindness: 'single blind', partially described • Design: parallel groups • Setting: inpatients, Taiwan • Duration: 24 weeks	
Participants	• Diagnosis: schizophrenia (DSM-IV[191]), Schooler and Kane's criteria[192] for persistent TD, $n = 80$ • Age: 50.2 (SD 7.1) years • Sex: 39 male and 41 female • History: duration of TD not reported; treatment with conventional antipsychotics for > 1 year	
Interventions	No washout period on the discontinuation of all conventional antipsychotics was reported: 1. olanzapine: dose not reported, 24 weeks, $n = 27$ 2. amisulpride: dose not reported, 24 weeks, $n = 27$ 3. FGA: dose not reported, 24 weeks, $n = 26$	
Outcomes	• TD symptoms: AIMS • Adverse effects: extrapyramidal side effects (SAS); akathisia (BAS); general (UKU) • General mental state (BPRS) • Leaving the study early	
Notes	Sponsorship source: the study was supported by grants from National Science Council, Taiwan	
Risk of bias		
Bias	***Authors' judgement***	***Support for judgement***
Random sequence generation (selection bias)	Unclear risk	'The subjects were randomized to three groups', further details not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias)	High risk	*. . . single-blind and controlled study*
Blinding of outcome assessment (detection bias)	Unclear risk	'. . . single-blind and controlled study'. Blinding details of outcome assessors not reported
Incomplete outcome data (attrition bias)	Low risk	*Finally 76 cases (95%) completed the 24-week study, 2 cases in the olanzapine groups withdrew due to impaired liver function, 1 case in the amisulpride group due to infectious disease, and 1 case in the FGA controlled groups withdrew due to unstable psychiatric condition* Intention-to-treat analyses with last-observation-carried-forward method applied
Selective reporting (reporting bias)	Low risk	All outcomes appear to have been reported
Other bias	Low risk	The study seems to have been free of other sources of bias

continued

TABLE 13 Characteristics and risk of bias of included studies evaluating antipsychotic drugs as treatment for TD (*continued*)

Included study	Description
***Caroff* et al., *2011*[117]**	
Study characteristics	
Characteristic	***Description***
Methods	• Allocation: 'randomly assigned', not described • Blindness: 'double blind', partially described • Design: post hoc analysis of parallel group RCT • Setting: inpatients, USA • Duration: 18 months
Participants	• Diagnosis: schizophrenia and TD (DSM-IV,[191] Schooler-Kane criteria[192]), $n = 200$ • Age: 47.2 (SD 9.4) years (range 18–65 years) • Sex: 158 male and 42 female • History: duration of TD not reported
Interventions	Overlap in administration of the antipsychotic drugs that patients received before study entry was permitted for the first 4 weeks after randomisation to allow a gradual transition to study medication: 1. olanzapine – flexible dose of 7.5 mg q.d./b.i.d./t.i.d./q.i.d. for 18 months, $n = 54$ 2. quetiapine – flexible dose of 200 mg q.d./b.i.d./t.i.d./q.i.d. for 18 months, $n = 62$ 3. risperidone – flexible dose of 1.5 mg q.d./b.i.d./t.i.d./q.i.d. for 18 months, $n = 56$ 4. ziprasidone – flexible dose of 40 mg q.d./b.i.d./t.i.d./q.i.d. for 18 months, $n = 28$ Medications were flexibly dosed with 1–4 capsules daily, as judged by the study doctor. Concomitant medications were permitted, except for additional antipsychotic agents
Outcomes	• Leaving the study early • Unable to use AIMS, PANSS, SAS, BAS Cognitive composite score (not reported in means and SDs for the separate intervention groups)[a]
Notes	Sponsorship source: supported by the Clinical Antipsychotic Trials of Intervention Effectiveness project, National Institute of Mental Health. This article was based on results from the Clinical Antipsychotic Trials of Intervention Effectiveness project, supported by the National Institute of Mental Health. Astra Zeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Forest Pharmaceuticals Inc., Janssen Pharmaceutical Products LP, Eli Lilly and Company, Otsuka Pharmaceutical Co. Ltd, Pfizer Inc. and Zenith Goldline Pharmaceuticals Inc. provided medications for the studies. This material is based on work also supported in part by the Department of Veterans Affairs, Veterans Health Administration, Office of Research Development, with resources and the use of facilities at the Philadelphia Veterans Affairs Medical Center
Risk of bias	

Bias	***Authors' judgement***	***Support for judgement***
Random sequence generation (selection bias)	Unclear risk	'Patients were initially randomly assigned', further details not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias)	Low risk	*. . ., double-blind conditions, . . . Identical-appearing capsules contained olanzapine (7.5 mg), quetiapine (200 mg), risperidone (1.5 mg), perphenazine (8 mg), or ziprasidone (40 mg)*
Blinding of outcome assessment (detection bias)	Unclear risk	Blinding of outcome assessors not reported

TABLE 13 Characteristics and risk of bias of included studies evaluating antipsychotic drugs as treatment for TD (*continued*)

Included study	Description	
Incomplete outcome data (attrition bias)	High risk	The primary clinical outcome measure was time to all-cause treatment discontinuation. Total population ($n = 200$): 74% discontinuation. Olanzapine: 31/54 (57%); quetiapine: 51/62 (82%); risperidone: 44/56 (79%); ziprasidone: 21/28 (75%). Reasons for withdrawal reported
Selective reporting (reporting bias)	High risk	Original CATIE study: *The primary clinical outcome measure was time to all-cause treatment discontinuation. Secondary outcomes included discontinuations for intolerability, inefficacy, and patient decision; rates of discontinuations; mean modal dose; and change from baseline in the PANSS and neurocognitive composite scores* All outcomes not fully reported for the TD population
Other bias	High risk	Post hoc analysis; modified diagnostic criteria for TD were applied at baseline and a 3-month history of antipsychotic exposure was not required
***Chan* et al., *2010*[115]** *Study characteristics*		
Characteristic	***Description***	
Methods	• Allocation: 'randomly assigned by coin method' • Blindness: single-blind (outcome assessor) • Design: parallel groups • Setting: inpatients, Taiwan • Duration: 24 weeks	
Participants	• Diagnosis: schizophrenia ($n = 58$) and schizoaffective disorder ($n = 2$) (DSM-IV criteria[191]); antipsychotic-induced TD, $n = 60$ • Age: 45.3 (SD 11.6) years (range 18–70 years) • Sex: 21 male and 39 female • History: duration of TD not reported. Antipsychotic exposure ≈10 years. All of the subjects received FGAs prior to participation in this study	
Interventions	Following a washout period of 3–7 days: 1. risperidone – flexible dose of 1.9 ± 0.7 mg/day (baseline) to 4.1 ± 1.4 mg/day (end point) for 24 weeks, $n = 30$ 2. olanzapine – flexible dose of 8.1 ± 2.0 mg/day (baseline) to 12.6 ± 5.4 mg/day (end point) for 24 weeks, $n = 30$	
Outcomes	• TD symptoms: no clinical improvement > 50% (AIMS) • TD symptoms: AIMS • Adverse effect: dyskinesia; parkinsonism; dystonia; akathisia; general adverse events • General mental state: BPRS • Leaving the study early	
Notes	Sponsorship source: supported by research grant from the Taoyuan Mental Hospital and from the Department of Health, Executive Yuan, Taiwan	
Risk of bias		
Bias	***Authors' judgement***	***Support for judgement***
Random sequence generation (selection bias)	Low risk	*. . . randomly assigned to receive either olanzapine or risperidone with a 1-to-1 ratio by coin method with a 6-block design*
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported

continued

TABLE 13 Characteristics and risk of bias of included studies evaluating antipsychotic drugs as treatment for TD (*continued*)

Included study	Description	
Blinding of participants and personnel (performance bias)	High risk	*. . . primary care physicians and patients were not blinded*
Blinding of outcome assessment (detection bias)	Low risk	*Two investigators (C.-H.C. and J.-J.C.) served as blinded raters . . . The BPRS, CGI-S, AIMS and global impression of ESRS were performed at baseline and at weeks 1, 2, 3, 4, 8, 12, 16, 20, and 24 or at end point visit by blinded-rater*
Incomplete outcome data (attrition bias)	Low risk	Nine out of 30 in the risperidone and 7 out of 30 in the olanzapine groups dropped out from the study; reasons reported *All patients who were randomly assigned and had at least 1 post-baseline assessment were included in the intent-to-treat (ITT) analysis. If the ITT subjects withdrew from the study earlier than scheduled, then the last observation carried forward method was employed to extend the end point scores*
Selective reporting (reporting bias)	Low risk	Data for all outcomes in the trial registry, NCT00621998, have been reported
Other bias	Low risk	The study seems to be free of other sources of bias
***Chouinard* et al., *1993*[102,103]** *Study characteristics*		
Characteristic	***Description***	
Methods	• Allocation: 'randomly assigned', not described • Blindness: 'double blind', partially described • Design: post-hoc analysis of parallel 6-group RCTs • Setting: inpatients, Canada • Duration: 8 weeks	
Participants	Diagnosis: chronic schizophrenia (DSM-III-R criteria[193]), $n = 135$ Age: mean 39 years, range 19–60 years Sex: 34 male and 14 female History: duration TD not reported; the most common pre-study medications were haloperidol, procyclidine, lorazepam, benztropine and chlorpromazine; the most commonly used depot antipsychotic agents were haloperidol decanoate, fluphenazine decanoate, flupentixol decanoate and pipothiazine palmitate	
Interventions	Mean duration of washout phase 6 days: 1. risperidone – dose 2 mg/day for 8 weeks, $n = 8$ 2. risperidone – dose 6 mg/day for 8 weeks, $n = 6$ 3. risperidone – dose 10 mg/day for 8 weeks, $n = 6$ 4. risperidone – dose 16 mg/day for 8 weeks, $n = 11$ 5. haloperidol – dose 20 mg/day for 8 weeks, $n = 6$ 6. placebo – $n = 11$ Psychotropic and antiparkinsonian medications were discontinued. Chloral hydrate or benzodiazepine was allowed if a sedative/hypnotic was required, biperiden or procyclidine was given if clinically significant drug-induced parkinsonism or dystonia emerged	
Outcomes	• Adverse events: use of antiparkinsonism medication • Unable to use (data does not have variability measures and only reports differences from baseline to worst scores) • ESRS: dyskinesia symptoms total score, CGI severity dyskinesia, buccolinguomasticatory factor, choreoathetoid factor	
Notes	Sponsorship source: not reported[a]	

TABLE 13 Characteristics and risk of bias of included studies evaluating antipsychotic drugs as treatment for TD (*continued*)

Included study	Description	
Risk of bias		
Bias	***Authors' judgement***	***Support for judgement***
Random sequence generation (selection bias)	Unclear risk	'. . . randomly assigned', details not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias)	Low risk	. . . *identical tablets*
Blinding of outcome assessment (detection bias)	Unclear risk	Blinding of raters not reported
Incomplete outcome data (attrition bias)	Low risk	33% of participants terminated the study early because of an insufficient therapeutic response. All early terminations were included in the intention-to-treat analysis
Selective reporting (reporting bias)	High risk	Outcomes not fully reported
Other bias	High risk	Subgroup with TD
Cookson, 1987[98] *Study characteristics*		
Characteristic	***Description***	
Methods	• Allocation: 'allocated randomly', not described • Blindness: 'double blind', not described • Design: parallel groups • Setting: inpatients, UK • Duration: 44 weeks	
Participants	• Diagnosis: hebephrenic or paranoid schizophrenia (ICD-9[194] and Feighner criteria), $n = 18$ (only three people had TD at baseline) • Age: mean 44.5 years • Sex: 12 male and six female • History: duration of TD not reported; patients resistant to low doses of antipsychotics but improved with higher dosages and maintained this improvement for at least 3 months	
Interventions	No washout period before study entry: 1. antipsychotic reduction – dose 50% previous dose of *cis*(z)-flupentixol decanoate, bi-weekly, $n = 9$ 2. antipsychotic maintenance – dose standard dosage of *cis*(z)-flupentixol decanoate, $n = 9$ Procyclidine allowed during study. Supplementary antipsychotics allowed were haloperidol (oral) or zuclopentixol decanoate (depot). Amitriptyline used for depression	
Outcomes	• Adverse effects: TD (AIMS derived) • Unable to use: adverse effects – GSES (no usable data) • General mental state: BPRS (no usable data)	
Notes	Dr Cookson kindly provided additional information	

continued

TABLE 13 Characteristics and risk of bias of included studies evaluating antipsychotic drugs as treatment for TD (*continued*)

Included study	Description
Risk of bias	
Bias	***Authors' judgement*** / ***Support for judgement***
Random sequence generation (selection bias)	Low risk — '. . . randomised in blocks of 4 and stratified by neuroleptic dose and gender', implies adequate random sequence generation
Allocation concealment (selection bias)	Unclear risk — No allocation concealment details
Blinding of participants and personnel (performance bias)	Unclear risk — '. . . double blind', no further details
Blinding of outcome assessment (detection bias)	Unclear risk — '. . . double blind', no further details
Incomplete outcome data (attrition bias)	Low risk — All patients seem to have completed the study
Selective reporting (reporting bias)	Unclear risk — All outcomes proposed in the methods were reported, but some were not presented adequately. No protocol available to check as well
Other bias	High risk — *The randomised allocation of the small number of patients in the pilot study results in inequalities between the 2 groups at entry and confounded comparisons of group mean values during the study*
***Emsley* et al.*, 2004*[110]**	
Study characteristics	
Characteristic	***Description***
Methods	• Allocation: 'randomly assigned', not described • Blindness: investigators blinded • Design: parallel group • Setting: inpatients and outpatients, South Africa • Duration: 50 weeks
Participants	Diagnosis: schizophrenia (DSM-IV[191]), TD (Schooler and Kane criteria[192]), $n = 45$ Age: 49.2 (SD 14.5) years, range 18–65 years Sex: 16 male and 29 female History: duration of TD not reported; at least 3 months antipsychotic exposure; patients with established psychiatric disorder who do not receive clozapine
Interventions	After an initial screening visit, subjects were tapered from all psychotropic medication over a 2-week period: 1. quetiapine – dose 100 mg/day increased to 400 mg/day, $n = 22$ 2. haloperidol – dose 5 mg/day increased to 10 mg/day, $n = 23$ Concomitant medication allowed were benzodiazepines for agitation or insomnia and anticholinergic agents in the event of treatment emergent or worsening EPS. Medications not allowed were other antipsychotics or other medication known to improve or exacerbate movement disorders
Outcomes	• TD symptoms: no clinical improvement • Leaving the study early • General mental health (PANSS) • Unable to use: adverse effects – ESRS, EPS (no usable data) • Global assessment: CGI (data in graphs, no variability)
Notes	Sponsorship source: supported in part by the Medical Research Council of South Africa, Cape Town and the University of Stellenbosch. Trial medication and monitoring of the study were provided by AstraZeneca, Wilmington, DE, USA

TABLE 13 Characteristics and risk of bias of included studies evaluating antipsychotic drugs as treatment for TD (*continued*)

Included study	Description	
Risk of bias		
Bias	***Authors' judgement***	***Support for judgement***
Random sequence generation (selection bias)	Unclear risk	'Subjects were then randomly assigned', further details not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias)	High risk	'. . . investigator-blinded', further blinding details not reported
Blinding of outcome assessment (detection bias)	Unclear risk	'. . . investigator-blinded', further blinding details not reported
Incomplete outcome data (attrition bias)	High risk	43% dropouts (including the two subjects excluded in the early stages). 10/22 (45%) patients in the quetiapine group and 8/23 (35%) haloperidol patients dropped out
Selective reporting (reporting bias)	High risk	Adverse effects: extrapyramidal symptoms (other than dyskinesia) not fully reported
Other bias	Low risk	The study seems to be free of other sources of bias. Baseline characteristics are balanced in the compared groups
***Kane* et al.*, 1983*[97]**		
Study characteristics		
Characteristic	***Description***	
Methods	• Allocation: randomised using random numbers table • Blindness: double • Design: parallel groups • Setting: outpatients, USA • Duration: 48 weeks	
Participants	• Diagnosis: schizophrenia or schizoaffective disorder (RDC), $n = 8$ • Age: range 17–60 years • Sex: not reported • History: in a state of remission or at a stable clinical plateau	
Interventions	1. Fluphenazine decanoate: low dose 1.25–5 mg/2 weeks, $n = 4$ 2. Fluphenazine decanoate: antipsychotic maintenance – standard dose 12.5–50 mg/2 weeks, $n = 4$ Procyclidine, 5–20 mg/day, was allowed if needed to treat extrapyramidal side effects. No other psychotropic medication except flurazepam or diazepam was allowed (these benzodiazepines were used sparingly for insomnia)	
Outcomes	TD ('no clinical improvement'; 'not any improvement'; 'deterioration'), reported as adverse effects: • incidence of TD (modified versions of SDS) • leaving the study early • general mental state – relapse • unable to use – GAS, BPRS, CGI, SAS	
Notes	Sponsorship source: this investigation was supported in part by grants from the National Institute of Mental Health. Dr Woerner kindly provided unpublished data for one site of the main study and only these are used in this review; the sex ratios are not available. If people in this study developed TD, participation was stopped and they were classified as leaving the study early	

continued

TABLE 13 Characteristics and risk of bias of included studies evaluating antipsychotic drugs as treatment for TD (*continued*)

Included study	Description	
Risk of bias		
Bias	***Authors' judgement***	***Support for judgement***
Random sequence generation (selection bias)	Low risk	Randomised using random numbers table
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias)	Unclear risk	'. . . double-blind'. Details not reported
Blinding of outcome assessment (detection bias)	Unclear risk	'. . . double-blind'. Details not reported
Incomplete outcome data (attrition bias)	High risk	4/8 participants left the study early
Selective reporting (reporting bias)	High risk	Not all data were reported
Other bias	High risk	Only subsample with TD from one site included in this review
***Kazamatsuri* et al., *1973*[96]**		
Study characteristics		
Characteristic	***Description***	
Methods	• Allocation: 'randomly' • Blindness: rater blind • Duration: 24 weeks (4-week antipsychotic and antiparkinsonian drug cessation and placebo administration, 18-week intervention and then 2-week placebo) • Design: parallel • Setting: inpatients, USA	
Participants	• Diagnosis: chronic psychotic patients – chronic schizophrenia ($n = 10$), mentally deficient ($n = 2$), chronic brain syndrome ($n = 1$); all manifesting typical bucco-linguo-masticatory oral dyskinesia associated with long-term antipsychotic medication, $N = 13$ • Sex: five female and eight male • Age: mean 55.8 years, range 41–63 years • History: duration of TD not reported	
Interventions	4-week washout from antiparkinsonian and antipsychotic medication (all replaced by placebo), then: 1. haloperidol – dose 4 mg b.i.d., from week 15 the dose was doubled to 16 mg/day, $n = 7$ 2. tetrabenazine – dose 50 mg b.i.d., from week 15 the dose was doubled to 200 mg/day, $n = 6$ Concomitant medications: *Other medications, such as antidiabetic or anticonvulsant drugs, were continued unchanged*	
Outcomes	• TD symptoms: not clinically improved • TD symptoms: not any improvement • TD symptoms: deterioration • Leaving the study early • Unable to use: TD scale scores and adverse effects – EPS; ward behaviour (NOSIE) (means, SDs not reported)	
Notes	Sponsorship source: Supported in part by Public Health Service grant from the National institute of Mental Health. Tetrabenazine and placebo tablets were provided by Hoffman-La Roche	

TABLE 13 Characteristics and risk of bias of included studies evaluating antipsychotic drugs as treatment for TD (*continued*)

Included study	Description	
Risk of bias		
Bias	***Authors' judgement***	***Support for judgement***
Random sequence generation (selection bias)	Unclear risk	*The 13 patients were divided randomly into two groups* Further details not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias)	High risk	Blinding of participants and personnel not reported
Blinding of outcome assessment (detection bias)	Low risk	*A frequency count of mouth movements (18), done by a psychiatrist blind to the study design was used to assess oral dyskinesia*
Incomplete outcome data (attrition bias)	High risk	Two out of seven (29%) subjects dropped out from the haloperidol group. There were no dropouts from the tetrabenazine group. The dropouts were not entered in the analysis (data reported for all subject up until week 16, inclusive)
Selective reporting (reporting bias)	High risk	TD scale scores and extrapyramidal symptoms scale scores not fully reported
Other bias	Unclear risk	Insufficient information to make a judgement
Tamminga* et al.*, 1994[104] *Study characteristics*		
Characteristic	***Description***	
Methods	• Allocation: randomised • Blindness: double • Design: parallel groups • Setting: not reported, USA • Duration: 12 months	
Participants	• Diagnosis: schizophrenia; diagnosis of TD of a moderate or severe degree, $n = 32$[b] • Age: mean 35.57 (SD 7.60) years • Sex: 20 male and 12 female • History: duration of TD not reported *Before beginning the protocol, each participant was treated with a clinically optimal dose of haloperidol for an initial 1- to 6-month stabilization period*	
Interventions	After the stabilisation period, each patient was withdrawn from antipsychotic treatment for 4 weeks to allow a antipsychotic-free assessment of their dyskinetic symptoms. Then: 1. clozapine plus placebo – mean dose at 293.8 ± 171.9 mg/day for 12 months, $n = 25$ 2. haloperidol plus benztropine – mean dose at 28.5 ± 23.8 mg/day for 12 months, $n = 14$	
Outcomes	• Leaving the study early • Unable to use: TD symptoms (reported means only in graph)	
Notes	Sponsorship source: sponsorship source not reported. Authors were contacted for updated data but at the time of preparing this review no more information had been received	

continued

TABLE 13 Characteristics and risk of bias of included studies evaluating antipsychotic drugs as treatment for TD (*continued*)

Included study	Description	
Risk of bias		
Bias	***Authors' judgement***	***Support for judgement***
Random sequence generation (selection bias)	Unclear risk	*Subjects were then blindly randomised to two different drug groups* Further details not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias)	Unclear risk	*Staff, patients, and all raters were blind to the drug group; one non rating physician and one nurse were non blind to dispense medication and monitor safety* No further details are provided
Blinding of outcome assessment (detection bias)	Low risk	*Staff, patients, and all raters were blind to the drug group; one non rating physician and one nurse were non blind to dispense medication and monitor safety'* No further details are provided
Incomplete outcome data (attrition bias)	High risk	Of 43 enrolled participants, four did not complete the study and seven were withdrawn *One subject from each treatment group was dropped for leukopenia. The other 5 clozapine subjects were dropped for noncompliance (1 patient), decompensation (1 patient), seizure (1 patient), hypotension (1 patient), and ECG [electrocardiogram] changes (1 patient)* Data has been reported for completers only
Selective reporting (reporting bias)	Unclear risk	Unclear if all predefined outcomes have been reported. Efficacy data reported in graphs as means only. A study protocol is needed for firm conclusions
Other bias	Unclear risk	Preliminary results as four subjects had not completed the study

BAS, Barnes Akathisia Scale; b.i.d., twice per day; CATIE, Clinical Antipsychotic Trials for Intervention Effectiveness; CGI, Clinical Global Impression; CGI-S, Clinical Global Impression – Severity scale; DSM-III, *Diagnostic and Statistical Manual of Mental Disorders*-Third Edition; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*-Fourth Edition; EPS, extrapyramidal symptoms; GAS, Global Assessment Scale; GSES, General Side Effects Scale; ICD-9, *International Classification of Diseases*, Ninth Edition; NOSIE, Nurses' Observation Scale for Inpatient Evaluation; q.d., one per day; q.i.d., four times per day; PANSS, Positive and Negative Syndrome Scale; RDC, Research Diagnostic Criteria; SD, standard deviation; SDS, Simpson Dyskinesia Scale; t.i.d., three times per day.

a Author kindly replied to our request for data. At the time of preparing this review no more outcome data were available.

b Forty-nine have been recruited for this study but only 32 completed the blind protocol. The authors report only on these 32 patients.

Anticholinergic drugs

TABLE 14 Characteristics and risk of bias of included studies evaluating anticholinergic drugs as treatment for TD

Included study	Description
***Greil* et al., *1984*[119]** *Study characteristics*	
Characteristic	***Description***
Methods	• Allocation: 'randomly assigned'; no further details provided • Blind: 'double-blind'; no further details provided • Design: parallel group • Setting: not reported if inpatients or outpatients or both, Germany • Duration: 7 weeks
Participants	• Diagnosis: chronic schizophrenics (ICD-9[194]) with TD based on the presence of a 'typical' bucco-linguo-masticatory syndrome and the absence of other adequate explanations for the movement disorder, $n = 10$ • Duration of TD: ≥ 1 year, severity of the symptoms stable for at least 1 month before admission to the study • Sex: seven female and three male • Age: mean 56.6 (SD 9.2) years; range 35–65 years
Interventions	1. Biperiden (same dose as before the trial) stopped after 4 weeks followed by placebo for 3 weeks, $n = 4$ 2. Biperiden (same dose as before the trial) stopped after 1 week followed by placebo for 6 weeks, $n = 6$ All stable on antipsychotics and anticholinergics for at least 5 months before entry and during the trial. Other concomitant medication: not reported
Outcomes	• Leaving the study early • Unable to use (results not reported per randomised group): TD symptoms – AIMS; EP symptoms – SAS Study author was contacted for additional data but no reply was received
Notes	• Sponsorship source: not reported. Knoll AG supplied placebo • Declarations of interest: not reported

Risk of bias

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

EP, extrapyramidal; ICD-9, *International Classification of Diseases*, Ninth Edition.

Benzodiazepines

TABLE 15 Characteristics and risk of bias of included studies evaluating benzodiazepines as treatment for TD

Included study	Description
***Bobruff* et al., *1981*[120]**	
Study characteristics	
Characteristic	***Description***
Methods	• Allocation: 'randomly assigned' • Blindness: 'double blind' • Design: parallel group • Duration: not reported (optimal dose + 2 weeks + taper off) • Setting: not reported, USA
Participants	Diagnosis: psychiatric patients (details not reported). Obvious TD (at least three scores of mild or one score of moderate on AIMS), $n = 21$ Duration of TD: not reported Age: mean 51.6 years; range 36–63 years Sex: 16 male and five female
Interventions	1. Clonazepam: dose 3.9 ± 2.6 mg daily; optimal dose + 2 weeks + taper, $n = 10$ 2. Phenobarbital (as active placebo): 88.6 ± 45.7 mg daily; optimal dose + 2 weeks + taper, $n = 11$ There were five patients who were taking no antipsychotics and one patient who was taking homeopathic doses; doses were stable throughout the study period. Concomitant medication: not reported
Outcomes	• TD symptoms: no improvement (AIMS) • TD symptoms: not improved more than 50% (AIMS) • Adverse effects • Leaving the study early • Unable to use: Mental State – Profile of Mood States
Notes	Sponsorship source: supported in part by NIMH grant. Declarations of interest: not reported

Risk of bias

Bias	***Authors' judgement***	***Support for judgement***
Random sequence generation (selection bias)	Unclear risk	'Patients were randomly assigned'; further details not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias)	Unclear risk	'. . . double-blind'. Details not reported
Blinding of outcome assessment (detection bias)	Unclear risk	'. . . double-blind'. Details not reported
Incomplete outcome data (attrition bias)	Low risk	Although not clearly reported, it seems that all subjects completed the double-blind phase (data reported for all 21 subjects)
Selective reporting (reporting bias)	Unclear risk	All outcomes seem to have been reported but not as mean (SD). Also, as protocol is not available, it is not possible to verify that all predefined outcomes were reported
Other bias	Unclear risk	Insufficient information to make a judgement

TABLE 15 Characteristics and risk of bias of included studies evaluating benzodiazepines as treatment for TD (*continued*)

Included study	Description
***Csernansky* et al., *1988*[121,122]**	
Study characteristics	
Characteristic	***Description***
Methods	• Allocation: 'randomly assigned'; no details reported • Blindness: 'double blind', described • Design: parallel group • Duration: 5–6 weeks • Setting: outpatients (most) and inpatients from Veterans Administration Medical Center, USA
Participants	• Diagnosis: schizophrenia (RDC criteria), $n = 17$ • Duration of TD: not reported • Age: not reported • Sex: not reported
Interventions	1. Alprozalam: dose 7.2 ± 1.8 mg daily for 5–6 weeks, $n = 5$ 2. Diazepam: dose 48.3 ± 17.4 mg daily for 5–6 weeks, $n = 5$ 3. Placebo for 5–6 weeks, $n = 6$ Participants were stable for at least 2 weeks prior to study and doses were unchanged during the study. Concomitant medication: 55 patients in the study were also taking anticholinergic medications
Outcomes	• TD symptoms: not improved by 50%; not any improvement; deterioration • Leaving the study early • Unusable data: mental state – BPRS, SANS (data not reported for TD subgroup); adverse effects (data not reported for TD subgroup)
Notes	Sponsorship source: supported by a Public Health Service grant and a grant from the National Institute of Mental Health, a VA Career Development Award to the first author, a grant from the Upjohn Company and the Research Service of the VA. Participants were extracted post hoc from a larger study examining benzodiazepines for the treatment of the negative symptoms of schizophrenia. Data on age, sex, baseline medication doses, side effects and dropout rate for the initial cohort are provided in the parent study
Risk of bias	

Bias	***Authors' judgement***	***Support for judgement***
Random sequence generation (selection bias)	Unclear risk	*Patients were randomly assigned to the treatment with either Alprozalam, Diadepam, or placebo . . .* Further details not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias)	Low risk	*Patients were randomly assigned to the treatment with either alprozalam, diadepam, or placebo under double-blind conditions. Identical capsules contained either 1 mg of alprozalam, 10 mg of diazepam, or the drug carrier as placebo*
Blinding of outcome assessment (detection bias)	Low risk	*Two independent raters*
Incomplete outcome data (attrition bias)	Unclear risk	*Fifty-five RDC schizophrenic outpatients were rated using the Gerlach Dyskinesia Scale (GDS) before, and at weekly intervals during, treatment . . . 17 patients were identified with rateable TD symptoms at baseline . . .*

continued

TABLE 15 Characteristics and risk of bias of included studies evaluating benzodiazepines as treatment for TD (*continued*)

Included study	Description	
		All 17 subjects were entered to analysis. However, as 72 subjects were enrolled in the original study, it is unclear if relevant data for any of the 17 out of 72 subjects that dropped out are missing
Selective reporting (reporting bias)	Unclear risk	All outcomes for the main study seem to have been reported. A protocol is not available for verification. Although mental state and adverse effects have not reported separately for subjects with TD symptoms, TD was not an inclusion criterion and thus does not seem to affect bias
		Since TD was not a criterion for inclusion into or exclusion from the trial, it was only by chance that we identified 17 patients with TD symptoms
Other bias	High risk	Participants with TD at baseline were extracted post hoc from a larger study examining benzodiazepines for the treatment of the negative symptoms of schizophrenia
***Weber* et al., *1983*[89]** *Study characteristics*		
Characteristic	***Description***	
Methods	• Allocation: randomised • Blindness: single • Design: crossover • Duration: 24 weeks (10 weeks followed by 4 weeks washout, then crossed over to another 10 weeks) • Setting: inpatients in a long-term state psychiatric hospital, USA	
Participants	• Diagnosis: schizophrenia ($n = 12$), organic brain syndrome ($n = 1$), unknown ($n = 2$). Baseline AIMS rating or two or more on one item, and drug-induced parkinsonian movements of six or less, $N = 15$ • Duration of TD: TD history of 2–6 years • Age: mean 57.4 years, 50–65 years (among completers) • Sex: 10 male and three female (among completers)	
Interventions	1. Standard care plus diazepam: dose 6–25 mg/day, mean 12 mg/day, $n = 8$ (completers) 2. Standard care, $n = 5$ (completers) Participants were on stable doses of both antipsychotic and anticholinergic medication for 2 weeks prior to study, and on stable doses throughout the study except two participants: medication was altered for two participants in the second period of crossover. During the study, 10 patients received antipsychotic drugs, whereas eight received anticholinergic agents, and one received amantadine	
Outcomes	• TD: AIMS • Leaving the study early • Mental state: BPRS	
Notes	Sponsorship source: not reported	
Risk of bias		
Bias	***Authors' judgement***	***Support for judgement***
Random sequence generation (selection bias)	Unclear risk	'Each patient was assigned randomly . . .'; further details not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported

TABLE 15 Characteristics and risk of bias of included studies evaluating benzodiazepines as treatment for TD (*continued*)

Included study	Description	
Blinding of participants and personnel (performance bias)	High risk	As one of the groups received an intervention and the second standard care, blinding of participants and personnel could not have been possible
Blinding of outcome assessment (detection bias)	Low risk	*. . . rater-blind . . . The rating scales were administered by trained observers who did not know which patients received diazepam*
Incomplete outcome data (attrition bias)	Low risk	13% dropout rate *Fifteen patients began the study. Two failed to complete the entire protocol (one because she continued to receive diazepam throughout the study and the other because she was discharged from the hospital)*
Selective reporting (reporting bias)	Unclear risk	The outcomes seem to have been reported. However, a protocol is not available for verification
Other bias	Unclear risk	Change in medication for two participants may have had a confounding effect; however, both substitutions occurred 4 weeks into the second phase of the study
Xiang and Zhen, 1997[75] *Study characteristics*		
Characteristic	***Description***	
Methods	• Allocation: 'randomized controlled trial' • Blinding: 'double blind'; 'The two drugs were contained in capsules with same appearance' • Duration: 8 weeks • Location: 'inpatients', China • Length of follow-up: 8 weeks	
Participants	• Diagnosis: schizophrenia (CCMD-2-R[195]) and antipsychotic-induced TD, $n = 24$ • Duration of TD: mean 2.7 (SD 1.21) years • Age: mean 39.44 (SD 8.43) years • Sex: 15 male and nine female	
Interventions	1. Standard care plus clonazepam: dose 4–6 mg/day, mean 5 mg/day, $n = 12$ 2. Standard care plus placebo, $n = 12$ All cases continued the use of antipsychotics and anticholinergic drugs	
Outcomes	• TD: AIMS • Leaving the study early	
Notes	Sponsorship source: sponsorship source not reported. Participants with stable or aggravating symptoms of TD after suspending antipsychotics for 2 weeks were excluded	
Risk of bias		
Bias	***Authors' judgement***	***Support for judgement***
Random sequence generation (selection bias)	Unclear risk	'. . . randomised controlled trial'. The author did not state the method of randomisation
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias)	Low risk	*. . . double blind . . . The two drugs were contained in capsules with same appearance* Blinding of participants and key study personnel ensured
Blinding of outcome assessment (detection bias)	Unclear risk	Blinding of outcome assessment not reported

continued

TABLE 15 Characteristics and risk of bias of included studies evaluating benzodiazepines as treatment for TD (*continued*)

Included study	Description	
Incomplete outcome data (attrition bias)	Low risk	All participants competed the study
Selective reporting (reporting bias)	Low risk	The author reported all measured outcomes
Other bias	Low risk	Free from other bias

CCMD-2-R, *Chinese Classification of Mental Disorders*, Second Edition, Revised; NIMH, National Institute of Mental Health; RDC, Research Diagnostic Criteria; SANS, Scale for Assessment of Negative Symptoms; SD, standard deviation; VA, Veteran's Administration.

Vitamin E

TABLE 16 Characteristics and risk of bias of included studies evaluating vitamin E as treatment for TD

Included study	Description	
***Adler* et al., *1993*[125,126]**		
Study characteristics		
Characteristic	***Description***	
Methods	• Allocation: 'random allocation', ratio of three vitamin E to two placebo • Blinding: double blind – no further details • Duration: 36 weeks (preceded by 2-week washout) • Setting: inpatients and outpatients of the Department of Veterans Affairs Medical Center, USA • Design: parallel group	
Participants	• Diagnosis: schizophrenia, depression (no criteria) and antipsychotic-induced TD (RDC, Schooler and Kane[192]). $n = 40$[a] • Sex: two female and 27 male[a] • Age: average vitamin E, 58.0 (SD 9.5) years; placebo, 61.0 (SD 9.2) years[a]	
Interventions	1. Vitamin E: dose increasing over 3 weeks to 1600 IU/day, $n = 24$[b] 2. Placebo, $n = 16$[b] Stable antipsychotic medication: dose average (CPZE) vitamin E 536 mg/day (SD 642 mg/day); placebo 921 mg/day (SD 1026 mg/day). Compliance assessed by pill counts	
Outcomes	• TD symptoms: AIMS • Leaving the study early	
Notes	• Source of funding: supported in part by the Department of Veterans Affairs • Declarations of interest: not reported	
Risk of bias		
Bias	***Authors' judgement***	***Support for judgement***
Random sequence generation (selection bias)	Unclear risk	*Patients were randomly assigned to treatment with Vitamin E, 400 IU, or one matching placebo capsule, by mouth, b.i.d.* No further details provided
Allocation concealment (selection bias)	Unclear risk	*We used a randomisation of 3 : 2 (vitamin E to placebo) to maximise the number of patients receiving active treatment while maintaining the blind* No further details provided

TABLE 16 Characteristics and risk of bias of included studies evaluating vitamin E as treatment for TD (*continued*)

Included study	Description	
Blinding of participants and personnel (performance bias)	Unclear risk	*Both rater and patient were blind to the patient's drug assignment* No further details provided
Blinding of outcome assessment (detection bias)	Unclear risk	*Both rater and patient were blind to the patient's drug assignment'* No further details provided
Incomplete outcome data (attrition bias)	Low risk	*One patient dropped out after 2 weeks due to non-compliance . . . Two patients developed significant medical illnesses . . . unrelated to study treatment . . . By prior design, treatment for the first 8 patients was terminated after 8 weeks*
Selective reporting (reporting bias)	Unclear risk	All expected outcomes have been reported but there is no study protocol to confirm that all planned outcomes were reported
Other bias	Unclear risk	Baseline AIMS scores were somewhat higher in the vitamin E group than in the placebo group; however, this difference was not statistically significant. Small sample size
***Adler* et al., *1999*[137]** *Study characteristics*		
Characteristic	***Description***	
Methods	• Allocation: randomisation co-ordinated centrally, allocation with 'biased coin' method, stratified by site, age and baseline TD • Double blind: no further details • Duration: 1 year • Setting: outpatients and inpatients, Department of Veterans Affairs Medical Center, USA • Design: parallel	
Participants	• Diagnosis: schizophrenia, schizoaffective (DSM-IV[191]), and antipsychotic-induced TD (RDC), $n = 158$ • Sex: five female and 153 male • Age: average 50 years (SD 10 years)	
Interventions	1. Vitamin E: 1600 IU/day, $n = 73$ 2. Placebo, $n = 85$ Antipsychotic medication: not stable dose, average (CPZE) vitamin E 380 mg/day (SD 110 mg/day); placebo 458 mg/day (SD 433 mg/day) Compliance assessed by pill counts	
Outcomes	• TD symptoms: AIMS • Mental state: BPRS • Leaving the study early • Adverse effects: extrapyramidal symptoms (Modified SAS); Akathisia (Barnes Akathisia Scale)	
Notes	Source of funding: Cooperative Studies Program of the Department of Veterans Affairs, Veterans Affairs Headquarters, Washington, DC, USA. Declarations of interest: not reported	
Risk of bias		
Bias	***Authors' judgement***	***Support for judgement***
Random sequence generation (selection bias)	Low risk	Randomisation co-ordinated centrally
Allocation concealment (selection bias)	Low risk	Allocation with 'biased coin' method, stratified by site, age and baseline TD

continued

TABLE 16 Characteristics and risk of bias of included studies evaluating vitamin E as treatment for TD (*continued*)

Included study	Description	
Blinding of participants and personnel (performance bias)	Unclear risk	Double blind: no further details
Blinding of outcome assessment (detection bias)	Unclear risk	Double blind: no further details
Incomplete outcome data (attrition bias)	Low risk	*Of the 51 subjects who did not complete 1 year, most changed their minds about participating (n = 18), moved too far away from a site to continue in the study (n = 11), or were classified as 'whereabouts unknown' (n = 8) . . . Per protocol, we analysed the data according to the intention-to-treat principle*
Selective reporting (reporting bias)	Unclear risk	All expected outcomes have been reported but there is no study protocol to confirm that all planned outcomes were reported
Other bias	Unclear risk	No significant differences between groups' baseline characteristics. Small sample size
***Akhtar* et al.*, 1993*[127]**		
Study characteristics		
Characteristic	***Description***	
Methods	• Allocation: 'random allocation', no further details • Double blind: no further details • Duration: 4 weeks (preceded by 2 weeks washout) • Setting: inpatients in a psychiatric hospital, India • Design: parallel group	
Participants	Diagnosis: psychiatric disorder (Spitzer criteria) and antipsychotic-induced TD (Schooler and Kane criteria[192]), $n = 32$ Sex: 14 female and 18 male Age: vitamin E, mean 53.06 years (SD 13.39 years); placebo, mean 56.87 years (SD 11.13 years)	
Interventions	• Vitamin E: initial dose 600 mg once daily, doubled in the second week to 600 mg b.i.d. (1200 mg/d), $n = 17$ • Placebo, $n = 15$ Stable antipsychotic medication: dose average (CPZE) 323 mg/day (SD 249 mg/day); placebo 187 mg/day (SD 189 mg/day)	
Outcomes	• TD symptoms: TDRS • Mental state: BPRS • Adverse effects • Leaving the study early	
Notes	Authors contacted but did not reply. Source of funding: not reported. Declarations of interest: not reported	
Risk of bias		
Bias	***Authors' judgement***	***Support for judgement***
Random sequence generation (selection bias)	Unclear risk	*The patients were then randomly assigned* Details not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias)	Low risk	*. . . double blind manner to receive either one capsule of 600 mg vitamin E or an identical placebo*

TABLE 16 Characteristics and risk of bias of included studies evaluating vitamin E as treatment for TD (*continued*)

Included study	Description	
Blinding of outcome assessment (detection bias)	Low risk	*Both, the investigators and raters were blind to the nature of therapy . . . active drug or placebo till the completion of analysis*
Incomplete outcome data (attrition bias)	Low risk	The study results seem to include all participants and there seem to be no dropouts from the study
Selective reporting (reporting bias)	Unclear risk	All expected outcomes have been reported but there is no study protocol to confirm that all planned outcomes were reported
Other bias	Unclear risk	There was no significant difference in the demographic profile of the two groups. Small sample size
***Dabiri* et al., *1994*[128]**		
Study characteristics		
Characteristic	***Description***	
Methods	• Allocation: 'random allocation', no further details • Double blind: yes • Duration: 12 weeks • Setting: outpatients, from San Mateo Country Mental Health Services, USA • Design: parallel group	
Participants	• Diagnosis: psychiatric disorder (no criteria) and antipsychotic-induced TD (Research diagnosis, Schooler and Kane criteria[192]), $n = 12$ • Sex: five female, six male and one not specified • Age: average 51 years; range 35–68 years	
Interventions	1. Vitamin E: 400 IU/day for the first week, 800 IU/day for the second week and 1200 IU/day during the remaining 10 weeks, $n = 7$ 2. Placebo, $n = 5$ Stable antipsychotic medication: dose average (CPZE) 444 mg/day; range 200–1000 mg/day	
Outcomes	• TD symptoms: AIMS • Leaving study early • Adverse effects: any	
Notes	Authors contacted but did not reply. Source of funding: not reported. Declarations of interest: not reported	
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)	Low risk	*. . . patients were randomly divided into treatment and placebo groups by a non-clinical staff member*
Blinding of participants and personnel (performance bias)	Unclear risk	'. . . double-blind study', details not reported
Blinding of outcome assessment (detection bias)	Unclear risk	*Each patient was rated blindly by one of us (L.M.D.) before and after treatment using the Abnormal Involuntary Movement Scale (AIMS)* Blinding details not reported
Incomplete outcome data (attrition bias)	Low risk	*One patient who was taking vitamin E stopped treatment after 2 weeks because of diarrhoea, leaving five patients taking placebo and six vitamin E*
Selective reporting (reporting bias)	Unclear risk	All expected outcomes have been reported, but there is no study protocol to confirm that all planned outcomes were reported

continued

TABLE 16 Characteristics and risk of bias of included studies evaluating vitamin E as treatment for TD (*continued*)

Included study	Description	
Other bias	Unclear risk	No statistically significant differences in AIMS baseline scores between groups. Very small sample size
***Dorevitch* et al., *1997*[91]** *Study characteristics*		
Characteristic	***Description***	
Methods	• Allocation: 'randomised', no further details • Double blind: yes • Duration: 20 weeks (4-week washout) • Setting: specific setting not reported, Israel • Design: crossover	
Participants	• Diagnosis: DSM-III-R[193] diagnosis of schizophrenia. All 10 candidates had TD for a minimum of 5 years and had been exposed to antipsychotic drugs for > 10 years, $n = 10$ • Sex: two female and eight male • Age: average 63.1 years, range 56–70 years	
Interventions	1. Vitamin E: dose increasing over 4 weeks to 1600 IU/day, $n = 5$ 2. Placebo, $n = 5$ At the start of the study, the patients were receiving an average dose of 652 mg/day chlorpromazine equivalents, with a range of 75 to 4000 mg/day	
Outcomes	• Leaving study early • Adverse effects: parkinsonism, akathisia • Unable to use: adverse effects – AIMS (data not reported)	
Notes	Source of funding: not reported. Teva Pharmaceuticals supplied the vitamin E and placebo for this study. Declarations of interest: not reported	
Risk of bias		
Bias	***Authors' judgement***	***Support for judgement***
Random sequence generation (selection bias)	Unclear risk	'. . . randomised'. Details not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias)	Unclear risk	'. . . double-blind'. Blinding details not reported
Blinding of outcome assessment (detection bias)	Unclear risk	'. . . double-blind'. Blinding details not reported
Incomplete outcome data (attrition bias)	Low risk	The study results seem to include all participants and there seem to be no dropouts from the study
Selective reporting (reporting bias)	High risk	TD symptoms (AIMS) were assessed but not reported
Other bias	Unclear risk	Baseline characteristics not reported. Very small sample size
***Dorevitch* et al., *1997*[90]** *Study characteristics*		
Characteristic	***Description***	
Methods	• Allocation: 'randomised', no further details • Double blind: yes • Duration: 20 weeks • Setting: inpatients, Israel • Design: crossover	

TABLE 16 Characteristics and risk of bias of included studies evaluating vitamin E as treatment for TD (*continued*)

Included study	Description		
Participants	• Diagnosis: DSM-III-R[193] diagnosis of schizophrenia or schizoaffective disorder, research diagnostic criteria for TD (Schooler and Kane criteria[192]), $n = 40$ • Sex: 17 female and 23 male • Age: average 64.4 years (SD 8.5 years); range 32–80 years		
Interventions	1. Vitamin E: 400 IU/day during the first week, titrated to 800 IU/day for the second week, 1200 IU/day for the third week and 1600 IU/day from week 4 until the end of week 8, $n = 18$ 2. Placebo, $n = 22$ Stable antipsychotic medication: dose average (CPZE) 594 mg/day, range 75–5000 mg/day		
Outcomes	• TD symptoms: AIMS • Leaving study early • Adverse effects • Unable to use: mental state – BPRS (data not reported)		
Notes	Source of funding: not reported. Teva Pharmaceuticals supplied the vitamin E and placebo for this study. Declarations of interest: not reported		
Risk of bias			
Bias	***Authors' judgement***	***Support for judgement***	
Random sequence generation (selection bias)	Unclear risk	'Randomised' – no further details	
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported	
Blinding of participants and personnel (performance bias)	Unclear risk	'. . . double-blind'; blinding details were not reported	
Blinding of outcome assessment (detection bias)	Low risk	*Two senior psychiatrists served as blinded raters*	
Incomplete outcome data (attrition bias)	Unclear risk	*Two patients did not complete the study. Both patients were from the placebo phase of the placebo-vitamin E sequence group. One died while choking on food and the second as the result of a traffic accident*	
Selective reporting (reporting bias)	High risk	*Addition of vitamin E or placebo did not adversely affect patient mental status as measured by brief psychiatric rating scale (BPRS)* BPRS data not fully reported	
Other bias	Unclear risk	Baseline characteristics not reported. Small sample size	
***Egan* et al., *1992*[92]** *Study characteristics*			
Characteristic	***Description***		
Methods	• Allocation: 'random allocation', no further details • Double blind: no further details • Duration: 12 weeks (6 weeks then crossed over to another 6 weeks, no washout) • Setting: inpatients and outpatients, USA • Design: crossover		
Participants	• Diagnosis: schizophrenia, schizoaffective, bipolar disorder, depression (DSM-III-R[193]) and antipsychotic-induced TD (Schooler and Kane criteria[192]), $n = 21$ • Sex: eight female and 13 male • Age: average 43.9 years (SD 2.8 years)		

continued

TABLE 16 Characteristics and risk of bias of included studies evaluating vitamin E as treatment for TD (*continued*)

Included study	Description
Interventions	1. Vitamin E: 400 IU/day for week 1, 800 IU/day for week 2, 1200 IU/day for week 3 and 1600 IU/day for weeks 4–6, $n = 10$ 2. Placebo, $n = 11$ Stable antipsychotic medication: dose average (CPZE) 1946 mg/day (no SD, $n = 15$)
Outcomes	• TD symptoms: AIMS • Side effects • Leaving study early • Unable to use: mental symptoms – PSAS, NSRS (means and SDs not reported)
Notes	Three patients were not included in the data analysis: one dropped out and two had inconsistent vitamin E blood levels. Source of funding: not reported. Declarations of interest: not reported
Risk of bias	

Bias	***Authors' judgement***	***Support for judgement***
Random sequence generation (selection bias)	Unclear risk	*Patients were assigned randomly* Details not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias)	Unclear risk	'. . . double-blind.' Details not reported
Blinding of outcome assessment (detection bias)	Low risk	*All raters were blind to treatment with either placebo or vitamin E*
Incomplete outcome data (attrition bias)	High risk	Not ITT analysis: *Eighteen patients who demonstrated high blood levels of vitamin E were included in the data analysis* Three patients were excluded from the analysis
Selective reporting (reporting bias)	High risk	Data for mental state (PSAS and NSAS) not reported
Other bias	Unclear risk	Baseline characteristics not reported. Very small sample size

Elkashef* et al.*, 1990[93]

Study characteristics

Characteristic	***Description***
Methods	• Allocation: 'random allocation', no further details • Double blind: no further details • Duration: 10 weeks (4 weeks then crossed over to another 4 weeks; randomisation was preceded by 2 weeks' washout) • Setting: outpatients, USA • Design: crossover
Participants	• Diagnosis: schizophrenia or schizoaffective disorder (DSM-III-R[193]) and antipsychotic-induced TD (Schooler and Kane criteria[192]), $n = 10$ • Sex: one female and seven males (among completers) • Age: average 56.6 years (SD 12 years) (among completers) • History: no description of chronicity of TD
Interventions	1. Vitamin E: 400 IU/day for the first week, 400 IU b.i.d. (800 IU/day) for the second week and 400 IU t.i.d. (1200 IU/day) for the final 2 weeks, $n = 5$ 2. Placebo, $n = 5$ Stable antipsychotic medication: dose not specified

TABLE 16 Characteristics and risk of bias of included studies evaluating vitamin E as treatment for TD (*continued*)

Included study	Description	
Outcomes	• TD symptoms: AIMS • Adverse effects • Leaving study early • Unable to use: mental state – BPRS	
Notes	Source of funding: not reported. Hollman-La Roche Inc., supplied the drug and placebo for this study. Declarations of interest: not reported	
Risk of bias		
Bias	***Authors' judgement***	***Support for judgement***
Random sequence generation (selection bias)	Unclear risk	*The subjects were then assigned in a random, double-blind manner . . .* No further details
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias)	Unclear risk	Double blind: no further details
Blinding of outcome assessment (detection bias)	Unclear risk	*The subjects were evaluated biweekly by a blind trained rater using the AIMS and the Brief Psychiatric Rating Scale (BPRS)* Details of blinding not reported
Incomplete outcome data (attrition bias)	High risk	2/5 participants in the placebo group dropped out, whereas none in the vitamin E group dropped out: *Two patients did not complete the study, one because of noncompliance and the other experienced substantial side effects (nausea) while taking placebo*
Selective reporting (reporting bias)	High risk	AIMS data partially reported and BPRS evaluated but not reported
Other bias	Unclear risk	The baseline severity of TD was closely matched in the two groups. Very small sample size
***Lam* et al.*, 1994*[94]** *Study characteristics*		
Characteristic	***Description***	
Methods	• Allocation: 'random allocation', no further details • Double blind: no further details • Duration: 16 weeks – 2-week placebo lead-in phase, 6 weeks' treatment, 2-week placebo washout phase, crossed over to 6 weeks of another treatment. Intervention followed by 2 weeks' washout, then crossed over to another 6 weeks • Setting: inpatients, Hong Kong • Design: crossover	
Participants	Diagnosis: schizophrenia (DSM-III-R[193]) and antipsychotic-induced TD (Schooler and Kane criteria[192]), $n = 16$ Sex: seven female and five male[c] Age: average 61.8 years (SD 12.8 years)[c] History: no history of chronicity of TD	

continued

TABLE 16 Characteristics and risk of bias of included studies evaluating vitamin E as treatment for TD (*continued*)

Included study	Description	
Interventions	1. Vitamin E: 400 IU/day for the first week, 400 IU b.i.d in the second week, 400 IU t.i.d. for weeks 3–6, $n = 5$[c] 2. Placebo, $n = 7$[c] Stable antipsychotic medication. For those taking antipsychotic medication, the average daily dose was 365 mg CPZE	
Outcomes	TD symptoms: AIMS Leaving study early (assuming equal randomisation into the two groups) Unable to use: mental state – BPRS (no mean or SD reported), adverse effects	
Notes	Four people left study early (no information about allocation), the reasons being death, deterioration of symptoms of schizophrenia, bacillary dysentery (all stated not to be related to treatment) and poor compliance. Authors contacted and replied, no more information available. Source of funding: not reported. Declarations of interest: not reported	
Risk of bias		
Bias	***Authors' judgement***	***Support for judgement***
Random sequence generation (selection bias)	Unclear risk	*Subjects were then selected randomly* No further details
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias)	Unclear risk	'. . . double-blind'. Details not reported
Blinding of outcome assessment (detection bias)	Low risk	*Subjects were evaluated weekly with the AIMS . . . and Brief Psychiatric Rating Scale . . ., respectively, by two independent blind raters at the initial stabilisation period, and the last 2 weeks of each test period*
Incomplete outcome data (attrition bias)	High risk	Twelve subjects completed the trial. One patient died of unrelated medical illness, one contracted bacillary dysentery and was dropped from the trial, and one had poor compliance and refused to continue medication. It was not reported which groups these participants were allocated to
Selective reporting (reporting bias)	High risk	TD symptoms data not reported as mean (SD); BPRS data not reported per period. Adverse effects not reported per group
Other bias	Unclear risk	Baseline characteristics not reported. Very small sample size
***Lohr* et al.*, 1996*[129]** *Study characteristics*		
Characteristic	***Description***	
Methods	• Allocation: 'random assigned', no further details provided • Double blind: participants and personnel blinded • Duration: 8 weeks • Setting: outpatients, USA • Design: parallel	
Participants	• Diagnosis: schizophrenia, bipolar disorder, unipolar depression (no specified criteria) and antipsychotic-induced TD (Schooler and Kane criteria[192]); $n = 55$ • Sex: two female, 33 male and 20 not informed • Age: average 48.9 years (SD 13.6 years)	

TABLE 16 Characteristics and risk of bias of included studies evaluating vitamin E as treatment for TD (*continued*)

Included study	Description	
Interventions	1. Vitamin E: 1600 IU/day, $n = 17$ (completers)[d] 2. Placebo, $n = 18$ (completers)[d] Stable psychotropic medication for at least 1 month prior to entry into study. Antipsychotic dose average (CPZE) vitamin E 706 mg/day (SD 680 mg/day); placebo 376 mg/day (SD 242 mg/day)	
Outcomes	• TD symptoms: mAIMS • Mental state: BPRS (reported for subgroup with schizophrenia, $n = 29$) • Leaving the study early	
Notes	Source of funding: Partial funding by a VA Merit Review grant and United States Public Health Service grants. Vitamin E and placebo supplied by Hoffmann-La Roche Inc. Declarations of interest: not reported	
Risk of bias		
Bias	***Authors' judgement***	***Support for judgement***
Random sequence generation (selection bias)	Unclear risk	*Patients were randomly assigned to receive either active vitamin E or sesame oil placebo gel caps*
Allocation concealment (selection bias)	Unclear risk	Allocation concealment details not reported
Blinding of participants and personnel (performance bias)	Low risk	*Patients were randomly assigned to receive either active vitamin E or sesame oil placebo gel caps, which were indistinguishable from the active gel caps*
Blinding of outcome assessment (detection bias)	Unclear risk	Insufficient information to make a judgement
Incomplete outcome data (attrition bias)	High risk	Dropout rate of 36% (20/55 patients) but not reported per study group: *2 developed manic symptoms necessitating medical changes, and 18 were non-compliant with either the vitamin E or the psychotropic medication. These 20 patients, who did not differ significantly from the remaining 35 patients in terms of age, gender, or diagnosis, were dropped from the study*
Selective reporting (reporting bias)	High risk	Adverse effects: extrapyramidal side effects (parkinsonism) – data not reported
Other bias	Unclear risk	There were no significant differences in baseline characteristics between the two study groups. Small sample size
Sajjad, 1998[130] *Study characteristics*		
Characteristic	***Description***	
Methods	• Allocation: 'random allocation' • Double blind: probably not, there was no placebo administered to the control group • Duration: 7 months • Setting: inpatients, UK • Design: parallel	
Participants	• Diagnosis: antipsychotic-induced TD (Schooler and Kane criteria[192]), $n = 20$ • Sex: seven female and 13 male • Age: average 68 years (SD 8.7 years)	

continued

TABLE 16 Characteristics and risk of bias of included studies evaluating vitamin E as treatment for TD (*continued*)

Included study	Description	
Interventions	1. Vitamin E: first week 400 mg/day, increased to 600 mg/day in the second week, 800 mg/day in the fourth month, 1200 mg/day in the fifth month and 1600 mg/day in the sixth month, $n = 11$ 2. Placebo, $n = 9$ Stable antipsychotic medication throughout the trial	
Outcomes	• TD symptoms: AIMS • Adverse effects • Leaving the study early	
Notes	Source of funding: not reported. Declarations of interest: not reported	
Risk of bias		
Bias	***Authors' judgement***	***Support for judgement***
Random sequence generation (selection bias)	Low risk	*. . . the patients were randomly divided into two groups using . . . a computer statistic programme*
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias)	High risk	As an active group was compared with TAU, the study could not be double blinded. The only person blinded seems to have been the doctor *. . . the dose increased by another doctor not involved in the ratings and who, therefore, was blind as to whether or not the patient was receiving a-tocopherol for the first month of the trial*
Blinding of outcome assessment (detection bias)	High risk	Rater initially blind. However, after 1 month, the rater performed statistical tests and, hence, blindness was not maintained
Incomplete outcome data (attrition bias)	High risk	40% dropout rate (12/20 participants completed the study): 6 out of 11 subjects in the intervention and 2 out of 9 subjects in the control group did not complete the trial. By the fourth month there were 12 patients left in the trial: five in the treatment group and seven in the control group. Patients excluded at this stage included those whose dose of antipsychotic medication was changed
Selective reporting (reporting bias)	Unclear risk	All expected outcomes have been reported but there is no study protocol to confirm that all planned outcomes were reported
Other bias	Unclear risk	Mean AIMS scores and age were similar between groups at baseline. Very small sample size
***Schmidt* et al.*, 1991*[95]** *Study characteristics*		
Characteristic	***Description***	
Methods	• Allocation: 'randomised pattern', no further details • Double blind: no further details • Duration: 4 weeks (2 weeks then crossed over to another 2 weeks, no washout period) • Setting: inpatients, Switzerland • Design: crossover	
Participants	Diagnosis: schizophrenia, depression, schizoaffective psychoses (no criteria) and antipsychotic-induced TD (no criteria), $n = 23$ Sex: 12 female and 11 male Age: average 45 years, range 21–88 years	

TABLE 16 Characteristics and risk of bias of included studies evaluating vitamin E as treatment for TD (*continued*)

Included study	Description
Interventions	1. Vitamin E: dose 1200 IU/day, $n = 13$ 2. Placebo, $n = 10$ Stable antipsychotic medication: dose unspecified
Outcomes	• TD symptoms: AIMS • Adverse effects • Leaving study early
Notes	It was observed that two of the patients who benefited from the vitamin E therapy continued taking it: after stopping vitamin E medication, one of them experienced an increase in TD, whereas in the other the beneficial effect was still observed even 3 months later. Source of funding: not reported. Declarations of interest: not reported
Risk of bias	
Bias	***Authors' judgement*** / ***Support for judgement***
Random sequence generation (selection bias)	Unclear risk / '. . . randomised pattern', no further details
Allocation concealment (selection bias)	Unclear risk / Allocation concealment not reported
Blinding of participants and personnel (performance bias)	Unclear risk / '. . . double-blind'. Details not reported
Blinding of outcome assessment (detection bias)	Unclear risk / Details not reported
Incomplete outcome data (attrition bias)	Low risk / Of the 13 patients initially randomised to vitamin E, two left before the end of the study (one died and the other withdrew). Of the 10 patients initially randomised to placebo, two left before the end of the study (one died and the other had his treatment modified)
Selective reporting (reporting bias)	Unclear risk / All expected outcomes have been reported but there is no study protocol to confirm that all planned outcomes were reported
Other bias	Unclear risk / Baseline characteristics similar between study groups. Very small sample size, crossover design
***Zhang* et al., *2004*[138]**	
Study characteristics	
Characteristic	***Description***
Methods	• Allocation: randomly assigned • Double blind: yes • Duration: 12 weeks • Setting: inpatients, China • Design: parallel
Participants	• Diagnosis: DSM-III-R[193] criteria for schizophrenia, using the Structured Clinical Interview for DSM-III-R; TD diagnosed by Schooler and Kane criteria,[192] $n = 41$ • Sex: 18 female and 23 male • Age: average vitamin E, 54.5 years (SD 10.1 years); placebo 53.3 years (SD 9.7 years)
Interventions	1. Vitamin E: 800 IU/day during the first week and increased up to 1200 IU/day for another 11 weeks, $n = 22$ 2. Placebo, $n = 17$ Clinically stable with duration of TD for at least 1 year; stable dose of oral antipsychotics

continued

TABLE 16 Characteristics and risk of bias of included studies evaluating vitamin E as treatment for TD (*continued*)

Included study	Description	
Outcomes	• TD symptoms: AIMS • Leaving study early • Unable to use: mental state: PANSS	
Notes	Source of funding: Not reported. Declarations of interest: not reported	
Risk of bias		
Bias	***Authors' judgement***	***Support for judgement***
Random sequence generation (selection bias)	Unclear risk	'Eligible patients were randomly assigned'; no further details
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not reported
Blinding of participants and personnel (performance bias)	Low risk	*. . . either capsulized vitamin E (n = 22) or identically capsulized placebo (n = 19) using a double-blind fashion*
Blinding of outcome assessment (detection bias)	Low risk	TD and psychotherapy were assess by blinded investigators
Incomplete outcome data (attrition bias)	Low risk	All randomised subjects seem to have completed the study
Selective reporting (reporting bias)	High risk	Outcome data were not reported for mental symptoms (PANSS)
Other bias	Low risk	*No significant differences in demographic data were observed between vitamin E and placebo groups*

b.i.d., twice per day; CPZE, chlorpromazine equivalents; DSM-III-R, *Diagnostic and Statistical Manual of Mental Disorders*-Third Edition, Revised; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*-Fourth Edition; ITT, intention to treat; mAIMS, modified Abnormal Involuntary Movement Scale; NSRS, Negative Symptom Rating Scale; PANSS, Positive and Negative Syndrome Scale; PSAS, Psychiatric Symptoms Assessment Scale; RDC, Research Diagnostic Criteria; SD, standard deviation; TDRS, Tardive Dyskinesia Rating Scale; t.i.d., three times per day; VA, Veteran's administration.

a Initial report at 8 weeks, $n = 29$.

b Three people left the study in the first 2 weeks and could not be considered in the analysis – original group assumed from 3 : 2 randomisation.

c Completers.

d Total numbers randomised per group were imputed from numbers analysed per group. Authors contacted but did not reply.

Buspirone

TABLE 17 Characteristics and risk of bias of included studies evaluating buspirone as treatment for TD

Included study	Description
Zeng, 1995[78]	
Study characteristics	
Characteristic	***Description***
Methods	• Allocation: 'randomly assigned . . .' • Blinding: double-blind study, details are provided • Duration: 6 weeks • Design: parallel • Setting: inpatients
Participants	• Diagnosis: antipsychotic-induced TD, $n = 42$ • Sex: 14 female and 28 male • Age: mean ≈32.5 years, SD ≈10.3 years • Length of illness (schizophrenia): mean ≈7.5 years, SD ≈3.4 years • History: duration of TD, on average, 5.4 ± 4.2 years in active group, whereas 5.7 ± 4.5 years in control group

TABLE 17 Characteristics and risk of bias of included studies evaluating buspirone as treatment for TD (*continued*)

Included study	Description	
Interventions	1. Buspirone group: management – the initial dosage, one capsule each day, was titrated to 6–12 capsules each day within 10 days, $n = 21$ 2. Placebo group: management – the initial dosage, one capsule each day, was titrated to 6–12 capsules each day within 10 days, $n = 21$ All participants received stable antipsychotic and concomitant anticholinergic drug	
Outcomes	Clinical response TD: AIMS Adverse events: dizziness, headache, nausea, vomiting Unable to use: blood routine examination, urine routine test and liver function test, electrocardiography, electroencephalography (the author only stated results of these tests were normal, but did not report the data)	
Notes	Funding source: not reported	
Risk of bias		
Bias	***Authors' judgement***	***Support for judgement***
Random sequence generation (selection bias)	Unclear risk	'. . . randomly assigned . . .', the author did not state the method of randomisation
Allocation concealment (selection bias)	Unclear risk	The author did not state the method of allocation concealment
Blinding of participants and personnel (performance bias)	Low risk	*. . . double blind study, the interventions were coded as intervention A or B by the researcher in pharmacy . . . 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)	Unclear risk	Not stated
Incomplete outcome data (attrition bias)	Low risk	All participants completed the study
Selective reporting (reporting bias)	Low risk	The author reported all measured outcomes
Other bias	Low risk	None obvious

SD, standard deviation.

Hypnosis and relaxation

TABLE 18 Characteristics and risk of bias of included studies evaluating hypnosis and relaxation as treatment for TD

Included study	Description	
Glover, 1980[139]		
Study characteristics		
Characteristic	***Description***	
Methods	• Allocation: randomised • Blindness: not mentioned • Duration: eight sessions • Design: parallel • Setting: outpatients, USA	
Participants	• Diagnosis: diagnosis of chronic schizophrenia, diagnoses of either acute extra pyramidal symptoms, TD and/or pseudo-parkinsonism, $n = 15$ • Sex: 12 females and three males • Age: mean 34.9 years • History: duration of TD not reported. Not reported whether patients were stabilised prior to study	
Interventions	1. Hypnosis: eight sessions, $n = 5$ 2. Relaxation: eight sessions, $n = 5$ 3. TAU (control group): eight sessions, $n = 5$ Psychotropic medication continued	
Outcomes	• Leaving the study early: number of dropouts	
Notes	Sponsorship source: sponsorship source not reported	
Risk of bias		
Bias	***Authors' judgement***	***Support for judgement***
Random sequence generation (selection bias)	High risk	Quasi-randomised. Assigned to the three groups in order of approaching the clinic
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias)	High risk	As subjects in group 1 received hypnosis, those in group 2 received relaxation training and those in group 3 received TAU without any other treatment, blinding could not be achieved
Blinding of outcome assessment (detection bias)	Unclear risk	Blinding of outcome assessors not reported
Incomplete outcome data (attrition bias)	Low risk	There were no refusals, or drop-outs among the referrals
Selective reporting (reporting bias)	Low risk	It seems that all outcomes have been reported. However, data is not usable
Other bias	Unclear risk	Baseline characteristics were similar but sample sizes very small

Appendix 8 Characteristics of studies awaiting classification and ongoing

TABLE 19 Studies awaiting classification

Kar-Ahmadi, 2002[141]	
Methods	• Allocation: 'randomised' no further details • Blindness: double – no further details • Duration: 6 weeks • Setting: inpatients • Design: parallel
Participants	• Diagnosis: antipsychotic-induced TD, $n = 30$ • Sex: unknown • Age: unknown
Interventions	1. Vitamin E: dose 600 mg/day, $n = 15$ 2. Placebo, $n = 15$ Stable antipsychotic medication: dose unspecified
Outcomes	• TD symptoms: AIMS
Notes	A copy of this study was not available in The British Library
Zeng *et al.*, 1996[140]	
Methods	RCT
Participants	Schizophrenia with drug-induced tremor, $n = 68$
Interventions	1. Dexetimide, $n = 36$ 2. Benzhexol, $n = 32$
Outcomes	• Clinical response • Adverse events • Treatment Emergent Symptom Scale
Notes	In Chinese, assessed by Sai Zhao. Study authors have been contacted to find out if participants were diagnosed with TD

TABLE 20 Ongoing studies

Garcia and Crismon, 1992[142]	
Study name	Double-blind placebo controlled study using buspirone in the treatment of tardive dyskinesia
Methods	• Allocation: randomised • Blindness: double blind • Duration: 12 weeks • Design: crossover • Setting: USA
Participants	• Diagnosis: TD patients criteria not reported, $n = 20$ • Sex: not reported • Age: not reported
Interventions	1. Buspirone: not reported, increasing dose, $n = 20$ 2. Placebo, $n = 20$
Outcomes	AIMS score
Notes	Abstract of a study protocol, there are no data to be extracted
Kajero, 2015[144]	
Study name	Investigation of the potential beneficial effects of cannabidiol in the treatment of tardive dyskinesia
Methods	Randomised, double-blind, placebo-controlled study
Participants	Target number of participants: 28 per group Adults aged > 18 years who currently meet the ICD-10[196] diagnosis of a psychotic disorder, verified with the Mini International Neuropsychiatric Interview questionnaire and who currently meet the clinical diagnosis of TD confirmed with the AIMS. Patients should currently be receiving treatment for a psychotic disorder and should be on either atypical or conventional antipsychotics
Interventions	1. Group 1 has high cannabidiol extract Nabidiolex® (GW Pharma Limited Corporation, Salisbury, UK) (CBD) (300 mg) administered twice a day for 6 weeks as an adjunctive treatment alongside their usual antipsychotic medication. CBD will be administered orally in capsules 2. Group 2 has vitamin E (400 IU) administered daily for 6 weeks as an adjunctive treatment alongside their usual antipsychotic medication
Outcomes	• Improvement in symptoms of TD measured using AIMS. Assessments will be conducted at baseline, 2-, 4-, 6- (post treatment) and 12-week follow-up • Side effects of CBD will be periodically assessed with the Glasgow Checklist and reported at each assessment • Improvement in psychotic symptoms
Starting date	1 December 2015
Notes	Source of funding: Federal Neuropsychiatric Hospital, Nigeria. Trial is part of a Stellenbosch University PhD. Intention to publish date: 1 January 2018
Reynolds, 2002[143]	
Methods	• Allocation: randomised • Blindness: rater blind • Design: not reported • Setting: not reported • Duration: 6 months
Participants	Schizophrenic patients with TD
Interventions	1. Quetiapine 2. Risperidone
Outcomes	Prevalence and severity of abnormal involuntary movements
Notes	Very limited information from two trial registries. We were unable to locate author contact details

ICD-10, *International Classification of Diseases*, Tenth Edition.

Appendix 9 Non-prioritised comparisons: results overview

TABLE 21 Overview of characteristics, selected outcome measures, and risk of bias for included studies not prioritised for the NHS[a]

Study; setting	Participant characteristics	Interventions	Outcome	Effect estimate (95% CI); *n*	Risk of bias			
					Selection	Performance	Detection	Attrition
Anticholinergics								
Bucci, 1971;[197] outpatients in the USA	• Diagnosis: schizophrenia and TD • Sex: F and M • Age: 45–60 years	• Procyclidine and AP vs. isocarboxacid and AP • Treatment duration: 40 weeks	TD: No clinical improvement	RR 4.20 (1.40 to 12.58); 20	UC	High	High	Low
			Adverse events: any	RR 0.33 (0.02 to 7.32); 20	UC	High	High	Low
			Leaving the study early	RR 0.33 (0.02 to 7.32); 20	UC	Low	Low	Low
Calcium channel blockers								
Loonen *et al.*, 1992;[198] inpatients in the Netherlands	• Diagnosis: various conditions and TD • Sex: F and M • Age: 37–69 years	• Diltiazem hydrochloride and AP vs. placebo and AP • Treatment duration: 3 weeks	Mental state: deterioration	Not estimable;[b] 18	UC	Low	UC	High
Schwartz *et al.*, 1997;[199,200] setting not reported, the USA	• Diagnosis: schizophrenia or schizoaffective disorder and TD • Sex: F and M • Age: 36–58 years	• Nifedipine and AP vs. placebo and AP • Treatment duration: 4 weeks	This study did not report on any of the selected outcomes	Not estimable; 15	UC	UC	UC	High
Zeng *et al.*, 1994;[80] inpatients in China	• Diagnosis: schizophrenia and TD • Sex: F and M • Age: mean 31 years	• Flunarizine and AP vs. placebo and AP • Treatment duration: 4 weeks	Adverse events: any	Not estimable;[b] 20	UC	Low	UC	Low
Cholinergic medication								
Beckham, 1981;[201] inpatients and outpatients in the USA	• Diagnosis: various conditions and TD • Sex: M • Age: 23–77 years	• Lecithin and AP vs. placebo and AP • Treatment duration: 2 weeks	Mental state: deterioration	RR 0.33 (0.01 to 7.81); 50	UC	Low	Low	High
			Leaving the study early	RR 0.50 (0.17 to 1.45); 50	UC	Low	Low	High
Caroff *et al.*, 2007;[202,203] inpatients in the USA	• Diagnosis: schizophrenia and TD • Sex: M • Age: mean 56.4 years	• Galantamine and AP vs. placebo and AP • Treatment duration: 12 weeks	Leaving the study early	RR 3.00 (0.96 to 9.39); 38	UC	Low	Low	UC

Study; setting	Participant characteristics	Interventions	Outcome	Effect estimate (95% CI); *n*	Risk of bias			
					Selection	Performance	Detection	Attrition
de Montigny *et al.*, 1979;[204] inpatients in Canada	• Diagnosis: schizophrenia and TD • Sex: F and M • Age: 34–73 years	• Deanol and AP vs. placebo and AP • Treatment duration: 3 weeks	Leaving the study early	Not estimable;[b] 20	UC	Low	Low	Low
Gelenberg *et al.*, 1990;[205] outpatients in the USA	• Diagnosis: various conditions and TD • Sex: F and M • Age: 19–70 years	• Lecithin and AP vs. placebo and AP • Treatment duration: 8 weeks	This study did not report on any of the selected outcomes	Not estimable; 14	UC	UC	UC	High
George *et al.*, 1981;[206] inpatients in Australia	• Diagnosis: various conditions and TD • Sex: F and M • Age: 49–89 years	• Deanol and AP vs. placebo and AP • Treatment duration: 4 weeks	Leaving the study early	Not estimable;[b] 33	UC	Low	Low	Low
Jackson, 1978;[207] inpatients in the USA	• Diagnosis: schizophrenia and TD • Sex: F • Age: 34–59 years	• Deanol and AP vs. placebo and AP • Treatment duration: 12 weeks	TD: no clinical improvement	RR 0.84 (0.39 to 1.81); 6	UC	UC	Low	UC
			TD: deterioration	RR 0.36 (0.09 to 1.51); 6	UC	UC	Low	UC
			Mental state: deterioration	Not estimable;[b] 6	UC	UC	Low	UC
			Leaving the study early	Not estimable;[b] 6	UC	Low	Low	UC
Jackson *et al.*, 1979;[208,209] inpatients in the USA	• Diagnosis: schizophrenia and TD • Sex: F and M • Age: 49–60 years	• Lecithin and AP vs. placebo and AP • Treatment duration: 2 weeks	TD: no clinical improvement	RR 0.71 (0.31 to 1.66); 6	UC	Low	Low	UC
			TD: deterioration	RR 0.33 (0.02 to 5.97); 6	UC	Low	Low	UC
			Mental state: deterioration	Not estimable;[b] 6	UC	Low	Low	UC
			Leaving the study early	Not estimable;[b] 6	UC	Low	Low	UC
Jahanian *et al.*, 2014;[87] inpatients in Iran	• Diagnosis: schizophrenia and TD • Sex: NR • Age: 18–65 years	• Rivastigmine and AP vs. placebo and AP • Treatment duration: 8 weeks	This study did not report on any of the selected outcomes	Not estimable; 40	UC	UC	UC	UC

continued

TABLE 21 Overview of characteristics, selected outcome measures, and risk of bias for included studies not prioritised for the NHS[a] (*continued*)

Study; setting	Participant characteristics	Interventions	Outcome	Effect estimate (95% CI); *n*	Risk of bias			
					Selection	Performance	Detection	Attrition
Kocher *et al.*, 1980;[82] inpatients in Switzerland	• Diagnosis: schizophrenia, dementia and TD • Sex: F and M • Age: 42–82 years	• Deanol and AP vs. placebo and AP • Treatment duration: 4 weeks	TD: deterioration	RR 1.00 (0.17 to 5.77); 20	UC	UC	Low	Low
			Leaving the study early	Not estimable;[b] 20	UC	Low	Low	Low
Lucius, 1978;[83,210] inpatients in Germany	• Diagnosis: various conditions and TD • Sex: F and M • Age: 28–75 years	• Deanol and AP vs. placebo and AP • Treatment duration: 5 weeks	TD: deterioration	RR 3.00 (0.45 to 19.93); 10	UC	UC	Low	UC
			Mental state: deterioration	RR 0.33 (0.02 to 6.65); 10	UC	UC	Low	UC
			Leaving the study early	RR 0.33 (0.02 to 6.65); 10	UC	Low	Low	UC
Ogunmefun *et al.*, 2009;[211] setting and country not reported	• Diagnosis: TD • Sex: F and M • Age: mean 61.4 years	• Donepezil and AP vs. placebo and AP • Treatment duration: 6 weeks	TD: no clinical improvement	RR 1.00 (0.70 to 1.43); 10	UC	UC	Low	UC
			TD: deterioration	RR 0.67 (0.06 to 7.85); 10	UC	UC	Low	UC
			Leaving the study early	Not estimable;[b] 10	UC	Low	Low	UC
Price, 1982;[212] inpatients in the USA	• Diagnosis: various conditions and TD • Sex: M • Age: 26–77 years	• Lecithin and AP vs. placebo and AP • Treatment duration: 2 weeks	TD: deterioration	RR 3.00 (0.13 to 68.26); 30	UC	Low	Low	Low
			Leaving the study early	Not estimable;[b] 30	UC	Low	Low	Low
Tarsy and Bralower, 1977;[213] inpatients and outpatients in the USA	• Diagnosis: various conditions and TD • Sex: M • Age: mean 54.8 years	• Deanol and AP vs. placebo and AP • Treatment duration: 8 weeks	TD: no clinical improvement	RR 1.00 (0.43 to 2.34); 5	UC	UC	UC	Low
			TD: deterioration	RR 2.00 (0.16 to 25.75); 5	UC	UC	UC	Low
			Mental state: deterioration	RR 1.20 (0.08 to 18.75); 5	UC	UC	UC	Low
			Leaving the study early	RR 1.20 (0.08 to 18.75); 5	UC	Low	Low	Low

Study; setting	Participant characteristics	Interventions	Outcome	Effect estimate (95% CI); *n*	Risk of bias			
					Selection	Performance	Detection	Attrition
Yagi, 1990;[86,214,215] inpatients in Japan	• Diagnosis: schizophrenia and TD • Sex: F and M • Age: 30–79 years	• Meclofenoxate hydrochloride and AP vs. placebo and AP • Treatment duration: 8 weeks	TD: deterioration	RR 1.87 (0.18 to 19.55); 60	UC	UC	UC	Low
			Adverse events: any	RR 0.56 (0.15 to 2.14); 60	UC	UC	UC	Low
			Leaving the study early	Not estimable;[b] 60	UC	Low	Low	Low
GABA agonists								
Ananth *et al.*, 1987;[216] inpatients in Canada	• Diagnosis: schizophrenia and TD • Sex: M • Age: 30–58 years	• Baclofen and AP vs. placebo and AP • Treatment duration: 4 weeks	TD: deterioration	Not estimable;[b] 10	UC	Low	UC	Low
			Mental state: deterioration	Not estimable;[b] 10	UC	Low	UC	Low
			Adverse events: any	Not estimable;[b] 10	UC	Low	UC	Low
			Leaving the study early	Not estimable;[b] 10	UC	Low	Low	Low
Burner *et al.*, 1989;[217] setting and country not reported	• Diagnosis: various conditions and TD • Sex: F and M • Age: mean 56 years	• Progabide and AP vs. placebo and AP • Treatment duration: 6 weeks	TD: no clinical improvement	RR 0.68 (0.36 to 1.25); 13	UC	Low	UC	Low
			Mental state: deterioration	RR 1.82 (0.11 to 30.27); 13	UC	Low	UC	Low
			Leaving the study early	RR 1.09 (0.05 to 21.67); 13	UC	Low	Low	Low
Fisk and York, 1987;[218] inpatients and outpatients in the UK	• Diagnosis: various conditions and TD • Sex: F and M • Age: mean 58 years	• Sodium valproate and AP vs. placebo and AP • Treatment duration: 6 weeks	TD: no clinical improvement	RR 0.94 (0.80 to 1.11); 62	Low	Low	Low	High
			TD: deterioration	RR 3.41 (0.77 to 15.19); 47	Low	Low	Low	High
			Mental state: deterioration	RR 2.27 (0.22 to 23.38); 47	Low	Low	Low	High
			Leaving the study early	RR 2.42 (0.86 to 6.77); 62	Low	Low	Low	High

continued

TABLE 21 Overview of characteristics, selected outcome measures, and risk of bias for included studies not prioritised for the NHS[a] (*continued*)

Study; setting	Participant characteristics	Interventions	Outcome	Effect estimate (95% CI); *n*	Risk of bias			
					Selection	Performance	Detection	Attrition
Gerlach, 1977;[219,220] inpatients in Denmark	• Diagnosis: various conditions and TD • Sex: F and M • Age: 47–79 years	• Baclofen and AP vs. placebo and AP • Treatment duration: 3 weeks	TD: deterioration	RR 2.45 (0.11 to 53.25); 18	UC	UC	UC	UC
			Mental state: deterioration	RR 4.09 (0.22 to 74.78); 18	UC	UC	UC	UC
			Leaving the study early	RR 0.20 (0.01 to 3.70); 20	UC	Low	Low	UC
Glazer *et al.*, 1985;[221] inpatients in the USA	• Diagnosis: various conditions and TD • Sex: F and M • Age: 26–67 years	• Baclofen and AP vs. placebo and AP • Treatment duration: 6 weeks	TD: no clinical improvement	RR 0.87 (0.66 to 1.14); 31	UC	UC	UC	High
			TD: deterioration	RR 0.94 (0.06 to 13.68); 31	UC	UC	UC	High
			Mental state: deterioration	Not estimable;[b] 31	UC	UC	UC	High
Linnoila *et al.*, 1976;[222] inpatients in Finland	• Diagnosis: various conditions and TD • Sex: F and M • Age: mean 62–78 years	• Sodium valproate and AP vs. placebo and AP • Treatment duration: 1 week	This study did not report on any of the selected outcomes	Not estimable; 32	UC	Low	UC	Low
Mei and Zhu, 2008;[73] inpatients in China	• Diagnosis: schizophrenia and TD • Sex: NR • Age: mean 43 years	• GABA and AP vs. placebo and AP • Treatment duration: 8 weeks	TD: no clinical improvement	RR 0.67 (0.45 to 0.98); 40	UC	Low	Low	Low
			Mental state: average end-point score	MD 0.03 (–3.29 to 3.35); 40	UC	Low	Low	Low
Nair *et al.*, 1978;[223,224] inpatients in the USA	• Diagnosis: schizophrenia and TD • Sex: F and M • Age: 40–64 years	• Baclofen and AP vs. placebo and AP • Treatment duration: 3 weeks	This study did not report on any of the selected outcomes	Not estimable; 10	UC	UC	Low	UC

Study; setting	Participant characteristics	Interventions	Outcome	Effect estimate (95% CI); *n*	Risk of bias			
					Selection	Performance	Detection	Attrition
Stewart *et al.*, 1982;[225,226] setting and country not reported	• Diagnosis: various conditions and TD • Sex: F and M • Age: mean 52 years	• Baclofen and AP vs. placebo and AP • Treatment duration: 6 weeks	TD: no clinical improvement	RR 0.90 (0.60 to 1.36); 33	UC	UC	UC	UC
			TD: deterioration	RR 0.65 (0.07 to 6.45); 30	UC	UC	UC	UC
			Leaving the study early	RR 0.68 (0.07 to 6.76); 33	UC	Low	Low	UC
Thaker *et al.*, 1987;[227] inpatients in the USA	• Diagnosis: schizophrenia and TD • Sex: F and M • Age: 22–36 years	• THIP and AP vs. placebo and AP • Treatment duration: 3 weeks	Mental state: deterioration	RR 3.00 (0.24 to 37.67); 2	UC	UC	Low	Low
Yin *et al.*, 2004;[77] inpatients in China	• Diagnosis: TD • Sex: M • Age: mean 44 years	• Sodium valproate and AP vs. placebo and AP • Treatment duration: 6 weeks	TD: no clinical improvement	RR 0.80 (0.68 to 0.94); 79	UC	Low	UC	Low
			Leaving the study early	RR 3.00 (0.13 to 71.51); 80	UC	Low	Low	Low
Miscellaneous treatments								
Cai, 1988;[71] setting and country not reported	• Diagnosis: TD • Sex: F and M • Age: 28–59 years	• L-stepholidine and AP vs. placebo and AP • Treatment duration: 8 weeks	TD: no clinical improvement	RR 0.54 (0.35 to 0.82); 57	UC	Low	Low	Low
			Mental state: average end-point score	MD –4.50 (–7.60 to –1.40); 20	UC	Low	Low	Low
			Adverse events: any	Not estimable;[b] 57	UC	Low	Low	Low
			Leaving the study early	Not estimable;[b] 57	UC	Low	Low	Low
Castro *et al.*, 2011;[228] inpatients and outpatients in Venezuela	• Diagnosis: various conditions and TD • Sex: F and M • Age: 46–75 years	• Melatonin and AP vs. placebo and AP • Treatment duration: 12 weeks	TD: no clinical improvement	RR 0.74 (0.44 to 1.23); 13	UC	Low	UC	Low
			Mental state: deterioration	Not estimable;[b] 13	UC	Low	UC	Low
			Adverse events: any	Not estimable;[b] 13	UC	Low	UC	Low
			Leaving the study early	Not estimable;[b] 13	UC	Low	Low	Low

continued

TABLE 21 Overview of characteristics, selected outcome measures, and risk of bias for included studies not prioritised for the NHS[a] (*continued*)

Study; setting	Participant characteristics	Interventions	Outcome	Effect estimate (95% CI); *n*	Risk of bias			
					Selection	Performance	Detection	Attrition
Emsley *et al.*, 2006;[229–233] inpatients and outpatients in South Africa	• Diangosis: schizophrenia or schizoaffective disorder and TD • Sex: F and M • Age: mean 42 years	• Omega-3 fatty acid and AP vs. placebo and AP • Treatment duration: 12 weeks	Mental state: deterioration	RR 0.49 (0.05 to 5.14); 75	UC	Low	UC	Low
			Adverse events: EPS	MD 0.30 (–1.17 to 1.77); 75	UC	Low	UC	Low
			Leaving the study early	RR 0.57 (0.27 to 1.22); 84	UC	Low	Low	Low
Gardos *et al.*, 1979;[234] inpatients in the USA	• Diagnosis: schizophrenia, dementia and TD • Sex: F and M • Age: 32–84 years	• Papaverine and AP vs. TAU and AP • Treatment duration: 6 weeks	This study did not report on any of the selected outcomes	Not estimable; 22	UC	High	Low	UC
Glazer *et al.*, 1985;[235] outpatients in the USA	• Diagnosis: various conditions and TD • Sex: F • Age: 50–65 years	• Oestrogen and AP vs. placebo and AP • Treatment duration: 3 weeks	TD: no clinical improvement	RR 1.18 (0.76 to 1.83); 12	UC	UC	UC	Low
			TD: deterioration	RR 0.20 (0.01 to 3.35); 11	UC	UC	UC	Low
			Adverse events: any	RR 0.33 (0.02 to 6.86); 12	UC	UC	UC	Low
			Leaving the study early	RR 1.00 (0.08 to 12.56); 12	UC	Low	Low	Low
Goff *et al.*, 1993;[236] outpatients in the USA	• Diagnosis: TD • Sex: F and M • Age: mean 49 years	• Selengiline and AP vs. placebo and AP • Treatment duration: 6 weeks	TD: no clinical improvement	RR 1.37 (0.96 to 1.94); 33	UC	Low	Low	High
			Leaving the study early	RR 10.39 (0.62 to 173.97); 33	UC	Low	Low	High
Hajioff and Wallace, 1983;[237] inpatients in the UK	• Diagnosis: various conditions and TD • Sex: F and M • Age: 60–92 years	• Co-dergocrine mesilate and AP vs. placebo and AP • Treatment duration: 6 weeks	Leaving the study early	RR 0.33 (0.02 to 7.32); 20	UC	Low	Low	Low

Study; setting	Participant characteristics	Interventions	Outcome	Effect estimate (95% CI); *n*	Risk of bias			
					Selection	Performance	Detection	Attrition
Kojima *et al.*, 1992;[238,239] inpatients and outpatients in Japan	• Diagnosis: schizophrenia and TD • Sex: F and M • Age: 31–75 years	• Ceruletide and AP vs. placebo and AP • Treatment duration: 6 weeks	TD: deterioration	RR 0.33 (0.01 to 7.90); 66	UC	UC	UC	High
			Adverse events: any	RR 1.13 (0.61 to 2.07); 85	UC	UC	UC	High
			Leaving the study early	RR 1.09 (0.49 to 2.40); 85	UC	Low	Low	High
Koshino *et al.*, 1979;[85] inpatients in Japan	• Diagnosis: various conditions and TD • Sex: F and M • Age: mean 56 years	• Cyproheptadine and AP vs. placebo and AP • Treatment duration: 4 weeks	TD: deterioration	RR 0.33 (0.01 to 7.74); 42	UC	UC	UC	Low
			Adverse events: any	RR 0.33 (0.04 to 2.95); 42	UC	UC	UC	Low
			Leaving the study early	RR 0.33 (0.01 to 7.74); 42	UC	Low	Low	Low
Koshino *et al.*, 1983;[84] inpatients in Japan	• Diagnosis: schizophrenia and TD • Sex: F and M • Age: mean 59 years	• Co-dergocrine mesilate and AP vs. placebo and AP • Treatment duration: 6 weeks	TD: no clinical improvement	RR 0.45 (0.21 to 0.97); 28	UC	UC	UC	Low
			TD: deterioration	RR 0.33 (0.01 to 7.55); 28	UC	UC	UC	Low
			Mental state: deterioration	RR 0.50 (0.05 to 4.90); 28	UC	UC	UC	Low
			Adverse events: any	RR 2.33 (0.75 to 7.23); 28	UC	UC	UC	Low
			Leaving the study early	Not estimable;[b] 28	UC	Low	Low	Low
Libov *et al.*, 2007;[240–243] inpatients in Israel	• Diagnosis: schizophrenia or schizoaffective disorder and TD • Sex: F and M • Age: 26–69 years	• Piracetam and AP vs. placebo and AP • Treatment duration: 4 weeks	Adverse events: EPS	MD 2.50 (–4.73 to 9.73); 35	UC	UC	Low	High
			Leaving the study early	RR 0.23 (0.03 to 1.85); 40	UC	Low	Low	High

continued

TABLE 21 Overview of characteristics, selected outcome measures, and risk of bias for included studies not prioritised for the NHS[a] (*continued*)

Study; setting	Participant characteristics	Interventions	Outcome	Effect estimate (95% CI); *n*	Risk of bias			
					Selection	Performance	Detection	Attrition
MacKay *et al.*, 1980;[244] inpatients in the UK	• Diagnosis: various conditions and TD • Sex: NR • Age: 56–70 years	• Lithium and AP vs. placebo and AP • Treatment duration: 5 weeks	TD: no clinical improvement	RR 1.59 (0.79 to 3.23); 11	UC	Low	Low	Low
			TD: deterioration	RR 4.29 (0.25 to 72.90); 11	UC	Low	Low	Low
			Adverse events: any	RR 6.00 (0.38 to 94.35); 11	UC	Low	Low	Low
			Leaving the study early	RR 2.57 (0.13 to 52.12); 11	UC	Low	Low	Low
Matsunaga *et al.*, 1988;[245] inpatients in Japan	• Diagnosis: various conditions and TD • Sex: F and M • Age: mean 59 years	• Ceruletide and AP vs. placebo and AP • Treatment duration: 4 weeks	TD: deterioration	RR 2.85 (0.12 to 65.74); 37	UC	UC	UC	High
			Adverse events: any	RR 3.79 (0.47 to 30.77); 37	UC	UC	UC	High
Meco *et al.*, 1989;[246] inpatients in Italy	• Diagnosis: schizophrenia and TD • Sex: F and M • Age: 33–72 years	• Ritanserin and AP vs. placebo and AP • Treatment duration: 4 weeks	TD: no clinical improvement	RR 1.00 (0.70 to 1.43); 10	UC	UC	UC	Low
			TD: Deterioration	RR 0.47 (0.02 to 9.26); 10	UC	UC	UC	Low
			Mental state: deterioration	RR 0.47 (0.02 to 9.26); 10	UC	UC	UC	Low
Mosnik *et al.*, 1995;[247–249] inpatients and outpatients in the USA	• Diagnosis: schizophrenia and TD • Sex: M • Age: 28–65 years	• Phenylalanine and AP vs. placebo and AP • Treatment duration: 1 day	Leaving the study early	RR 2.45 (0.11 to 53.25); 18	UC	Low	Low	Low
Mouret *et al.*, 1991;[250] inpatients in Morocco	• Diagnosis: schizophrenia and TD • Sex: F and M • Age: 20–67 years	• Insulin and AP vs. placebo and AP • Treatment duration: 12 weeks	TD: no clinical improvement	RR 0.52 (0.29 to 0.96); 20	UC	UC	UC	UC
			TD: deterioration	RR 0.14 (0.01 to 2.45); 20	UC	UC	UC	UC
			Leaving the study early	Not estimable;[b] 20	UC	Low	Low	UC

Study; setting	Participant characteristics	Interventions	Outcome	Effect estimate (95% CI); *n*	Risk of bias			
					Selection	Performance	Detection	Attrition
O'Brien *et al.*, 2014;[251,252] inpatients and outpatients in the USA	• Diagnosis: various conditions and TD • Sex: NR • Age: 18–85 years	• NBI-98854 (VMAT2 inhibitor) and AP vs. placebo and AP • Treatment duration: 6 weeks	TD: no clinical improvement	RR 0.58 (0.41 to 0.82); 88	UC	UC	Low	UC
			Adverse events: any	RR 1.88 (0.73 to 4.84); 88	UC	UC	Low	UC
			Leaving the study early	RR 1.26 (0.39 to 4.03); 88	UC	Low	Low	UC
Rastogi *et al.*, 1982;[253] inpatients in the UK	• Diagnosis: various conditions and TD • Sex: F and M • Age: mean 70 years	• Co-dergocrine mesilate and AP vs. placebo and AP • Treatment duration: 6 weeks	This study did not report on any of the selected outcomes	Not estimable; 40	UC	Low	UC	UC
Richardson *et al.*, 2003;[254] inpatients and outpatients in the USA	• Diagnosis: various conditions and TD • Sex: M • Age: mean 45 years	• Branched-chain amino acids and AP vs. placebo and AP • Treatment duration: 3 weeks	TD: no clinical improvement	RR 0.79 (0.63 to 1.00); 52	UC	UC	Low	UC
			TD: deterioration	RR 0.29 (0.07 to 1.19); 36	UC	UC	Low	UC
			Leaving the study early	RR 0.84 (0.37 to 1.92); 52	UC	Low	Low	UC
Shamir *et al.*, 2000;[255] inpatients in Israel	• Diagnosis: schizophrenia and TD • Sex: F and M • Age: 62–91 years	• Melatonin and AP vs. placebo and AP • Treatment duration: 4 weeks	TD: no clinical improvement	RR 1.00 (0.83 to 1.21); 19	Low	Low	Low	Low
			TD: deterioration	RR 0.22 (0.01 to 4.05); 19	Low	Low	Low	Low
			Adverse events: any	Not estimable;[b] 19	Low	Low	Low	Low
			Leaving the study early	Not estimable;[b] 19	Low	Low	Low	Low
Shamir *et al.*, 2001;[256,257] inpatients in Israel	• Diagnosis: schizophrenia and TD • Sex: F and M • Age: 28–82 years	• Melatonin and AP vs. placebo and AP • Treatment duration: 6 weeks	Adverse events: any	Not estimable;[b] 22	Low	Low	UC	Low
			Leaving the study early	Not estimable;[b] 22	Low	Low	Low	Low

continued

TABLE 21 Overview of characteristics, selected outcome measures, and risk of bias for included studies not prioritised for the NHS[a] (*continued*)

Study; setting	Participant characteristics	Interventions	Outcome	Effect estimate (95% CI); *n*	Risk of bias			
					Selection	Performance	Detection	Attrition
Shi *et al.*, 2009;[74] inpatients in China	• Diagnosis: TD • Sex: F and M • Age: mean 56 years	• Melatonin and AP vs. TAU and AP • Treatment duration: 12 weeks	This study did not report on any of the selected outcomes	Not estimable; 76	UC	High	UC	Low
UCB Pharma, 2005;[258] inpatients in Belgium and Bulgaria	• Diagnosis: TD • Sex: F and M • Age: 18–80 years	• Levetiracetam and AP vs. placebo and AP • Treatment duration: 8 weeks	Adverse events: any	RR 0.51 (0.25 to 1.04); 69	UC	UC	UC	High
			Leaving the study early	RR 0.21 (0.03 to 1.67); 69	UC	Low	Low	High
Wolkin *et al.*, 1986;[259] inpatients and outpatients in the USA	• Diagnosis: schizophrenia and TD • Sex: M • Age: mean 54 years	• Evening primrose oil and AP vs. placebo and AP • Treatment duration: 6 weeks	TD: no clinical improvement	RR 1.00 (0.69 to 1.45); 16	UC	UC	UC	Low
			TD: deterioration	RR 1.50 (0.34 to 6.70); 16	UC	UC	UC	Low
			Mental state: average end-point score	MD –6.00 (–15.99 to 3.99); 10	UC	UC	UC	Low
			Leaving the study early	Not estimable;[b] 16	UC	Low	Low	Low
Woods *et al.*, 2008;[260,261] outpatients in the USA	• Diagnosis: various conditions and TD • Sex: F and M • Age: mean 47 years	• Levetiracetam and AP vs. placebo and AP • Treatment duration: 12 weeks	Mental state: deterioration	RR 0.67 (0.12 to 3.65); 50	UC	UC	UC	Low
			Leaving the study early	RR 1.80 (0.70 to 4.62); 50	UC	Low	Low	Low
Yang *et al.*, 1999;[76] inpatients in China	• Diagnosis: schizophrenia and TD • Sex: F and M • Age: mean 50 years	• Promethazine and AP vs. placebo and AP • Treatment duration: 12 weeks	TD: no clinical improvement	RR 0.24 (0.11 to 0.55); 34	Low	UC	Low	Low
			Mental state: average end-point score	MD 0.70 (–3.77 to 5.17); 34	Low	UC	Low	Low
			Adverse events: any	MD –0.10 (–0.53 to 0.33); 34	Low	UC	Low	Low
			Adverse events: EPS	MD –0.50 (–1.36 to 0.36); 34	Low	UC	Low	Low

Study; setting	Participant characteristics	Interventions	Outcome	Effect estimate (95% CI); *n*	Risk of bias			
					Selection	Performance	Detection	Attrition
Zeng, 1996;[79] inpatients in China	• Diagnosis: schizophrenia and TD • Sex: F and M • Age: mean 33 years	• Pemoline and AP vs. placebo and AP • Treatment duration: 6 weeks	TD: no clinical improvement	RR 0.48 (0.29 to 0.77); 46	UC	Low	UC	Low
			Leaving the study early	Not estimable;[b] 46	UC	Low	Low	Low
Zhang *et al.*, 2011;[262–264] inpatients in China	• Diagnosis: schizophrenia and TD • Sex: M • Age: mean 45 years	• *Ginkgo biloba* and AP vs. placebo and AP • Treatment duration: 12 weeks	TD: no clinical improvement	RR 0.88 (0.81 to 0.96); 157	Low	Low	Low	Low
			Mental state: deterioration	RR 0.34 (0.01 to 8.16); 157	Low	Low	Low	Low
			Leaving the study early	RR 0.25 (0.03 to 2.22); 157	Low	Low	Low	Low
AP reduction and/or cessation and APs								
Glazer and Hafez, 1990;[189,190] outpatients in the USA	• Diagnosis: schizophrenia or schizoaffective disorder and TD • Sex: F and M • Age: mean 47 years	• Molindone vs. haloperidol • Treatment duration: 2 weeks	Leaving the study early	Not estimable;[b] 18	UC	Low	Low	Low
Kazamatsuri *et al.*, 1972;[169] inpatients in the USA	• Diagnosis: various conditions and TD • Sex: F and M • Age: 44–70 years	• Thiopropazate vs. haloperidol • Treatment duration: 4 weeks	TD: no clinical improvement	RR 1.53 (0.58 to 4.05); 20	UC	UC	Low	Low
			TD: deterioration	RR 1.22 (0.09 to 16.92); 20	UC	UC	Low	Low
			Leaving the study early	RR 0.24 (0.01 to 4.44); 20	UC	Low	Low	Low
Lublin *et al.*, 1991;[188] inpatients in Denmark and Finland	• Diagnosis: psychosis and TD • Sex: F and M • Age: 47–79 years	• Zuclopentixol vs. haloperidol • Treatment duration: 3 weeks	TD: no clinical improvement	RR 1.00 (0.79 to 1.27); 15	UC	High	Low	Low
			TD: deterioration	RR 0.88 (0.16 to 4.68); 15	UC	High	Low	Low
			Adverse events: EPS	MD –4.81 (–12.15 to 2.53); 15	UC	High	Low	Low

continued

TABLE 21 Overview of characteristics, selected outcome measures, and risk of bias for included studies not prioritised for the NHS[a] (*continued*)

Study; setting	Participant characteristics	Interventions	Outcome	Effect estimate (95% CI); *n*	Risk of bias			
					Selection	Performance	Detection	Attrition
Non-AP catecholaminergic drugs								
Buruma *et al.*, 1982;[265,266] inpatients in the Netherlands	• Diagnosis: various conditions and TD • Sex: F and M • Age: 39–70 years	• Tiapride and AP vs. placebo and AP • Treatment duration: 2 weeks	Leaving the study early	Not estimable;[b] 12	UC	Low	Low	Low
Chen *et al.*, 1995;[72] inpatients in China	• Diagnosis: TD • Sex: F and M • Age: mean 35 years	• Bromocriptine and AP vs. placebo and AP • Treatment duration: 4 weeks	Leaving the study early	Not estimable;[b] 20	UC	Low	Low	Low
Hebenstreit *et al.*, 1986;[81] inpatients in Austria	• Diagnosis: TD • Sex: F • Age: 43–82 years	• Celiprolol and AP vs. placebo and AP • Treatment duration: 3 months	Quality of life: no improvement	RR 0.87 (0.68 to 1.12); 35	UC	Low	UC	UC
			Leaving the study early	RR 5.28 (0.27 to 102.58); 35	UC	Low	Low	UC
Huang *et al.*, 1980;[267,268] inpatients in the USA	• Diagnosis: psychosis and TD • Sex: NR • Age: 40–65 years	• Alpha-methyldopa and AP vs. placebo and AP • Treatment duration: 2 weeks	TD: no clinical improvement	RR 0.33 (0.14 to 0.80); 20	UC	Low	UC	UC
			TD: deterioration	RR 0.33 (0.02 to 7.32); 20	UC	Low	UC	UC
		• Alpha-methyldopa and AP vs. reserpine and AP • Treatment duration: 2 weeks	TD: no clinical improvement	RR 0.60 (0.19 to 1.86); 20	UC	Low	UC	UC
			TD: deterioration	Not estimable;[b] 20	UC	Low	UC	UC
		• Reserpine and AP vs. placebo and AP • Treatment duration: 2 weeks	TD: no clinical improvement	RR 0.52 (0.29 to 0.96); 20	UC	Low	UC	UC
			TD: deterioration	RR 0.33 (0.02 to 7.32); 20	UC	Low	UC	UC

Study; setting	Participant characteristics	Interventions	Outcome	Effect estimate (95% CI); *n*	Risk of bias			
					Selection	Performance	Detection	Attrition
Karniol *et al.*, 1983;[88] inpatients in Brazil	• Diagnosis: various conditions and TD • Sex: F and M • Age: mean 58 years	• L-Dopa and AP vs. placebo and AP • Treatment duration: 5 weeks	This study did not report on any of the selected outcomes	Not estimable; 20	UC	Low	UC	Low
Pappa *et al.*, 2010;[269–271] outpatients in Greece	• Diagnosis: schizophrenia and TD • Sex: F and M • Age: 32–68 years	• Amantadine and AP vs. placebo and AP • Treatment duration: 4 weeks	Leaving the study early	Not estimable;[b] 22	UC	Low	Low	Low
Rust, 1984;[272] inpatients in France	• Diagnosis: various conditions and TD • Sex: M • Age: mean 48 years	• Tiapride and AP vs. placebo and AP • Treatment duration: 8 weeks	Leaving the study early	Not estimable;[b] 50	UC	Low	Low	Low
Simpson *et al.*, 1988;[273] inpatients in the USA	• Diagnosis: TD • Sex: F and M • Age: 32–70 years	• Carbidopa/levodopa and AP vs. placebo and AP • Treatment duration: 6 weeks	TD: deterioration	RR 1.78 (0.44 to 7.25); 17	UC	Low	UC	High
			Leaving the study early	RR 0.18 (0.01 to 3.27); 17	UC	Low	Low	High
Soni *et al.*, 1986;[274] inpatients in the UK	• Diagnosis: schizophrenia and TD • Sex: F and M • Age: 42–71 years	• Oxypertine and AP vs. placebo and AP • Treatment duration: 24 weeks	Mental state: deterioration	RR 2.20 (0.22 to 22.45); 42	UC	UC	Low	High
			Leaving the study early	RR 1.73 (0.83 to 3.58); 42	UC	Low	Low	High

AP, antipsychotics; EPS, extrapyramidal symptoms; F, female; M, male; NR, not reported; THIP, 4,5,6,7-tetrahydroisoxazolo[5,4-c]pyridin-3-ol; UC, unclear; VMAT2, vesicular monoamine transporter-2.

a Please see Cochrane reviews for syntheses, full details of study characteristics and risk of bias, and for more outcome measures.[18,23,43–49]

b No reported events.

Appendix 10 Analyses: forest plots for prioritised comparisons

Antipsychotic reduction versus continuation

Reduced versus standard dose of flupentixol decanoate[98] or fluphenazine decanoate[97]

Figures 23–26 present forest plots of outcome analyses for antipsychotic reduction versus continuation.

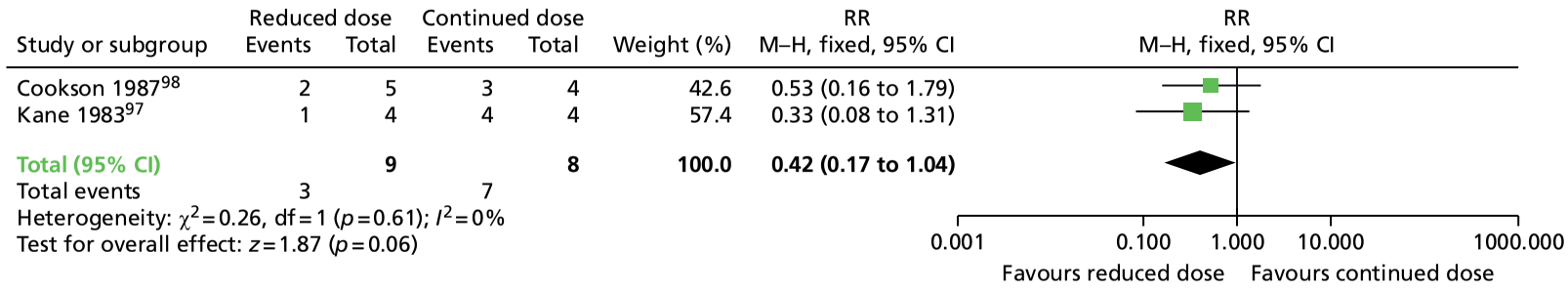

FIGURE 23 Antipsychotic reduction vs. continuation: forest plot for the outcome 'TD – no clinically important improvement' (follow-up 44–48 weeks). df, degrees of freedom; M–H, Mantel–Haenszel.

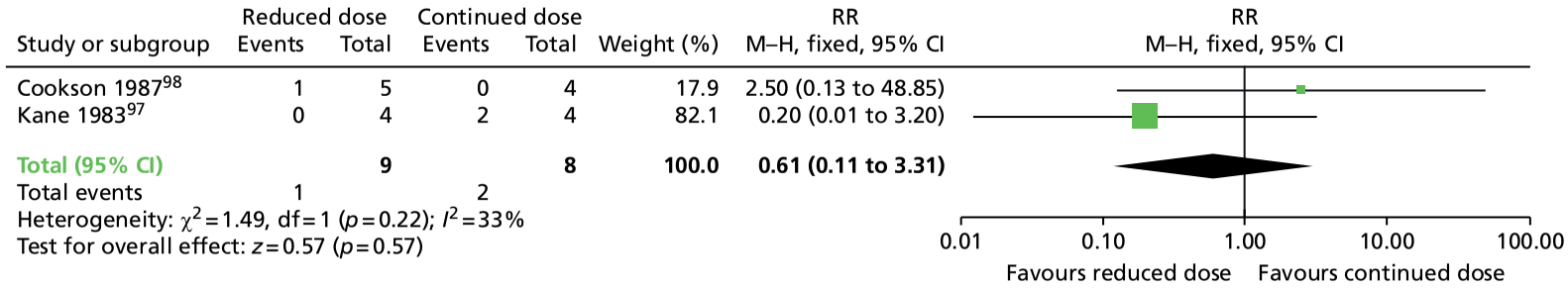

FIGURE 24 Antipsychotic reduction vs. continuation: forest plot for the outcome 'TD – deterioration' (follow-up 44–48 weeks). df, degrees of freedom; M–H, Mantel–Haenszel.

Study or subgroup	Reduced dose Events	Total	Continued dose Events	Total	Weight (%)	RR M–H, fixed, 95% CI
Kane 1983[97]	1	4	0	4	100.0	3.00 (0.16 to 57.36)
Total (95% CI)		**4**		**4**	**100.0**	**3.00 (0.16 to 57.36)**
Total events	1		0			

Heterogeneity: not applicable
Test for overall effect: $z = 0.73$ ($p = 0.47$)

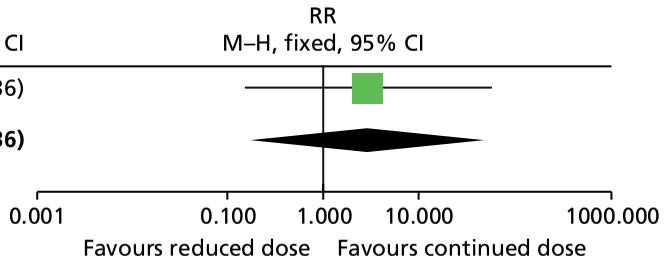

FIGURE 25 Antipsychotic reduction vs. continuation: forest plot for the outcome 'mental state – relapse' (follow-up 44–48 weeks). M–H, Mantel–Haenszel.

Study or subgroup	Reduced dose Events	Total	Continued dose Events	Total	Weight (%)	RR M–H, fixed, 95% CI
Kane 1983[97]	1	4	3	4	100.0	0.33 (0.06 to 1.99)
Total (95% CI)		**4**		**4**	**100.0**	**0.33 (0.06 to 1.99)**
Total events	1		3			

Heterogeneity: not applicable
Test for overall effect: $z = 1.20$ ($p = 0.23$)

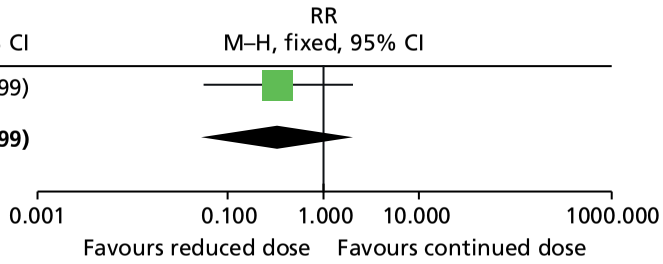

FIGURE 26 Antipsychotic reduction vs. continuation: forest plot for the outcome 'leaving the study early' (follow-up 44–48 weeks). M–H, Mantel–Haenszel.

Antipsychotic switch versus withdrawal (with placebo)

Figures 27–30 present forest plots of outcome analyses for antipsychotic switch versus antipsychotic withdrawal.

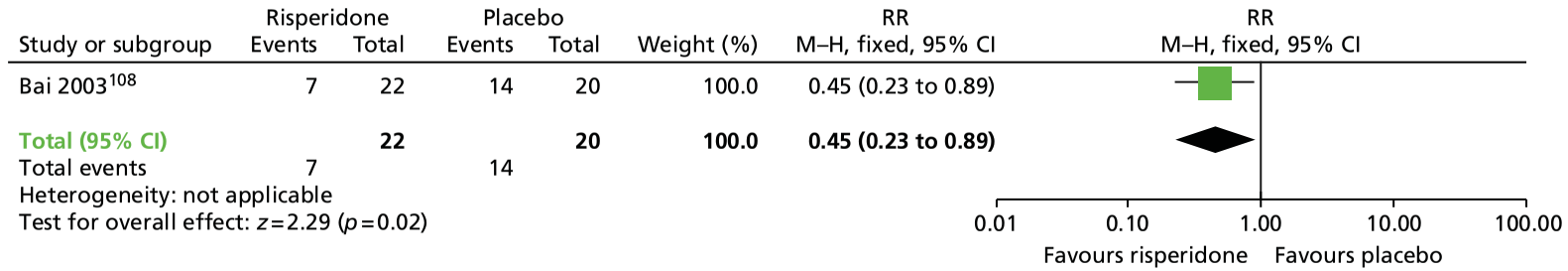

FIGURE 27 Antipsychotic switch vs. withdrawal: forest plot for the outcome 'TD: no clinically important improvement' (follow-up 12 weeks). M–H, Mantel–Haenszel.

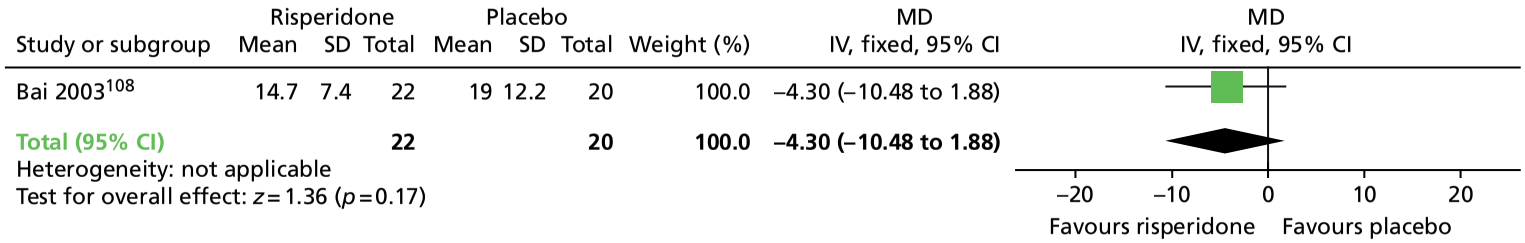

FIGURE 28 Antipsychotic switch vs. withdrawal: forest plot for the outcome 'general mental state – average end-point score (BPRS, high score means worse outcome)' (follow-up 12 weeks). IV, inverse variance.

Study or subgroup	Risperidone/haloperidol Events	Total	Placebo Events	Total	Weight (%)	RR IV, fixed, 95% CI
Haloperidol						
[a]Chouinard 1993[102,103]	4	6	2	6	66.8	2.00 (0.56 to 7.09)
Subtotal (95% CI)		**6**		**6**	**66.8**	**2.00 (0.56 to 7.09)**
Total events	4		2			
Heterogeneity: not applicable						
Test for overall effect: $z = 1.07$ ($p = 0.28$)						
Risperidone						
[a]Chouinard 1993[102,103]	14	31	1	5	33.2	2.26 (0.37 to 13.60)
Subtotal (95% CI)		**31**		**5**	**33.2**	**2.26 (0.37 to 13.60)**
Total events	14		1			
Heterogeneity: not applicable						
Test for overall effect: $z = 0.89$ ($p = 0.37$)						
Total (95% CI)		**37**		**11**	**100.0**	**2.08 (0.74 to 5.86)**
Total events	18		3			
Heterogeneity: $\chi^2 = 0.01$, df = 1 ($p = 0.91$); $I^2 = 0\%$						
Test for overall effect: $z = 1.39$ ($p = 0.16$)						
Test for subgroup differences: $\chi^2 = 0.01$, df = 1 ($p = 0.91$); $I^2 = 0\%$						

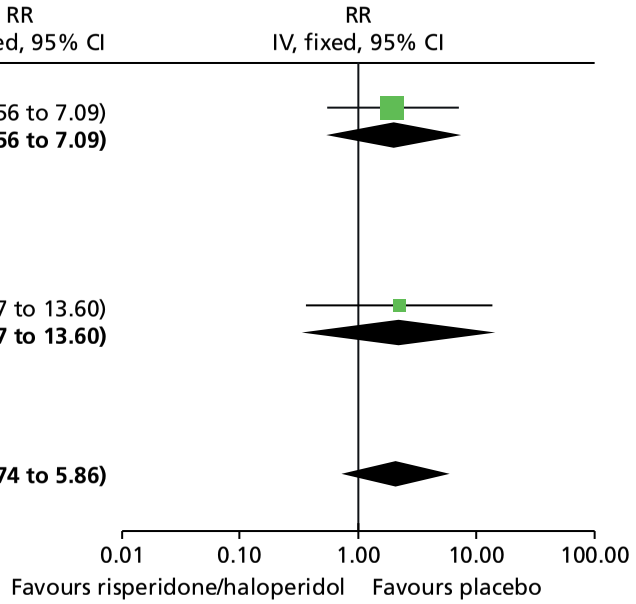

FIGURE 29 Antipsychotic switch vs. withdrawal: forest plot for the outcome 'adverse events – need of antiparkinsonism drugs' (follow-up 8–12 weeks). df, degrees of freedom; IV, inverse variance. a, Split placebo group.

Study or subgroup	Risperidone Events	Total	Placebo Events	Total	Weight (%)	RR IV, fixed, 95% CI
Bai 2003[108]	3	25	5	25	100.0	0.60 (0.16 to 2.25)
Total (95% CI)		**25**		**25**	**100.0**	**0.60 (0.16 to 2.25)**
Total events	3		5			
Heterogeneity: not applicable						
Test for overall effect: $z = 0.76$ ($p = 0.45$)						

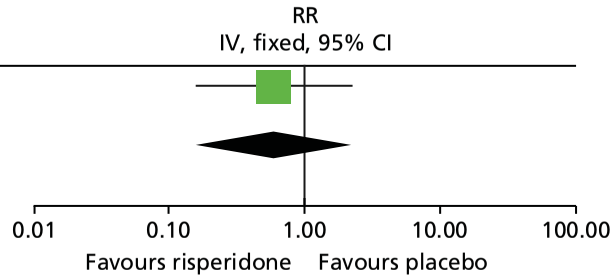

FIGURE 30 Antipsychotic switch vs. withdrawal: forest plot for the outcome 'leaving the study early' (follow-up 12 weeks). IV, inverse variance.

Switch to second-generation antipsychotic versus switch to first-generation antipsychotic

Figures 31–35 present forest plots of outcome analyses for switch to SGA versus switch to FGA.

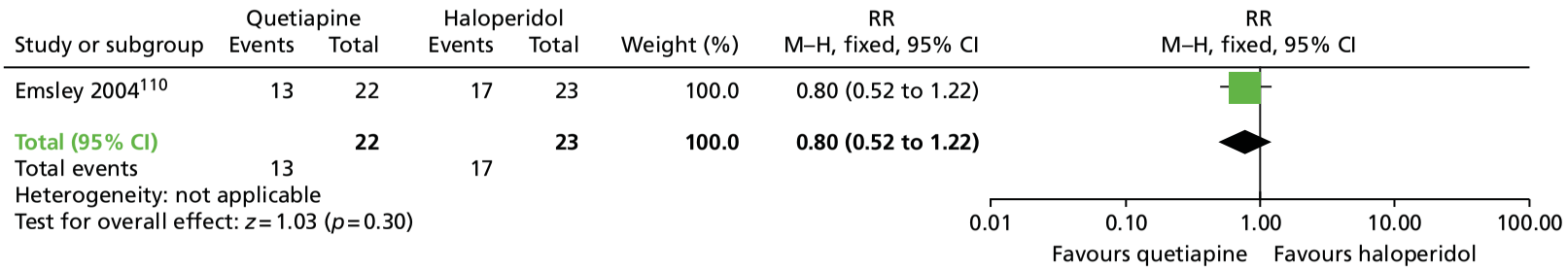

FIGURE 31 Switch to SGA vs. switch to FGA: forest plot for the outcome 'TD – no clinically important improvement' (follow-up 6 months). M–H, Mantel–Haenszel.

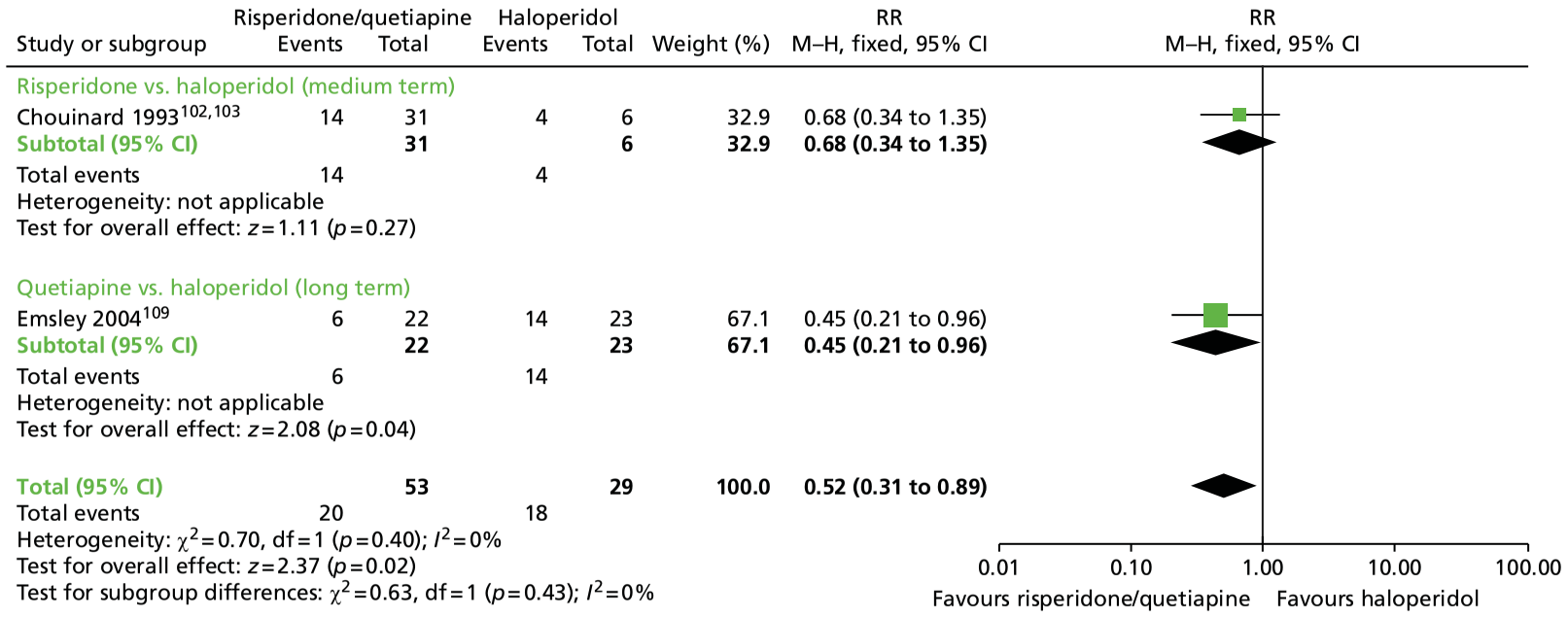

FIGURE 32 Switch to SGA vs. switch to FGA: forest plot for the outcome 'adverse events – need of antiparkinsonism drugs' (follow-up 1 year). df, degrees of freedom; M–H, Mantel–Haenszel.

Study or subgroup	OLZ/ASP Mean	SD	Total	FGA Mean	SD	Total	Weight (%)	MD IV, fixed, 95% CI
Olanzapine vs. FGA								
Bai 2005[112]	−0.96	3.24	27	−1.04	3.9	26	100.0	0.08 (−1.85 to 2.01)
Subtotal (95% CI)			**27**			**26**	**100.0**	**0.08 (−1.85 to 2.01)**
Heterogeneity: not applicable								
Test for overall effect: $z = 0.08$ ($p = 0.94$)								
Amisulpiride vs. FGA								
Bai 2005[112]	−1.59	2.55	27	−1.04	3.9	26	100.0	−0.55 (−2.33 to 1.23)
Subtotal (95% CI)			**27**			**26**	**100.0**	**−0.55 (−2.33 to 1.23)**
Heterogeneity: not applicable								
Test for overall effect: $z = 0.61$ ($p = 0.55$)								

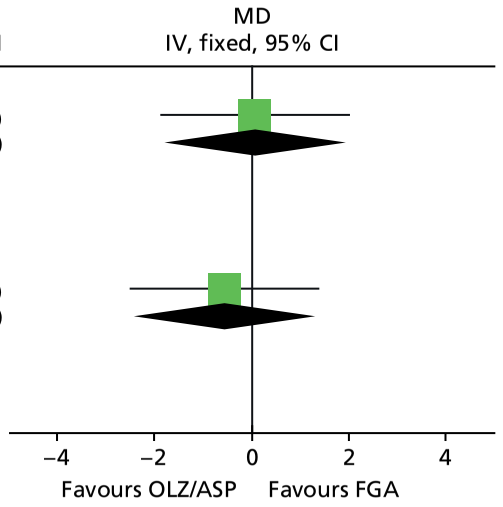

FIGURE 33 Switch to SGA vs. switch to FGA: forest plot for the outcome 'adverse events: general – average change scores (UKU, high score means worse outcome)' (follow-up 6 months). ASP, amisulpride; IV, inverse variance; OLZ, olanzapine; SD, standard deviation.

Study or subgroup	Quetiapine Events	Total	Haloperidol Events	Total	Weight (%)	RR M–H, fixed, 95% CI
Emsley 2004[110]	7	22	4	23	100.0	1.83 (0.62 to 5.39)
Total (95% CI)		**22**		**23**	**100.0**	**1.83 (0.62 to 5.39)**
Total events	7		4			
Heterogeneity: not applicable						
Test for overall effect: $z = 1.10$ ($p = 0.27$)						

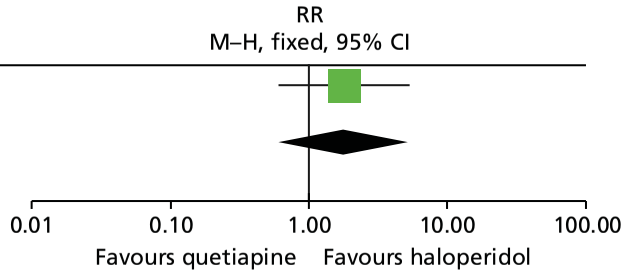

FIGURE 34 Switch to SGA vs. switch to FGA: forest plot for the outcome 'mental state – deterioration' (follow-up 1 year). M–H, Mantel–Haenszel.

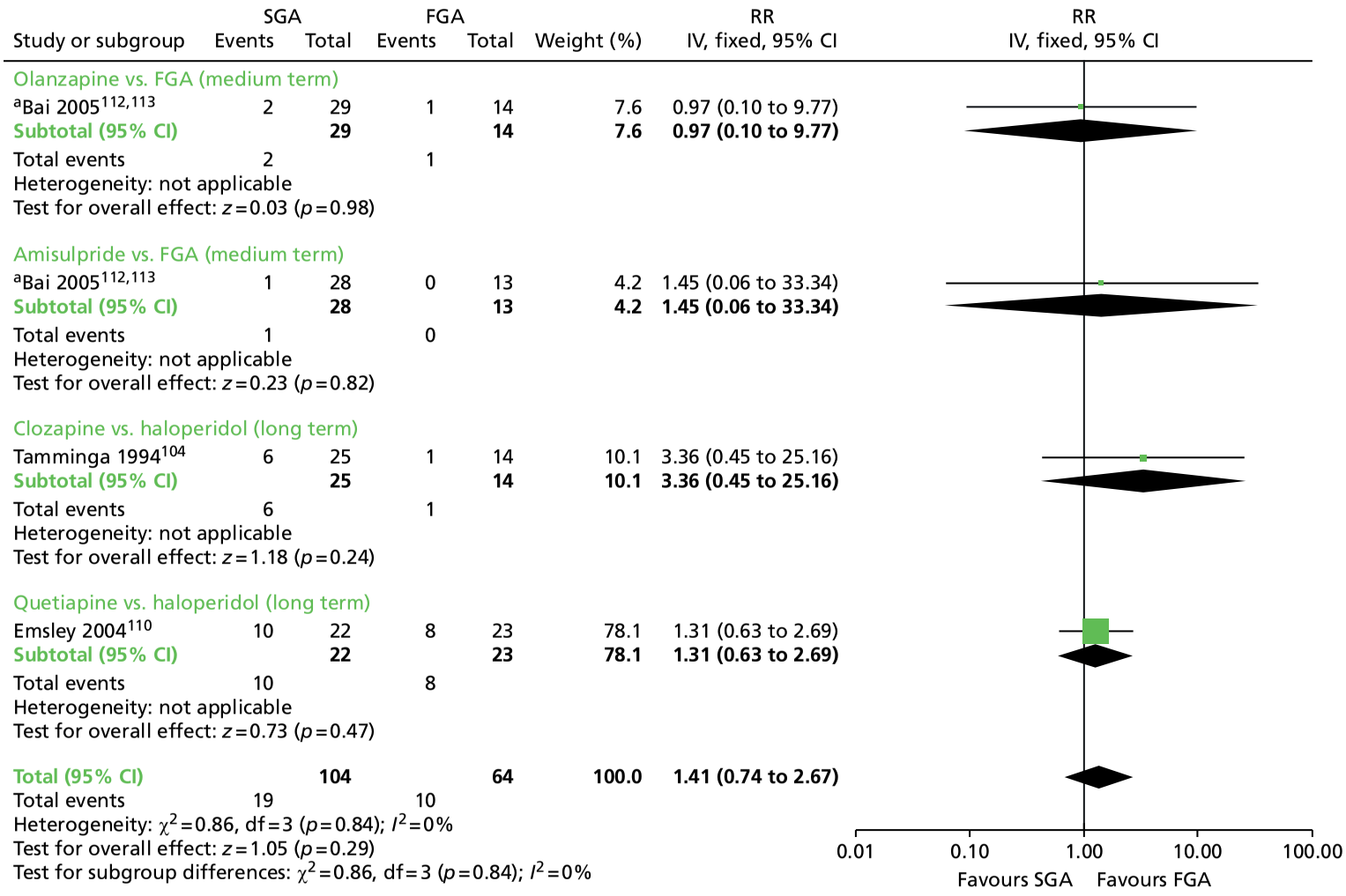

FIGURE 35 Switch to SGA vs. switch to FGA: forest plot for the outcome 'leaving the study early' – medium term (follow-up 24–52 weeks). df, degrees of freedom; IV, inverse variance. a, FGA group split.

Switch to second-generation antipsychotic versus switch to another second-generation antipsychotic

Figures 36–48 present forest plots of outcome analyses for switch to SGA versus switch to another SGA.

Olanzapine versus amisulpride

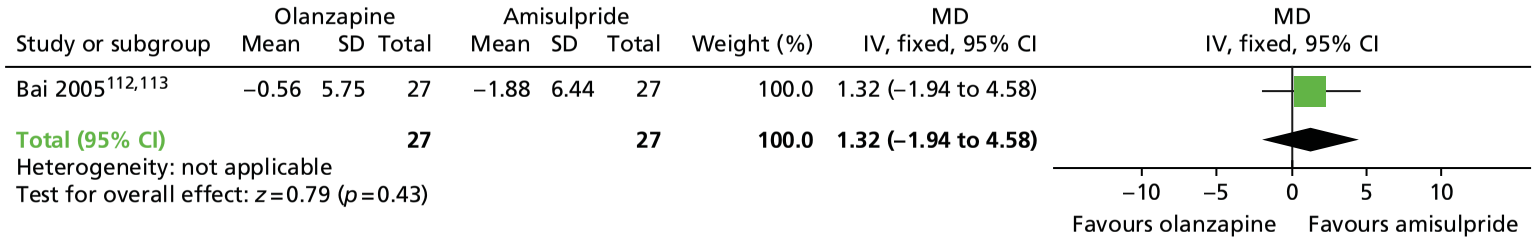

FIGURE 36 Olanzapine vs. amisulpride: forest plot for the outcome 'general mental state – average change score (BPRS, high score means worse outcome)' (follow-up 6 months). IV, inverse variance; SD, standard deviation.

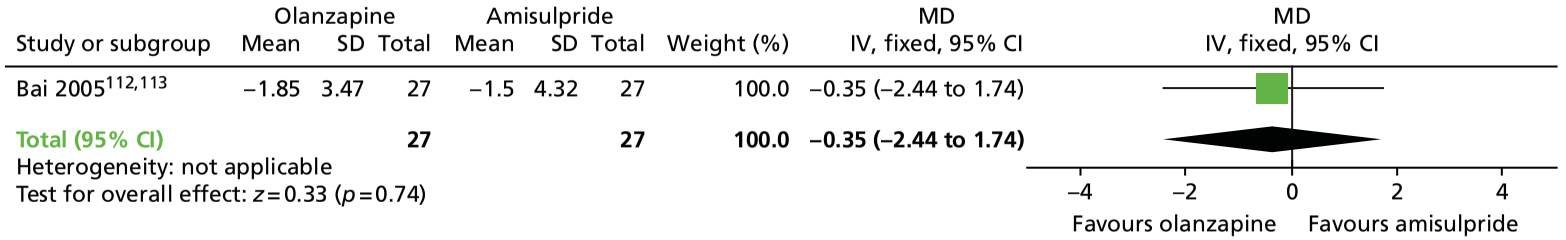

FIGURE 37 Olanzapine vs. amisulpride: forest plot for the outcome 'adverse events: parkinsonism – average change score (SAS, high score means worse outcome)' (follow-up 6 months). IV, inverse variance; SD, standard deviation.

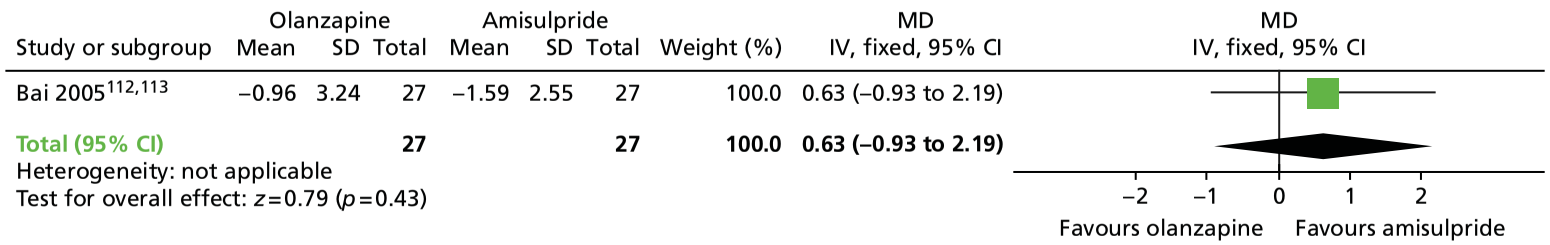

FIGURE 38 Olanzapine vs. amisulpride: forest plot for the outcome 'adverse events: general – average change scores (UKU, high score means worse outcome)' (follow-up 6 months). IV, inverse variance; SD, standard deviation.

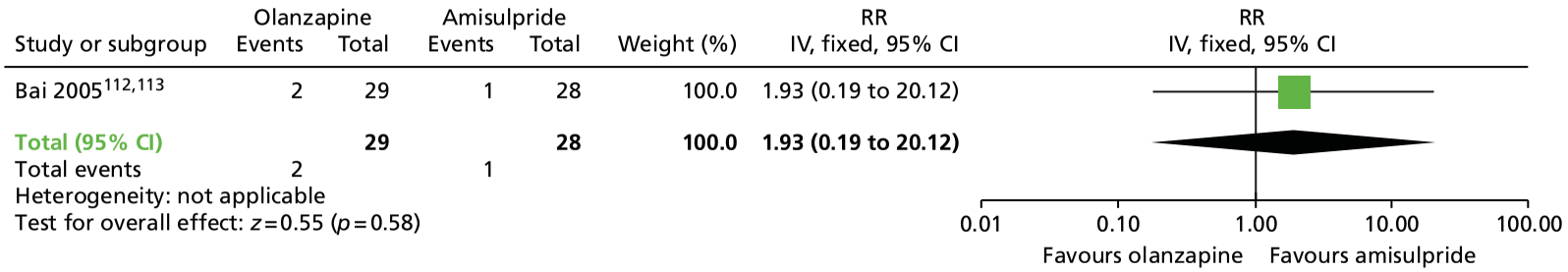

FIGURE 39 Olanzapine vs. amisulpride: forest plot for the outcome 'leaving the study early' (follow-up 6 months). IV, inverse variance.

Olanzapine versus risperidone

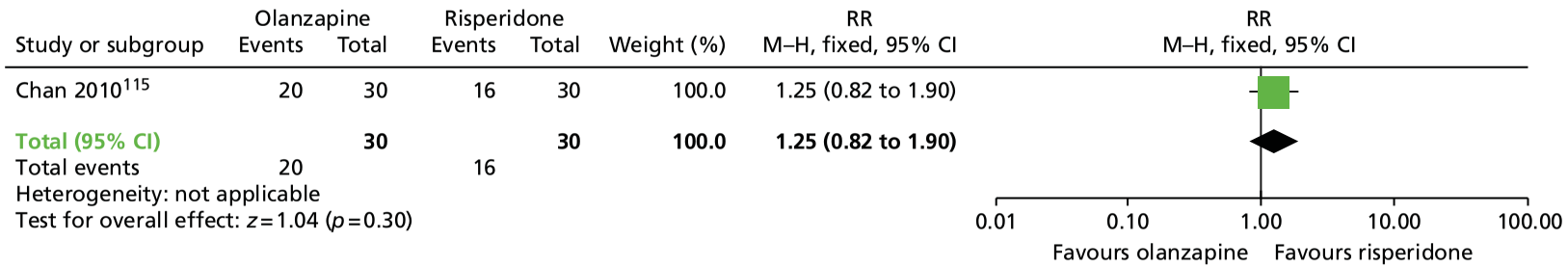

FIGURE 40 Olanzapine vs. risperidone: forest plot for the outcome 'TD – no clinically important improvement' (follow-up 6 months). M–H, Mantel–Haenszel.

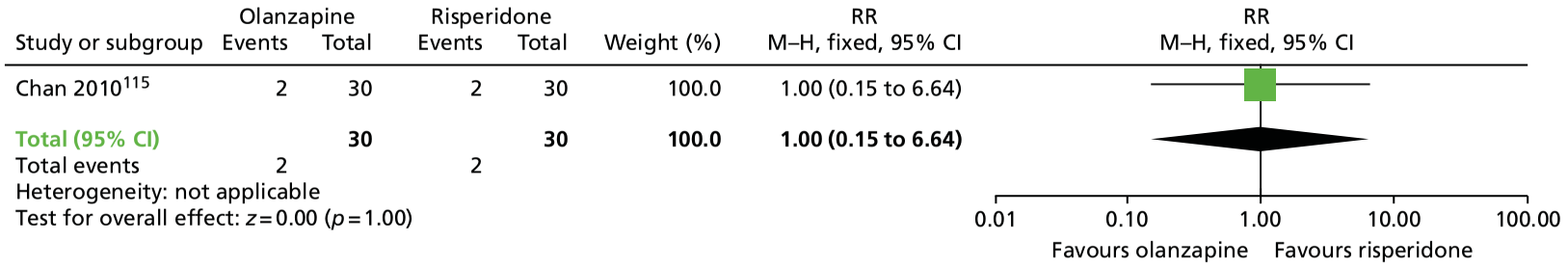

FIGURE 41 Olanzapine vs. risperidone: forest plot for the outcome 'mental state – deterioration' (follow-up 6 months). M–H, Mantel–Haenszel.

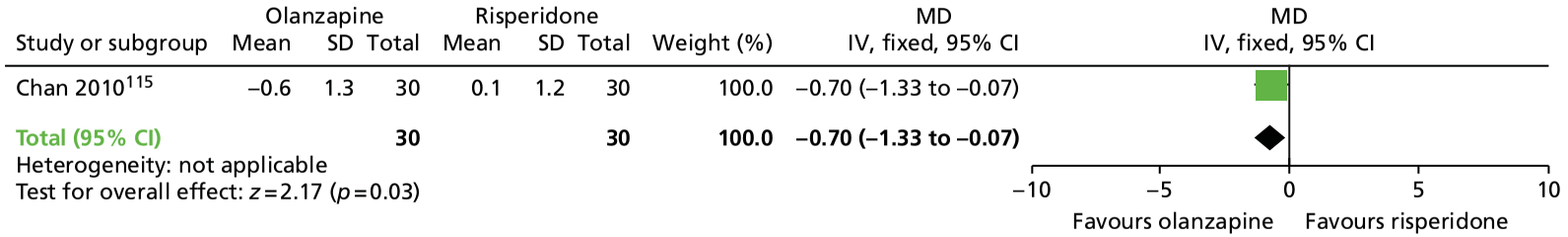

FIGURE 42 Olanzapine vs. risperidone: forest plot for the outcome 'adverse effects: parkinsonism – average change score (ESRS, high score means worse outcome)' (follow-up 6 months). IV, inverse variance; SD, standard deviation.

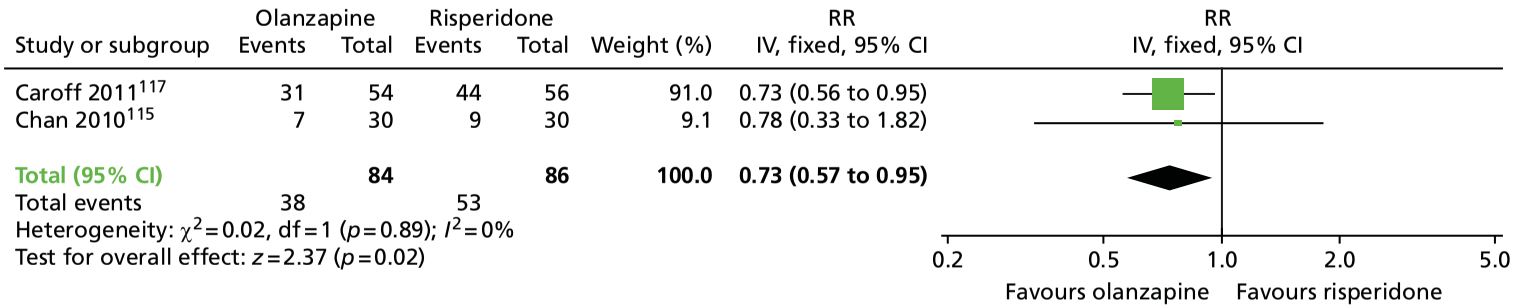

FIGURE 43 Olanzapine vs. risperidone: forest plot for the outcome 'leaving the study early' (follow-up 6–18 months). df, degrees of freedom; IV, inverse variance.

Olanzapine versus quetiapine

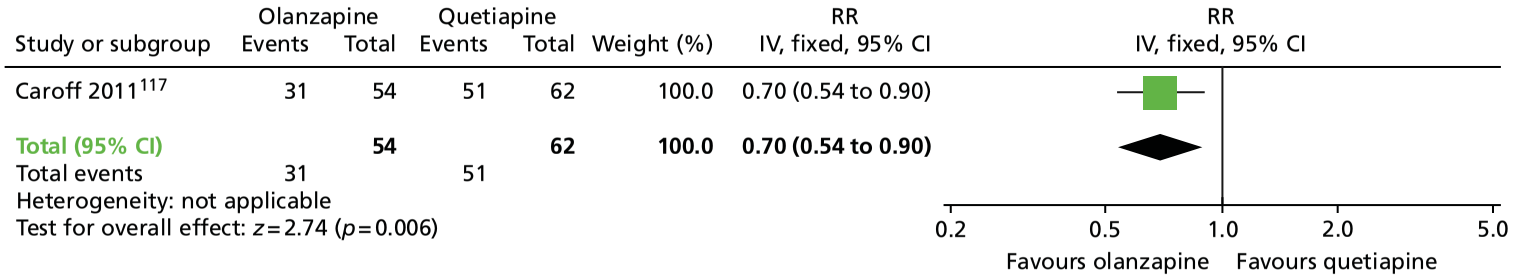

FIGURE 44 Olanzapine vs. quetiapine: forest plot for the outcome 'leaving the study early' (follow-up 18 months). IV, inverse variance.

Olanzapine versus ziprasidone

Study or subgroup	Olanzapine Events	Olanzapine Total	Ziprasidone Events	Ziprasidone Total	Weight (%)	RR IV, fixed, 95% CI
Caroff 2011[117]	31	54	21	28	100.0	0.77 (0.56 to 1.05)
Total (95% CI)		**54**		**28**	**100.0**	**0.77 (0.56 to 1.05)**
Total events	31		21			
Heterogeneity: not applicable						
Test for overall effect: $z = 1.67$ ($p = 0.10$)						

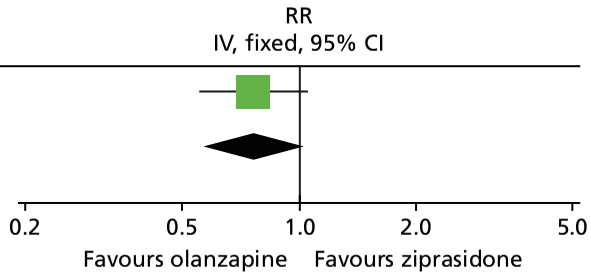

FIGURE 45 Olanzapine vs. ziprasidone: forest plot for the outcome 'leaving the study early' (follow-up 18 months). IV, inverse variance.

Quetiapine versus risperidone

Study or subgroup	Quetiapine Events	Quetiapine Total	Risperidone Events	Risperidone Total	Weight (%)	RR IV, fixed, 95% CI
Caroff 2011[117]	51	62	44	56	100.0	1.05 (0.88 to 1.25)
Total (95% CI)		**62**		**56**	**100.0**	**1.05 (0.88 to 1.25)**
Total events	51		44			
Heterogeneity: not applicable						
Test for overall effect: $z = 0.50$ ($p = 0.62$)						

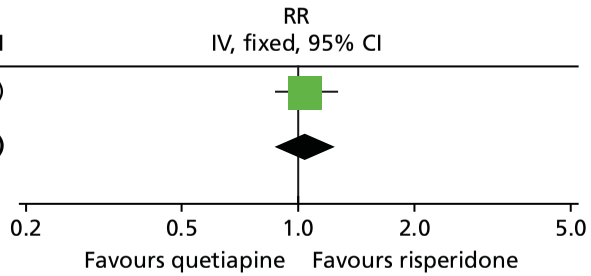

FIGURE 46 Quetiapine vs. risperidone: forest plot for the outcome 'leaving the study early' (follow-up 18 months). IV, inverse variance.

Quetiapine versus ziprasidone

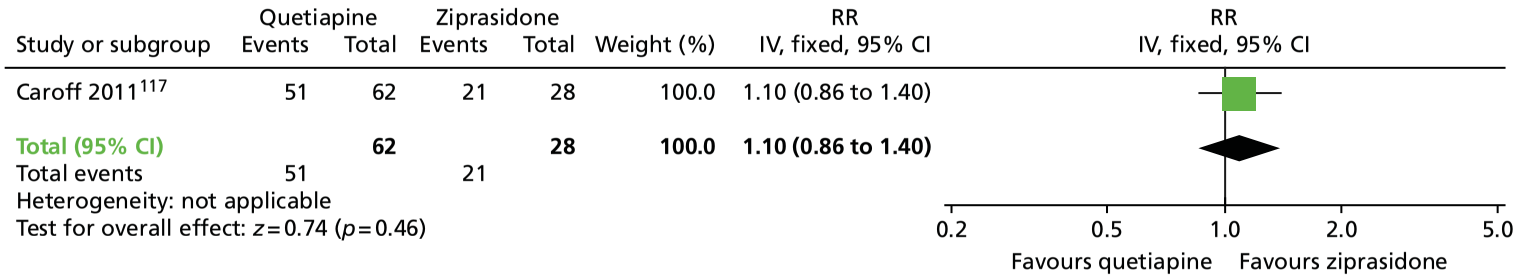

FIGURE 47 Quetiapine vs. ziprasidone: forest plot for the outcome 'leaving the study early' (follow-up 18 months). IV, inverse variance.

Ziprasidone versus risperidone

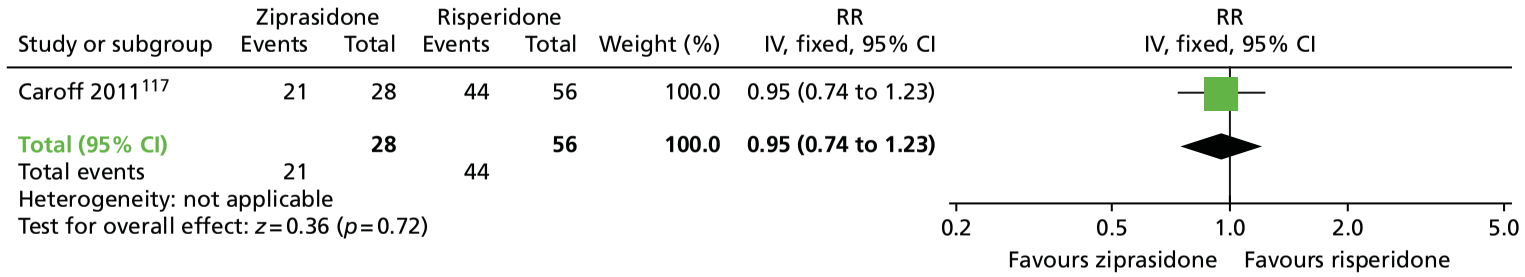

FIGURE 48 Ziprasidone vs. risperidone: forest plot for the outcome 'leaving the study early' (follow-up 18 months). IV, inverse variance.

Antipsychotic versus other drug

Haloperidol versus tetrabenazine

Figures 49–51 present forest plots of outcome analyses for haloperidol versus tetrabenazine.

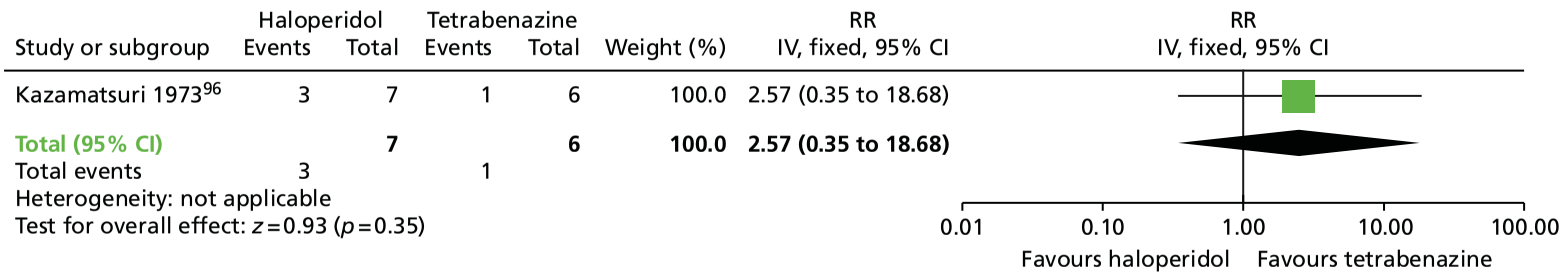

FIGURE 49 Haloperidol vs. tetrabenazine: forest plot for the outcome 'TD – no clinically important improvement' (follow-up 18 weeks). IV, inverse variance.

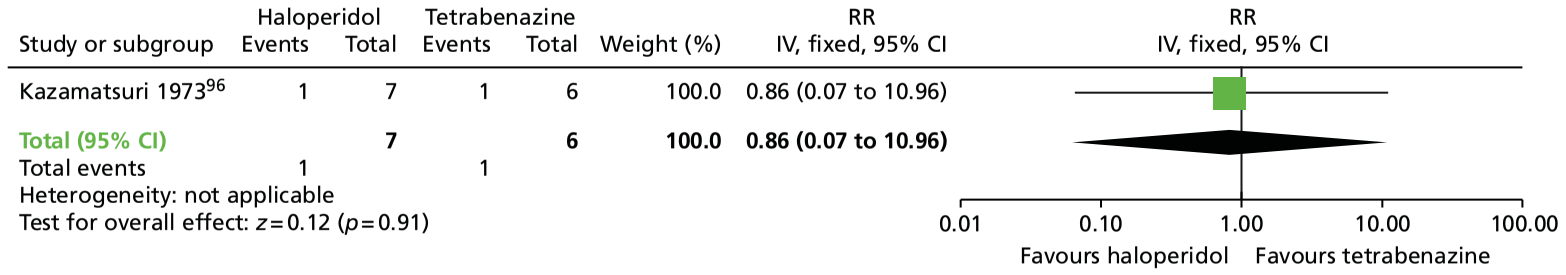

FIGURE 50 Haloperidol vs. tetrabenazine: forest plot for the outcome 'TD – deterioration' (follow-up 18 weeks). IV, inverse variance.

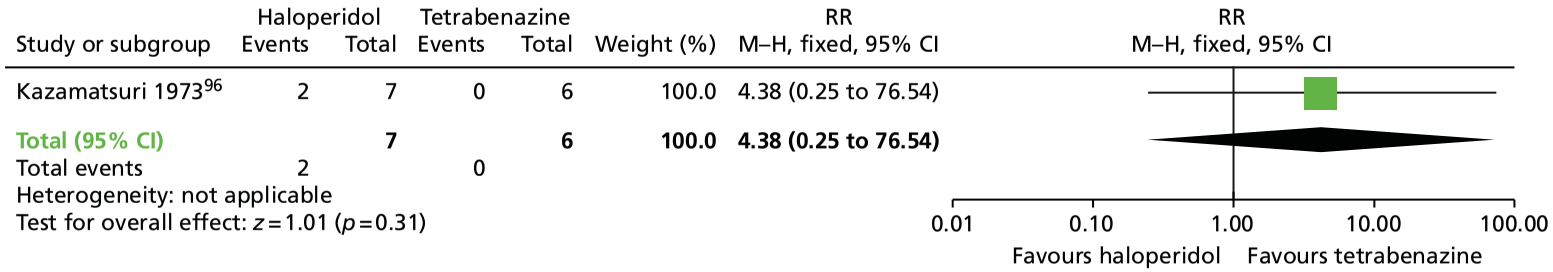

FIGURE 51 Haloperidol vs. tetrabenazine: forest plot for the outcome 'leaving the study early' (follow-up 18 weeks). M–H, Mantel–Haenszel.

Anticholinergic withdrawal versus continuation

Figure 52 presents a forest plot of outcome analysis for anticholinergic withdrawal versus continuation.

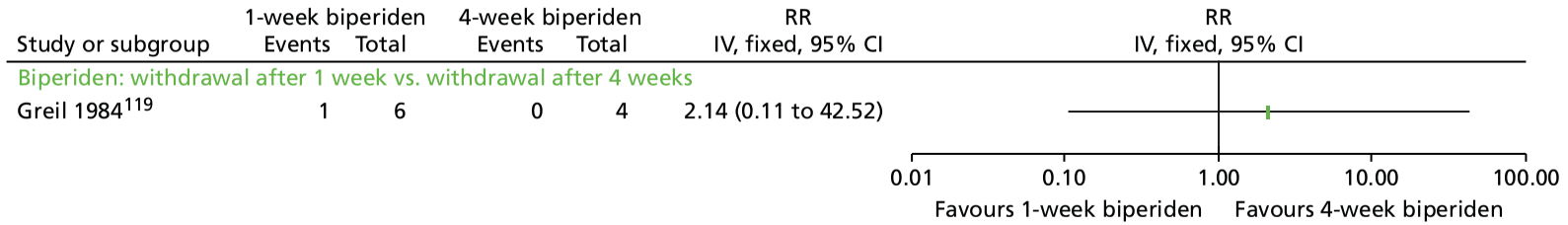

FIGURE 52 Anticholinergic withdrawal vs. continuation: forest plot for the outcome 'leaving the study early' (follow-up 7 weeks). IV, inverse variance.

Benzodiazepines versus placebo/treatment as usual

Figures 53–56 present forest plots of outcome analyses for benzodiazepines versus placebo or TAU.

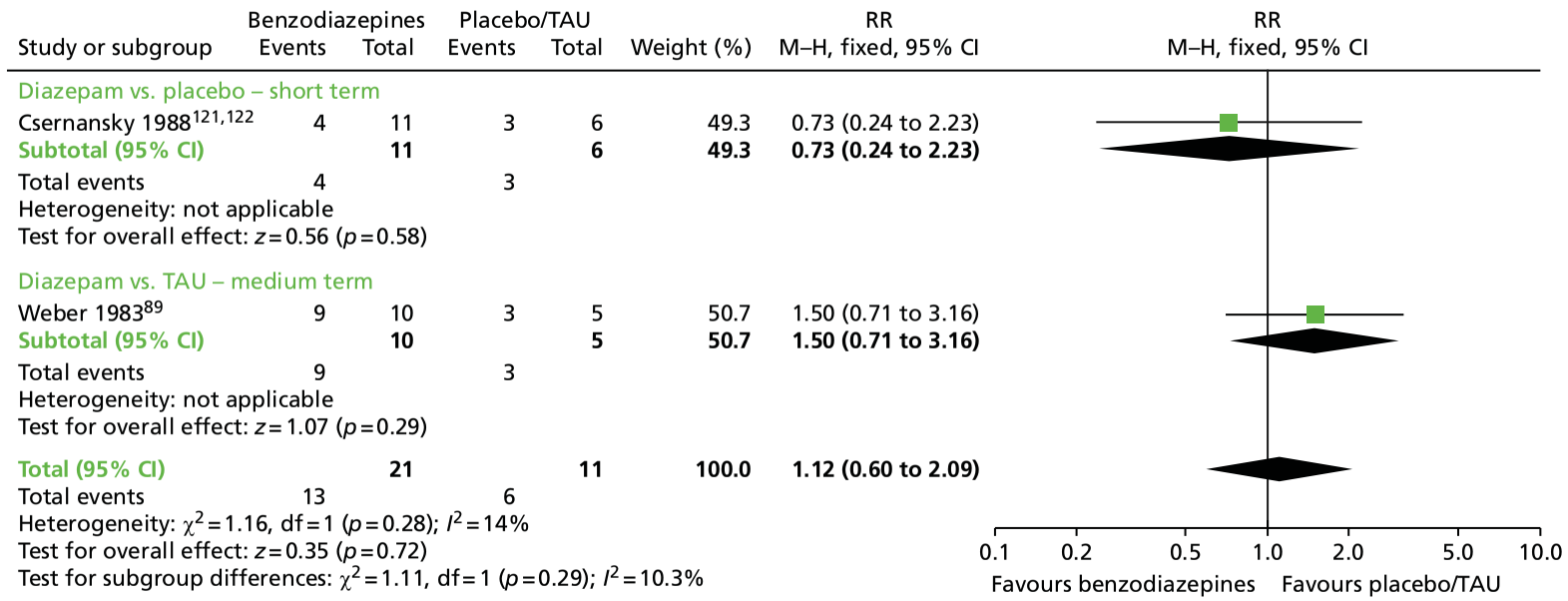

FIGURE 53 Benzodiazepines vs. placebo/TAU: forest plot for the outcome 'TD – no clinically important improvement' (follow-up 5–10 weeks). df, degrees of freedom; M–H, Mantel–Haenszel.

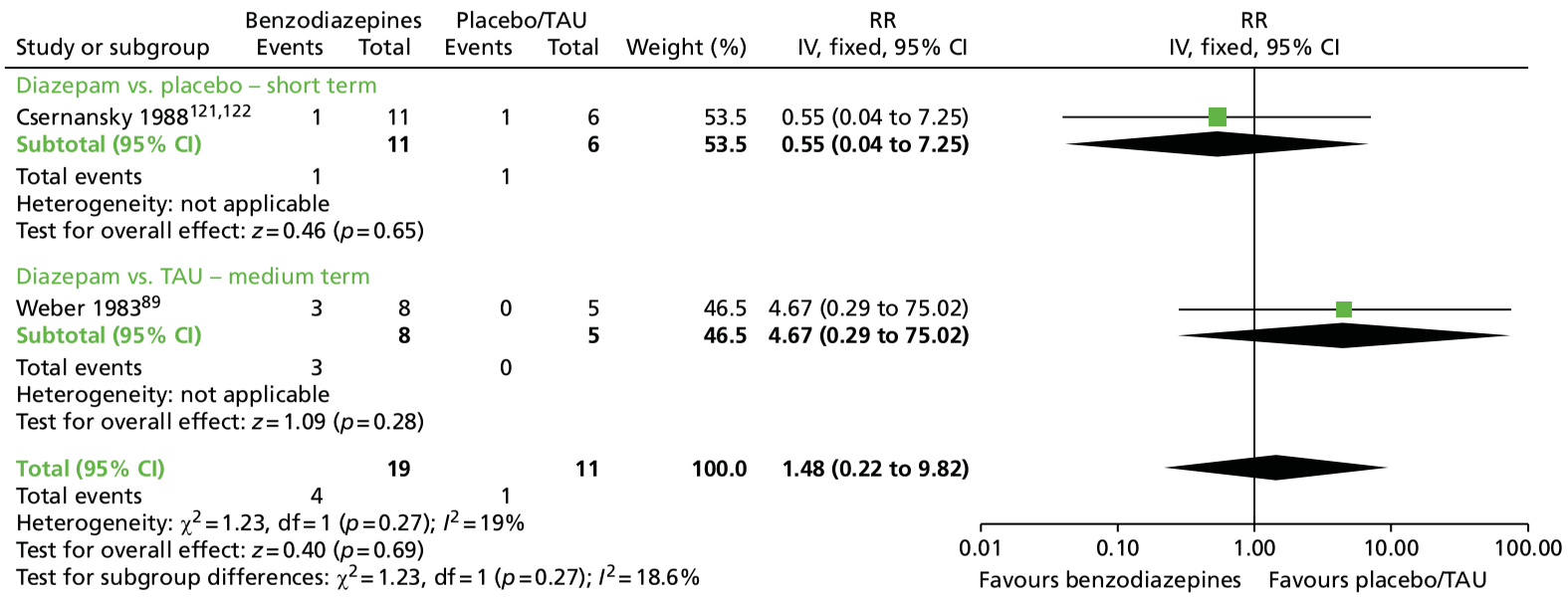

FIGURE 54 Benzodiazepines vs. placebo/TAU: forest plot for the outcome 'TD – deterioration' (follow-up 5–10 weeks). df, degrees of freedom; IV, inverse variance.

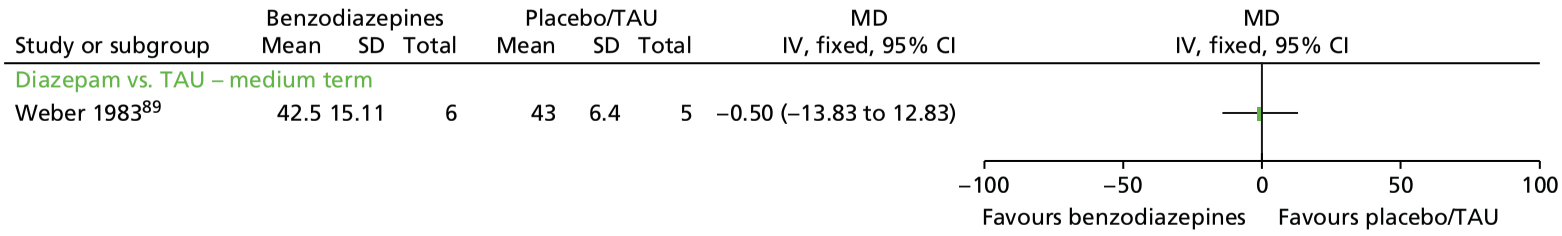

FIGURE 55 Benzodiazepines vs. placebo/TAU: forest plot for the outcome 'mental state – average end-point score (BPRS, high score means worse outcome)' (follow-up 5–10 weeks). IV, inverse variance; SD, standard deviation.

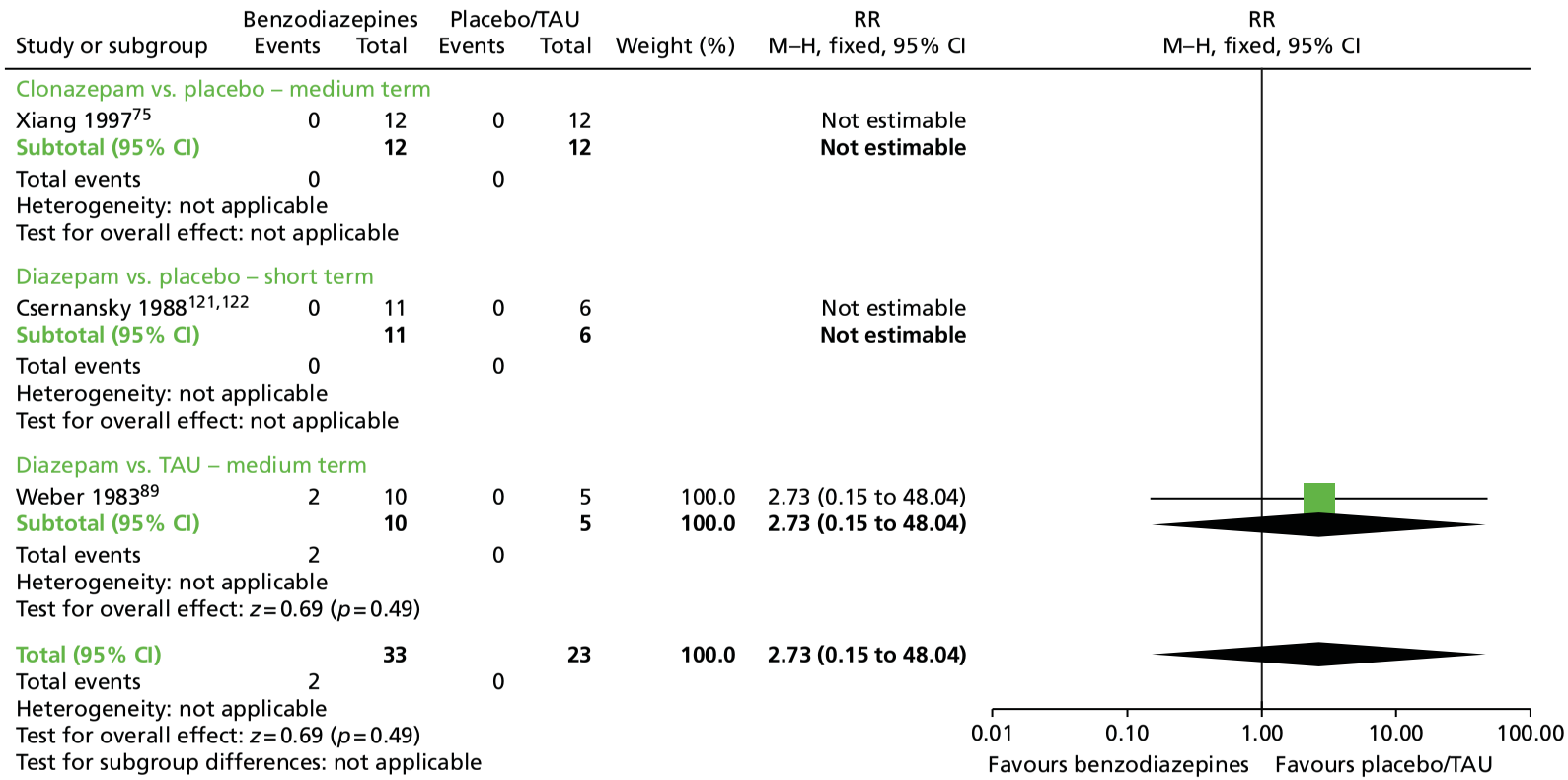

FIGURE 56 Benzodiazepines vs. placebo/TAU: forest plot for the outcome 'leaving the study early' (follow-up 5–10 weeks). M–H, Mantel–Haenszel.

Benzodiazepines versus phenobarbital (as active placebo)

Figures 57–59 present forest plots of outcome analyses for benzodiazepines versus phenobarbital (as active placebo).

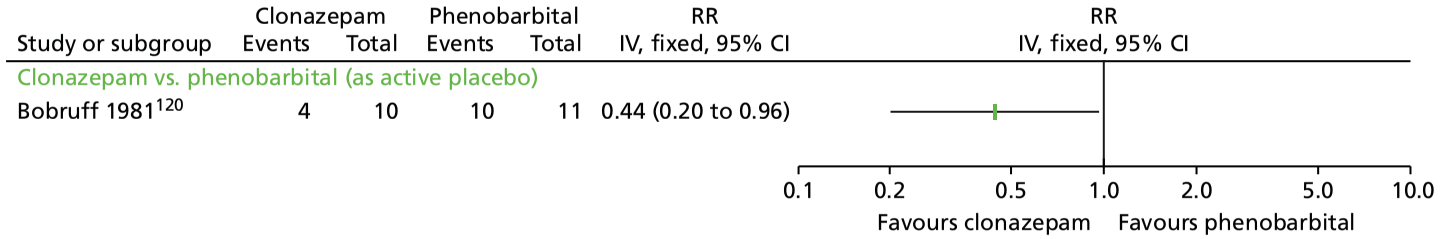

FIGURE 57 Benzodiazepines vs. phenobarbital: forest plot for the outcome 'TD – no clinically important improvement' (follow-up 2 weeks). IV, inverse variance.

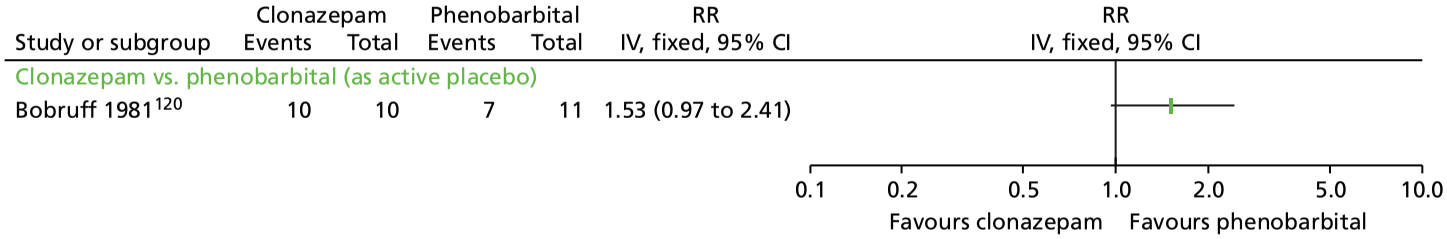

FIGURE 58 Benzodiazepines vs. phenobarbital: forest plot for the outcome 'adverse events – short term' (follow-up 2 weeks). IV, inverse variance.

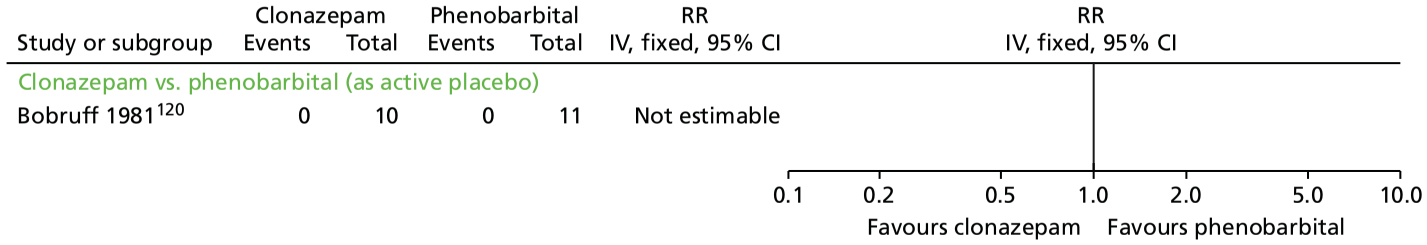

FIGURE 59 Benzodiazepines vs. phenobarbital: forest plot for the outcome 'leaving the study early' (follow-up 2 weeks). IV, inverse variance.

Vitamin E versus placebo

Figures 60–65 present forest plots of outcome analyses for vitamin E versus placebo.

Study or subgroup	Vitamin E Events	Vitamin E Total	Placebo Events	Placebo Total	Weight (%)	RR M–H, fixed, 95% CI
Short term						
Schmidt 1991[95]	12	13	10	10	9.1	0.94 (0.75 to 1.17)
Elkashef 1990[93]	5	5	5	5	4.3	1.00 (0.71 to 1.41)
Subtotal (95% CI)		**18**		**15**	**13.4**	**0.96 (0.79 to 1.15)**
Total events	17		15			
Heterogeneity: $\chi^2 = 0.10$, df = 1 ($p = 0.75$); $I^2 = 0\%$						
Test for overall effect: $z = 0.47$ ($p = 0.64$)						
Medium term						
Lam 1993[94]	8	8	8	8	6.6	1.00 (0.80 to 1.25)
Adler 1993[125,126]	20	22	14	15	13.0	0.97 (0.81 to 1.18)
Subtotal (95% CI)		**30**		**23**	**19.6**	**0.98 (0.85 to 1.14)**
Total events	28		22			
Heterogeneity: $\chi^2 = 0.03$, df = 1 ($p = 0.86$); $I^2 = 0\%$						
Test for overall effect: $z = 0.23$ ($p = 0.82$)						
Long term						
Adler 1999[137]	68	73	82	85	58.9	0.97 (0.90 to 1.04)
Sajjad 1998[130]	8	11	9	9	8.1	0.75 (0.50 to 1.10)
Subtotal (95% CI)		**84**		**94**	**67.0**	**0.94 (0.87 to 1.02)**
Total events	76		91			
Heterogeneity: $\chi^2 = 1.88$, df = 1 ($p = 0.17$); $I^2 = 47\%$						
Test for overall effect: $z = 1.57$ ($p = 0.12$)						
Total (95% CI)		**132**		**132**	**100.0**	**0.95 (0.89 to 1.01)**
Total events	121		128			
Heterogeneity: $\chi^2 = 2.04$, df = 5 ($p = 0.84$); $I^2 = 0\%$						
Test for overall effect: $z = 1.55$ ($p = 0.12$)						
Test for subgroup differences: $\chi^2 = 0.29$, df = 2 ($p = 0.86$); $I^2 = 0\%$						

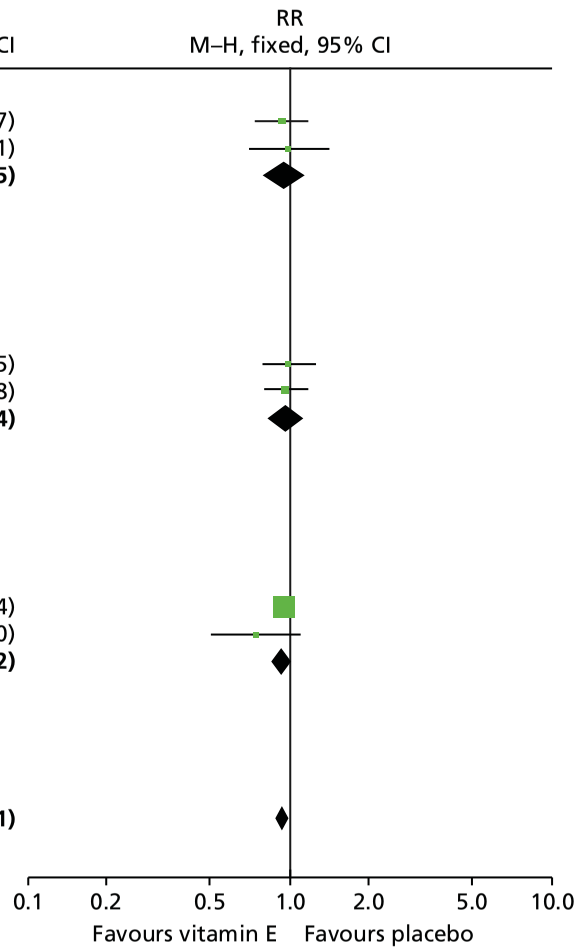

FIGURE 60 Vitamin E vs. placebo: forest plot for the outcome 'TD – no clinically important improvement' (follow-up up to 1 year). df, degrees of freedom; M–H, Mantel–Haenszel.

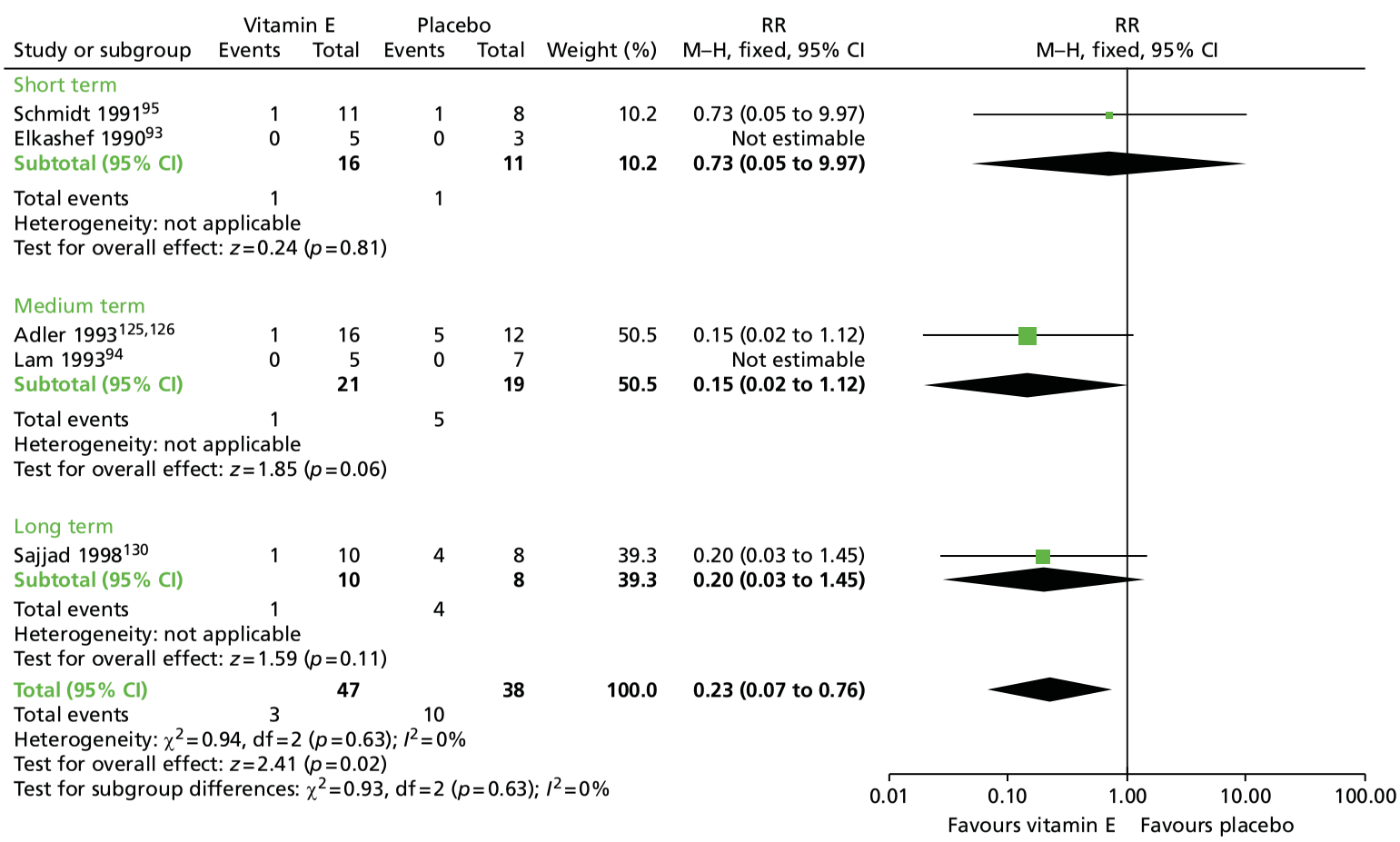

FIGURE 61 Vitamin E vs. placebo: forest plot for the outcome 'TD – deterioration of symptoms' (follow-up up to 1 year). df, degrees of freedom; M–H, Mantel–Haenszel.

Study or subgroup	Vitamin E Mean	Vitamin E SD	Vitamin E Total	Placebo Mean	Placebo SD	Placebo Total	Weight (%)	MD IV, fixed, 95% CI
Adler 1999[137]	6	5.4	49	4.9	5.6	55		1.10 (–1.02 to 3.22)

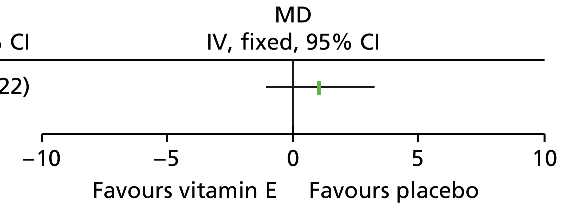

FIGURE 62 Vitamin E vs. placebo: forest plot for the outcome 'adverse events: extrapyramidal adverse events – long term (SAS, high score means worse outcome)' (follow-up up to 1 year). IV, inverse variance; SD, standard deviation.

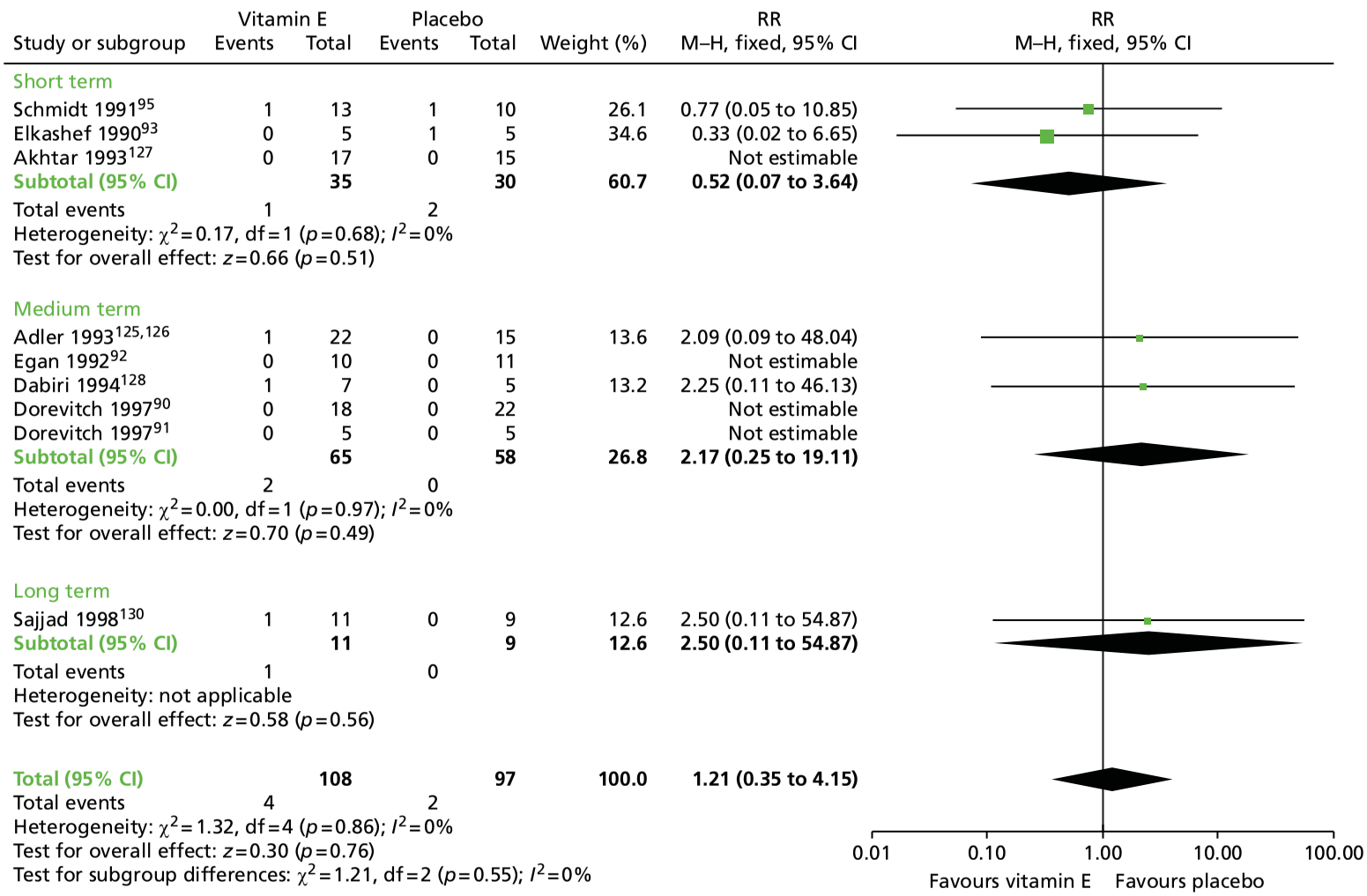

FIGURE 63 Vitamin E vs. placebo: forest plot for the outcome 'any adverse effect' (follow-up up to 1 year). df, degrees of freedom; M–H, Mantel–Haenszel.

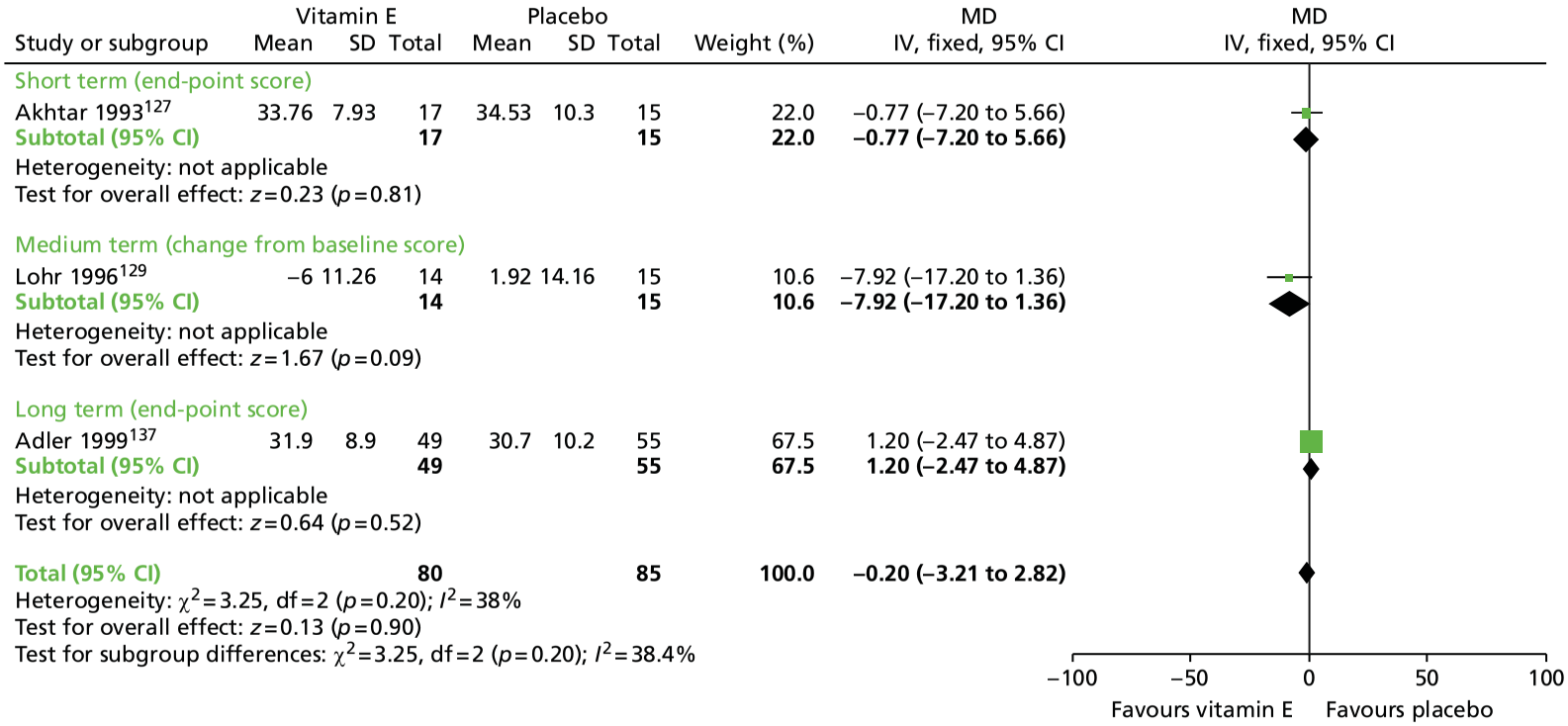

FIGURE 64 Vitamin E vs. placebo: forest plot for the outcome 'mental state – Average score (BPRS, high score means worse outcome)' (follow-up up to 1 year). df, degrees of freedom; IV, inverse variance; SD, standard deviation.

Study or subgroup	Vitamin E Events	Total	Placebo Events	Total	Weight (%)	RR M–H, fixed, 95% CI
Short term						
Schmidt 1991[95]	2	13	2	10	47.5	0.77 (0.13 to 4.55)
Elkashef 1990[93]	0	5	2	5	52.5	0.20 (0.01 to 3.35)
Akhtar 1993[127]	0	17	0	15		Not estimable
Subtotal (95% CI)		**35**		**30**	**100.0**	**0.47 (0.11 to 2.00)**
Total events	2		4			
Heterogeneity: $\chi^2 = 0.65$, df = 1 ($p = 0.42$); $I^2 = 0\%$						
Test for overall effect: $z = 1.02$ ($p = 0.31$)						
Medium term						
Adler 1993[125,126]	7	22	4	15	23.4	1.19 (0.42 to 3.37)
Egan 1992[92]	1	10	2	11	9.4	0.55 (0.06 to 5.18)
Lam 1994[94]	3	8	1	8	4.9	3.00 (0.39 to 23.07)
Dorevitch 1997[90]	0	18	2	22	11.1	0.24 (0.01 to 4.74)
Zhang 2004[138]	0	22	0	19		Not estimable
Lohr 2004[129]	10	27	10	28	48.3	1.04 (0.52 to 2.09)
Dorevitch 1997[91]	0	5	0	5		Not estimable
Dabiri 1994[128]	1	7	0	5	2.8	2.25 (0.11 to 46.13)
Subtotal (95% CI)		**119**		**113**	**100.0**	**1.07 (0.64 to 1.80)**
Total events	22		19			
Heterogeneity: $\chi^2 = 2.56$, df = 5 ($p = 0.77$); $I^2 = 0\%$						
Test for overall effect: $z = 0.26$ ($p = 0.80$)						
Long term						
Adler 1993[125,126]	7	22	5	15	17.0	0.95 (0.37 to 2.45)
Adler 1999[137]	22	73	29	85	76.7	0.88 (0.56 to 1.40)
Sajjad 1998[130]	6	11	2	9	6.3	2.45 (0.65 to 9.34)
Subtotal (95% CI)		**106**		**109**	**100.0**	**0.99 (0.67 to 1.47)**
Total events	35		36			
Heterogeneity: $\chi^2 = 2.02$, df = 2 ($p = 0.36$); $I^2 = 1\%$						
Test for overall effect: $z = 0.03$ ($p = 0.98$)						

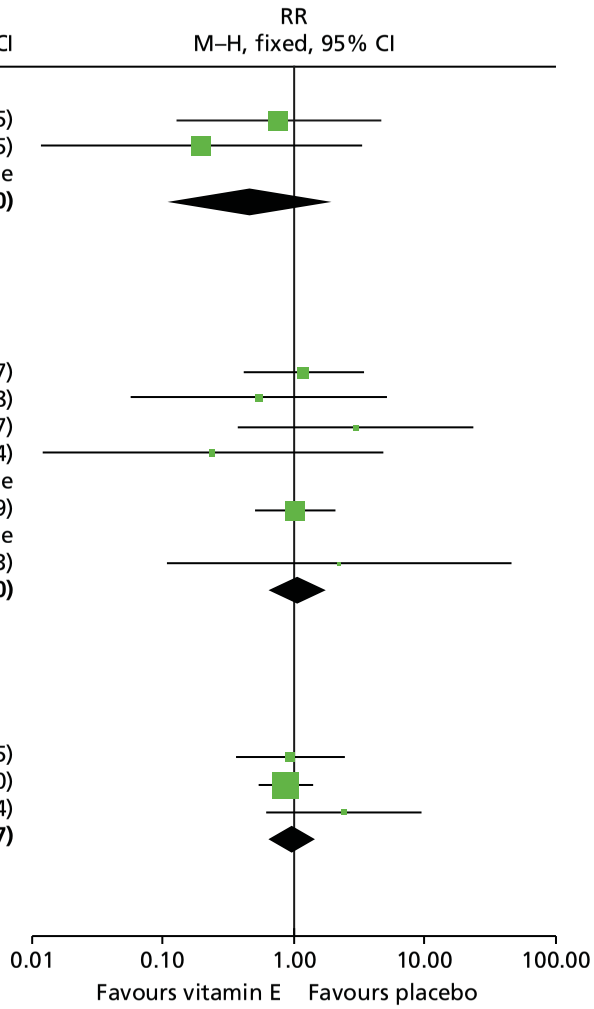

FIGURE 65 Vitamin E vs. placebo: forest plot for the outcome 'leaving the study early' (follow-up up to 1 year). df, degrees of freedom; M–H, Mantel–Haenszel.

Buspirone versus placebo

Figures 66 and *67* present forest plots of outcome analyses for buspirone versus placebo.

Study or subgroup	Buspirone Events	Total	Placebo Events	Total	Weight (%)	RR M–H, fixed, 95% CI
Zeng 1995[78]	10	21	19	21	100.0	0.53 (0.33 to 0.84)
Total (95% CI)		**21**		**21**	**100.0**	**0.53 (0.33 to 0.84)**
Total events	10		19			
Heterogeneity: not applicable						
Test for overall effect: $z = 2.68$ ($p = 0.007$)						

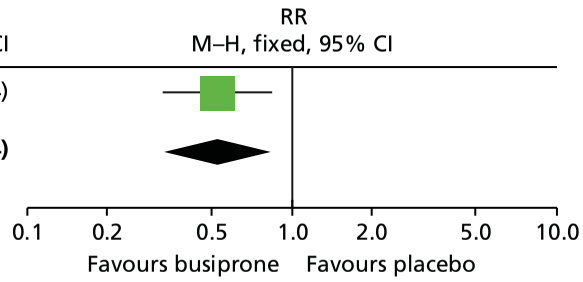

FIGURE 66 Buspirone vs. placebo: forest plot for the outcome 'TD – no clinically important improvement' (follow-up 6 weeks). M–H, Mantel–Haenszel.

Study or subgroup	Buspirone Events	Total	Placebo Events	Total	Weight (%)	RR M–H, fixed, 95% CI
Zeng 1995[78]	0	21	0	21		Not estimable
Total (95% CI)		**21**		**21**		**Not estimable**
Total events	0		0			
Heterogeneity: not applicable						
Test for overall effect: not applicable						

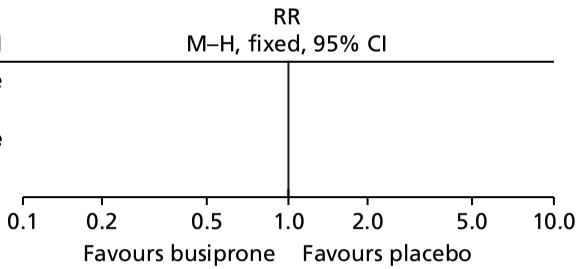

FIGURE 67 Buspirone vs. placebo: forest plot for the outcome 'leaving the study early' (follow-up 6 weeks). M–H, Mantel–Haenszel.

Hypnosis or relaxation versus treatment as usual

Figures 68–70 present forest plots of outcome analyses for hypnosis or relaxation versus TAU.

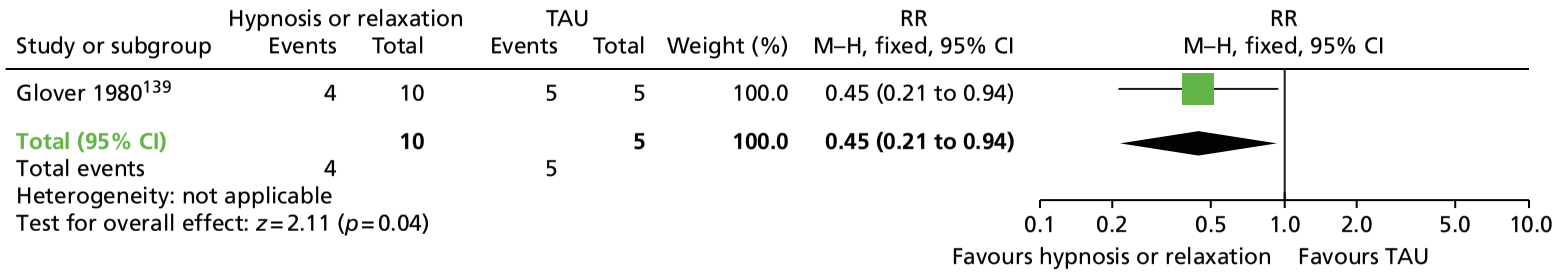

FIGURE 68 Hypnosis or relaxation vs. TAU: forest plot for the outcome 'TD – no clinically important improvement' (follow-up eight sessions). M–H, Mantel–Haenszel.

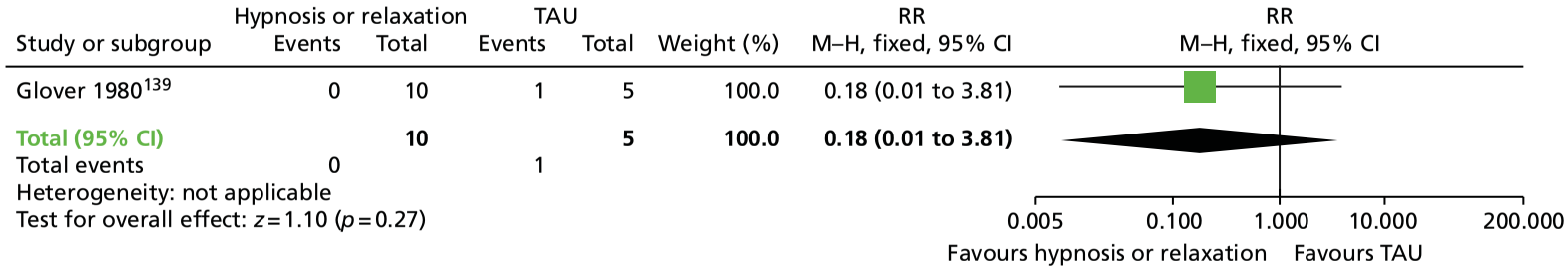

FIGURE 69 Hypnosis or relaxation vs. TAU: forest plot for the outcome 'TD – deterioration' (follow-up eight sessions). M–H, Mantel–Haenszel.

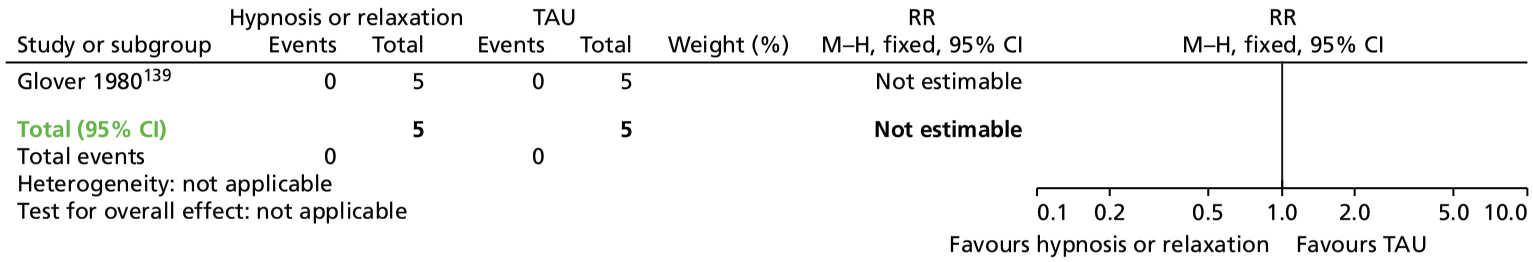

FIGURE 70 Hypnosis or relaxation vs. TAU: forest plot for the outcome 'leaving the study early' (follow-up eight sessions). M–H, Mantel–Haenszel.

EME
HS&DR
HTA
PGfAR
PHR

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