Cholinergic medication for neuroleptic-induced tardive dyskinesia (Review)

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[Intervention Review]

Cholinergic medication for neuroleptic-induced tardive dyskinesia

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ABSTRACT

Background

Tardive dyskinesia remains a troublesome adverse effect of conventional antipsychotic (neuroleptic) medication. It has been proposed that tardive dyskinesia could have a component of central cholinergic deficiency. Cholinergic drugs have been used to treat tardive dyskinesia.

Objectives

To determine the effects of cholinergic drugs (arecoline, choline, deanol, lecithin, meclofenoxate, physostigmine, RS 86, tacrine, metoxytacrine, galantamine, ipidacrine, donepezil, rivastigmine, eptastigmine, metrifonate, xanomeline, cevimeline) for treating neuroleptic-induced tardive dyskinesia in people with schizophrenia or other chronic mental illness.

Search methods

An electronic search of the Cochrane Schizophrenia Group's register (October 2001) was undertaken. This register is assembled by extensive searches for randomised controlled trials in many electronic databases, registers of conference proceedings and dissertations. References of all identified studies were searched for further trial citations. Principal authors of trials were contacted.

Selection criteria

Reports identified by the search were included if they were of controlled trials dealing with people with neuroleptic-induced tardive dyskinesia and chronic mental illness, who had been randomly allocated to either a cholinergic agent or to a placebo or no intervention. Two reviewers independently assessed methodological quality of trials.

Data collection and analysis

Two researchers extracted data and, where possible, estimated relative risks (RR) or weighted mean differences (WMD), with 95% confidence intervals (CI). Data were analysed on an intention-to-treat basis, with the assumption that people who dropped out had no improvement.

Main results

We included eleven studies investigating the use of older cholinergic drugs compared with placebo. Most studies involved small numbers of participants (5-20 people). We found no completed trials of the new cholinergic Alzheimer drugs for the treatment of tardive dyskinesia.

Cholinergic drugs did not result in any substantial improvement in tardive dyskinesia symptoms when compared with placebo (8 RCTs, 170 people, RR no important improvement 0.84 CI 0.68 to 1.04). Neither did tardive dyskinesia symptoms increase (7 RCTs, 137 people, RR deterioration in tardive dyskinesia 1.17 CI 0.55 to 2.50). Pooled results for endpoint AIMS scores were equivocal (4 RCTs, 86 people, WMD -0.19 CI -0.53 to 0.14). Deanol may cause gastric adverse effects (5 RCTs, 61 people, RR 9.00 CI 0.55-148) and other adverse effects such as sedation and peripheral cholinergic effects (6 RCTs, 94 people, RR 6.83 CI 0.99-47). One study reported on global outcome. Meclofenoxate was neither clearly helpful nor harmful when compared with placebo (1 RCT, 60 people, RR not of global benefit 0.89 CI 0.59 to 1.32). We found no difference between people allocated cholinergics and those given placebo for the outcome of leaving the study before completion (10 RCTs, 240 people, RR 0.52 CI 0.21 to 1.33).

Authors' conclusions

Tardive dyskinesia remains a major public health problem. The clinical effects of older cholinergic drugs are unclear, as too few, too small studies leave many questions unanswered. Cholinergic drugs should remain of interest to researchers and currently have little place in routine clinical work. However, with the advent of new cholinergic agents now used for treating Alzheimer's disease, scope exists for more informative trials. If these new cholinergic agents are to be investigated for treating people with tardive dyskinesia, their effects should be demonstrated in well-designed, conducted and reported randomised trials.

PLAIN LANGUAGE SUMMARY

Cholinergic medication for neuroleptic-induced tardive dyskinesia

Drug-induced tardive dyskinesia is a common adverse effect of some antipsychotics, especially when these are given for an extended period of time. Tardive dyskinesia consists of involuntary repetitive movements, mainly in the oral region, but sometimes also in the limbs. It may become persistent. Cholinergic drugs, such as deanol, lecithin and meclofenoxate, have been used to treat tardive dyskinesia. This review did not identify any evidence to suggest that they are effective and found some to suggest that these old drugs may be toxic. New cholinergic drugs have been developed for the treatment of Alzheimer's disease, and it will be of interest to know if these drugs have an effect on the movements of tardive dyskinesia. We found one ongoing randomised trial.

BACKGROUND

Antipsychotic medication has been used extensively to treat people with chronic mental illnesses such as schizophrenia since the 1950's. These drugs can effectively control symptoms such as abnormal perceptions (hallucinations), disordered thinking and fixed false beliefs (delusions). In addition, maintenance therapy with antipsychotic drugs is associated with a reduced risk of relapses (Schooler 1993). Conventional antipsychotic (neuroleptic) medication may cause a wide range of adverse effects, including movement disorders. The appearance of these movement disorders can contribute to poor compliance with antipsychotic drug treatment (Barnes 1993).

Tardive dyskinesia is one such movement disorder and is characterised by abnormal, repetitive and involuntary movements. Tardive dyskinesia is a chronic condition of insidious onset, the severity of which spontaneously fluctuates (APA 1992). The incidence of tardive dyskinesia in patients undergoing long-standing therapy with conventional antipsychotics is estimated to be 20-50% depending on the characteristics of the population studied (Glazer 2000), elderly patients being at greater risk for developing tardive dyskinesia (Jeste 2000). The estimated annual risk of tardive dyskinesia in patients on conventional antipsychotics ranges between 4-8% per year (Glazer 2000). This disorder can result in considerable social and physical disability (Barnes 1993). A problem in tardive dyskinesia research is that spontaneous, age-related, non-neuroleptic-induced dyskinesias occur in people with schizophre-

nia (Fenton 2000). The spontaneous dyskinetic movements are more prevalent in older age and appear identical to the movements of neuroleptic-induced tardive dyskinesia (Fenton 2000).

OUTLINE OF THE SERIES OF REVIEWS

Various types of drug treatments have been evaluated for treating people with neuroleptic-induced TD. The Cochrane Library contains a series of relevant systematic reviews

1. Anticholinergics (Soares 2001a)

2. Benzodiazepines (McGrath 2001a)

3. Calcium-channel blockers (Soares 2001b)

4. Catecholaminergics (non-neuroleptic compounds that impact on the dopamine and noradrenaline systems) (Lyra da Silva 2001)

5. Cholinergics

6. GABA-ergics (Soares 2001c)

7. Neuroleptic medications (including dose reduction and cessation) (McGrath 2001c)

8. Vitamin E (Soares 2001d)

9. Compounds not otherwise classified (McGrath 2001b)

Although the most frequent cause of tardive dyskinesia is the use of neuroleptic medication, it is striking that, at least in the short term, dose reduction can lead to a temporary exacerbation in symptoms. Conversely, increasing the dose is often associated with a temporary remission. Neuroleptic drugs block certain chemical receptor sites in the brain including those related to dopamine. It is thought that long-term blockade of the dopamine receptors may lead to a change in neuronal systems related to dopaminergic neurons. An imbalance between the activity of dopamine cells and others that employ choline has been one of the main theories to explain tardive dyskinesia (Casey 1995, Alphs 1983). This theory implies that there is an over activity of dopaminergic transmission in relation to cholinergic transmission in the striatum.

The exact mechanisms of the pathophysiology of tardive dyskinesia are unknown. Many preclinical models, one of them being the dopamine receptor hypersensitivity hypothesis, have been developed to explain the underlying pathophysiology, but none has yet provided an unequivocal explanation (Casey 2000). Recent research suggests that neurotoxic and neurodegenerative processes, caused by excitotoxic mechanisms and oxidative stress, may contribute to the pathophysiology of tardive dyskinesia (Andreassen 2000, Andreassen 2001). This theory is supported by the persistent nature of the syndrome, once established. The role of cholinergic neurons is unclear, but a recent study indicates that the neurotoxic events, originally activated by the changes in dopaminergic transmission, might specifically lead to damage in cholinergic cells in striatal subregions, supporting previous hypotheses of alterations in striatal cholinergic cell activity resulting from chronic neuroleptic treatment (Grimm 2001).

This theory supports the use of cholinergic drugs for treating tardive dyskinesia. In the 1970's and -80's physostigmine, choline, lecithin and deanol were used to treat tardive dyskinesia. Meclofenoxate has been used in Japan. These compounds are thought to be either precursors or agonists to acetylcholine. The precise mechanism of action by which these cholinergic medications moderate tardive dyskinesia remains unclear and their use has been hindered by many undesirable adverse effects (undesirable body odour, sedation, lacrimation, anorexia, vomiting and diarrhoea). During the last decade many new CNS-active cholinergic compounds, predominantly acetylcholinesterase-inhibitors such as tacrine, rivastigmine and donepezil, have emerged for the treatment of Alzheimer's disease. These compounds have been used only infrequently to treat tardive dyskinesia.

OBJECTIVES

The primary objective of this review was to determine whether using cholinergic drugs is clinically effective for the treatment of neuroleptic-induced tardive dyskinesia in people with schizophrenia or other serious mental illness.

The secondary objectives were:

1. To examine whether duration of treatment has an effect on treatment response.

2. To examine whether there is difference in treatment effect for the various cholinergic compounds.

3. To examine whether treatment response differs in people with schizophrenia who are older (above 65 years) and for whom the prevalence of spontaneous dyskinesias is estimated to be higher. (This secondary objective was added in response to a comment from peer review in the first substantial up-date of the review).

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials.

Types of participants

People with schizophrenia or any other serious mental illness, diagnosed by any criteria, irrespective of gender, age or nationality who:
1. Required the use of neuroleptics for more than three months.

2. Developed tardive dyskinesia during neuroleptic treatment (diagnosed by any criteria at baseline of the trial and at least one other occasion).
3. For whom the dose of neuroleptic medication had been stable for one month or more before the trial and during the trial.

Types of interventions

1. The cholinergic drugs arecoline, choline, deanol, lecithin, meclofenoxate, physostigmine, RS 86.
In the first substantial update of the review the following cholinergic compounds were assessed to be relevant and added to the scope of the review: tacrine, 7-methoxytacrine, ipidacrine, galantamine, donepezil, rivastigmine, eptastigmine, metrifonate, xanomeline and cevimeline.
2. Control condition: Placebo or no intervention.

Types of outcome measures

Clinical efficacy (clinically relevant improvement of tardive dyskinesia symptoms) is defined in this review as an improvement in tardive dyskinesia symptoms of more than 50% on any validated tardive dyskinesia scale.
The outcomes of interest were:
1. Global outcome measures (this category of outcome measures was added in the first substantial up-date of the review).
1.1 The number of people per treatment group who died for any reason.
1.2 Treatment group mean and standard deviation of endpoint score on any scale of quality of life.
1.3 Treatment group mean and standard deviation of endpoint score on any scale of level of functioning.
2. Tardive dyskinesia changes
2.1 The number of people per treatment group who did not show a clinically relevant improvement (improvement of more than 50% on any validated tardive dyskinesia scale) as assessed by the rater.
2.2 The number of people per treatment group who did not show any improvement by any means of tardive dyskinesia assessment as assessed by the rater.
2.3 The number of people per treatment group who deteriorated by any means of tardive dyskinesia assessment as assessed by the rater.
2.4 The number of people per treatment group who did not experience any improvement in tardive dyskinesia symptoms as rated by self-assessment (this outcome was added in the first substantial up-date of the review).
2.5 The number of people per treatment group who deteriorated in tardive dyskinesia symptoms as rated by self-assessment (this outcome was added in the first substantial up-date of the review).
2.6 Treatment group mean and standard deviation of endpoint score on any validated tardive dyskinesia scale.
2.7 Treatment group mean and standard deviation of change (baseline minus endpoint) in score on any validated tardive dyskinesia scale.
3. General mental state changes
3.1 The number of people per treatment group who deteriorated in psychiatric symptoms (such as delusions and hallucinations) by any means of assessment of psychiatric symptoms or mental state.
3.2 Treatment group mean and standard deviation of endpoint score on any scale of psychiatric symptoms.
4. Acceptability of the treatment
4.1 The number of people per treatment group who had any adverse effect (other than deterioration of tardive dyskinesia symptoms or change in mental state).
4.2 The number of people per treatment group who dropped out during the trial.
When appropriate, the outcomes were grouped into time periods - short term (less than 6 weeks), medium term (between 6 weeks and 6 months) and long term (over 6 months).

Search methods for identification of studies

1. Electronic searching
1.1 In the original version of the review relevant randomised trials were identified by searching the following electronic databases:
1.1.1 Biological Abstracts (January 1982 to May 1995) was searched using the CSG's phrase for randomised controlled trials (see Group search strategy) combined with the phrase:
[and ((tardive near (dyskine* or diskine*) or (abnormal near movement* near disorder*) or (involuntar* near movement*))]
The set of reports that resulted from this was hand searched for possible trials and researched, within the bibliographic package ProCite, with the phrase [cholinergic* or arecoline or choline or deanol or lecithin or meclofenoxate or physostigmine or RS?86]
1.1.2 The Cochrane Schizophrenia Group's Register was searched using the phrase:
[cholinergic* or arecoline or choline or (#42 = 12) or deanol or (#42 = 353) or (#42 = 355) or lecithin or (#42 = 151) or meclofenoxate or physostigmine or RS?86]
1.1.3 EMBASE (January 1980 to May 1995) was searched using the CSG's phrase for randomised controlled trials (see Group search strategy) combined with the phrase:
[and ((tardive dyskinesia in thesaurus -subheadings, prevention, drug therapy, side effect and therapy) or (neuroleptic dyskinesia in thesaurus -all subheadings) or (tardive or dyskines*) or (movement* or disorder*) or (abnormal or movement* or disorder*))]
The set of reports that resulted from this was hand searched for possible trials and researched, within the bibliographic package ProCite, with the phrase [cholinergic* or arecoline or choline or deanol or lecithin or meclofenoxate or physostigmine or RS?86]
1.1.4 LILACS (January 1982 to September 1996) was searched using the CSG's phrase for randomised controlled trials (see Group search strategy) combined with the phrase:

[and (tardive or (dyskinesia* or diskinesia*)) or (drug induced movement disorders in thesaurus))]
This downloaded set of reports was hand searched for possible trials and researched, within the bibliographic package ProCite, with the phrase [cholinergic* or arecoline or choline or deanol or lecithin or meclofenoxate or physostigmine or RS?86]
1.1.5 MEDLINE (January 1966 to May 1995) was searched using the CSG's phrase for randomised controlled trials (see Group search strategy) combined with the phrase:
[and (movement-disorders in MeSH / explode all subheadings) or (anti-dyskinesia-agents in MeSH / explode all subheadings) or (dyskinesia-drug-induced in MeSH / explode all subheadings) and (psychosis in MeSH / explode all subheadings) or (schizophrenic disorders in MeSH / explode all subheadings) or (tardive near (dyskine* or diskine*)) or (abnormal* near movement* near disorder*) or (involuntar* near movement*))]
The set of reports that resulted from was hand searched for possible trials and researched, within the bibliographic package ProCite, with the phrase [cholinergic* or arecoline or choline or deanol or lecithin or meclofenoxate or physostigmine or RS?86]
1.1.6 PsycLIT (January 1974 to May 1995) was searched using the CSG's phrase for randomised controlled trials (see Group search strategy) combined with the phrase:
[and (explode movement-disorders in DE) or (explode tardive-dyskinesia in DE) or (tardive near (dyskine* or diskine*) or (abnormal* near movement* near disorder*) or (involuntar* near movement*))]
The set of reports that resulted from this was hand searched for possible trials and researched, within the bibliographic package ProCite, with the phrase [cholinergic* or arecoline or choline or deanol or lecithin or meclofenoxate or physostigmine or RS?86]
1.1.7 SCISEARCH - Science Citation Index. Each of the included studies was sought as a citation on the SCISEARCH database. Reports of articles that had cited these studies were inspected so that further trials could be identified.
1.2 In the first substantial up-date of the review the Cochrane Schizophrenia Group's Register was searched (October 2001) using the phrase:
[cholinergic* OR arecolin* OR arecholin* OR meclofenoxat* OR meclophenoxat* OR centrofenoxin* OR centrophenoxin* OR 'ANP 235' OR 'EN 1627' OR deanol* OR demanol* OR 'CR 121' OR 'RS 86' OR physostigmin* OR fysostigmin* OR lecithin* OR lecitin* OR choline OR cholin OR coline OR tacrin* OR takrin* OR tetrahydroaminoacridin* OR tetrahydroaminacrin* OR 'CI 970' OR THA OR THAA OR 7-methoxyacridin* OR 7-metoxyacridin* OR methoxytacrin* OR metoxytacrin* OR metoxytakrin* OR methoxycrin* OR metoxycrin* OR MEOTA OR ipidacrin* OR amiridin* OR NIK247 OR 'NIK 247' OR donepezil* OR E2020 OR 'E 2020' OR galanthamin* OR galantamin* OR 'CGP 37267' OR rivastigmin* OR ENA713 OR 'ENA 713' OR '212 713' OR eptastigmin* OR heptylstigmin* OR heptylphysostigmin* OR heptylfysostigmin* OR 'L 693 487' OR MF201 OR 'MF 201' OR metrifonat* OR metriphonat* OR trichlorfon* OR trichlorphon* OR trichlorfen* OR trichlorphen* OR 'L 1359' OR 'Bay a 9826' OR 'Bay 1 1359' OR xanomelin* OR 'LY 246708' OR 'FG 10232' OR cevimelin* OR AF102B OR 'AF 102B' OR 'FKS 508' OR 'SND 5008' OR SNK508 OR SNI2011]
The Cochrane Schizophrenia Group's Register is assembled by extensive searches of randomised controlled trials in electronic databases, registers for conference proceedings and dissertations etc. The search strategy of the CSG's Register contains a search strategy for trials on tardive dyskinesia. Please see search strategy in CSG module in Cochrane Library.
2. Reference searching
The references of all identified studies were inspected for more studies.
3. Personal contact
The first author of each included study was contacted for information regarding unpublished trials.

Data collection and analysis

[For definitions of terms used in this, and other sections, please refer to the Glossary.]
1. Selection of trials
The title or abstract of each reference identified by the search was inspected independently by two reviewers (IT and ES) to assess relevance. For articles that could possibly have been RCTs, or in cases of disagreement, the full article was obtained. In turn these articles were independently inspected. There was no disagreement between the two reviewers regarding which trials were relevant.
2. Assessment of methodological quality
The methodological quality of each included trial was assessed independently by two reviewers (IT and ES). Quality was evaluated using criteria described in the Cochrane Reviewers' Handbook (Clarke 2001) and the Jadad Scale (Jadad 1996). The former is based on evidence of a strong relationship between allocation concealment (blinding of random assignment of participants to intervention groups) and the potential for bias in the results (Schulz 1995), i.e. lack of adequate allocation concealment is associated with selection bias (systematic differences in comparison groups). Thus trials can, to a certain extent, be evaluated by their method of allocation concealment. The method for assigning participants to interventions undergoing comparison should be robust against selection bias (i.e. the trialist should not be able to influence which intervention the participant will receive nor should any foreknowledge of treatment assignment influence recruitment) and its description should be clear (Clarke 2001). The risk for bias in the results of a study is defined as below (Clarke 2001):
A. Low risk of bias (adequate allocation concealment)
B. Moderate risk of bias (some doubt about the results)
C. High risk of bias (inadequate allocation concealment)

The Jadad Scale measures a wider range of factors that impact on the quality of a trial. The scale includes three items:
1. Was the study described as randomised?
2. Was the study described as double blind?
3. Was there a description of withdrawals and drop-outs?
Each item receives 1 point if the answer is positive. In addition: 1 additional point each is given, if randomisation and/or blinding procedures are described and adequate. 1 point each can be deducted if either the randomisation or the blinding/masking procedures described were inadequate. Thus the maximum score is 5 points. (Jadad 1996).
Only trials described as randomised (category A or B) were included in the statistical analysis. The Jadad scale was used as an extra assessment of quality, however Jadad points were not used to exclude trials. If there was not enough information in the publication to assess adequate randomisation and methodological quality, or there was disagreement between the two reviewers, the article was added to those awaiting assessment and authors of the study were contacted for clarification. Justification for excluding trials from the analysis was documented.
3. Data extraction
Data from the included trials were extracted by two researchers. Two kinds of measures were extracted: dichotomous (binary, yes/no) data and continuous (scale) data.
Trials in which a crossover design was used included the risk of carry over effects of a medication in the second or more stages of the trial (after crossover). To exclude potential carry over effects, only data from the first stage of the trial (before crossover) were used in the analysis.
In the case of incomplete data, the article was added to those awaiting assessment and authors were contacted for clarification. If a trial met the criteria for methodological quality, but it was impossible to extract any data or collect unpublished data from the authors, the study had to be excluded from statistical analysis.
4. Data analysis
4.1 Intention to treat analysis
Where possible, all data were analysed using the intention-to-treat principle (once randomised, always analyse). Data were excluded from studies where more than 50% of participants in any group were lost to follow up. (This did not include the outcome of 'drop-outs'.) In studies with less than a 50% drop-out rate, people leaving early were considered to have had the negative outcome, except for the event of death. When possible and appropriate, the 'Last Observation Carried Forward' technique was used in analysis of continuous outcomes.
4.2 Dichotomous data
For dichotomous outcomes a standard estimation of the risk ratio (RR) and its 95% confidence interval (CI) was calculated. If overall results were significant, the number needed to treat (NNT) was calculated from the absolute risk difference between treatment and control groups. If heterogeneity was found it was investigated and a random effects model used.
4.3 Continuous data
4.3.1 Normally distributed versus skewed data
Continuous data on clinical and social outcomes are often not normally distributed. A reliable statistical analysis of groups undergoing comparison requires that samples tested attain a normal distribution. To avoid including non-normally distributed samples in the statistical analysis, the following standards were applied to all continuous data before inclusion:
1) Standard deviations and means were reported or derivable from data in the publication, or were obtainable from authors.
2) When a scale started from a finite number (such as zero), the standard deviation, when multiplied by two, was less than the mean (as otherwise the mean was unlikely to be an appropriate measure of the centre of the distribution - Altman 1996).
3) If a scale started from a positive value (such as PANSS which can have values from 30 to 210) the calculation described above was modified to take the scale starting point into account. In these cases skewness is present if 2SD>(S-Smin), where S is the mean score and Smin is the minimum score of the scale. Endpoint scores on scales used in clinical practice often have a definite minimum and maximum on the scale, and so these rules can be applied to them.
4.3.2 Summary statistic
For continuous outcomes a pooled weighted mean difference (WMD) between groups was calculated. If heterogeneity was found it was investigated and a random effects model used.
4.3.3 Valid scales
A wide range of instruments are available to measure mental health outcomes. These instruments vary in quality and many are not valid. Unpublished instruments are more likely to report statistically significant findings than those that have been published (Marshall 2000). The following minimum standards were set for valid scales: 1. The instrument had to have been described in a peer reviewed journal. 2. The instrument had to be either a self report scale or completed by an independent rater.
4.3.4 Endpoint versus change data
When continuous data are presented on a scale which includes the possibility of negative values (such as change on a scale), it is impossible to tell whether data is non-normally distributed (skewed) or not. It is thus preferable to use end point data of a scale (participants' total scores at the end of study - not change in score from baseline), which typically cannot have negative values. Where possible endpoint data were presented, and if both endpoint and change (from baseline) data were available for the same outcome, then only the former were used.
5. Test for heterogeneity
It is important not to pool heterogeneous studies together, as heterogeneity might reflect differences in study design or sample population, rather than true variation in results of the outcome measured. To investigate the possibility of heterogeneity of trial results, a Mantel-Haenszel Chi-square test was used, as well as visual inspection of graphs. A significance level less than 0.10 was pre-

defined as evidence of heterogeneity. If heterogeneity was found, the reasons for it were explored. If no study-related explaining factor was found, data were tested pooled using the random effects model which takes into account the variation between studies. (The random effects model is more conservative in estimating treatment effect, and takes into account that some trials will produce odd results by chance.) If using the random effects model did not change the statistical significance level of the results, the results remained pooled. If the random effects model did change the statistical significance of the result, studies responsible for heterogeneity were not added to the main body of homogeneous trials, but summated and presented separately and reasons for heterogeneity investigated.

6. Addressing publication bias

Data from all included studies were entered into a funnel graph (trial effect against trial size) in an attempt to investigate the likelihood of overt publication bias.

7. Sensitivity analyses

Four sensitivity analyses were prespecified: 1.Treatment effect differs according to difference in the quality of trials, 2. Treatment effect differs according to different lengths of treatment, 3. Treatment effect differs for the various drugs and 4. Treatment effect differs according to the age of the participants (this sensitivity analysis was added in the first substantial up-date of the review). These analyses were evaluated by looking at separate subgroups of trials.

8. General

Data were entered into Revman in such a way that the area to the left of the line of no effect in the graph indicated a favourable outcome for cholinergic agents.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

For a detailed description, please see the Tables of Included and Excluded Studies.

1. Excluded studies

The reviewers decided to list all identified studies to give an overview of what has been published on the topic, as well as to give an overview of the comprehensiveness of the search. The excluded studies table lists all identified reports where a cholinergic agent had been given to one or several persons in attempt to treat tardive dyskinesia. Most are case reports or open trials. Three trials, Domino 1985, Jus 1978 and Penovich 1978, were randomised and of fine methodological quality, but they were of crossover design and data from the first segment could not be extracted. The authors were contacted to confirm the lack of additional data.

Physostigmine has been used in trials of exploratory nature, but it cannot be used as a treatment for tardive dyskinesia since the mode of administration is intravenous. Trials on physostigmine were therefore not included in the analysis, but any identified trials were listed in the Excluded studies table.

2. Awaiting assessment

Four studies are awaiting assessment (Gelenberg 1989, Joe 1985, Marsalek 1994, Perez-Cruet 1981). For these trials it was not possible to extract data from the publication. Authors have been contacted and further information is awaited.

3. Ongoing study

Caroff 2002 is, as far as we know, ongoing. We have little information on this study except that it is randomised, corssover, comparing galantamine with placebo (please see table).

4. Included studies

Eleven studies were included.

4.1 Study design and duration

Tardive dyskinesia is often a chronic condition and symptoms tend to fluctuate and show considerable variability across time. Only four studies, however, had a treatment and observation period of longer than six weeks (Gelenberg 1990, Jackson 1978, Tarsy 1977, Yagi 1990). Three trials lasted between four and five weeks (George 1981, Kocher 1980, Lucius 1976), and two less than two weeks (Beckham 1981, Price 1982). For crossover trials, duration refers to the first part of the study before the first exchange of medication. Five trials were of parallel, and six of crossover, design. One trial, from Japan (Yagi 1990), was the only multicentre trial. Sixty people were randomised to parallel groups of meclofenoxate and placebo for eight weeks. Despite the comparatively long trial duration, there were no losses to follow up; a problem of several of the shorter trials. Yagi 1990 used both live and video ratings, conducted at regular intervals, to rate outcome.

4.2 Participants

People involved in these trials were mostly long-term inpatients. In many cases, participants were sought by visiting long-term wards. Only two studies specifically recruited outpatients (Gelenberg 1990, Tarsy 1977). Both sexes were recruited and the age range was wide, though most people were middle aged. Only Jackson 1978 and Jackson 1979 included participants who were all younger than 65 years. Only Lucius 1976 stated that people over than 75 were excluded, to diminish the possibility of spontaneous age related dyskinesia. Most people had been diagnosed as suffering from schizophrenia. The number of people in the studies ranged from five (Tarsy 1977) to 60 (Yagi 1990).

4.3 Interventions

Four trials involved lecithin, six deanol and one meclofenoxate. Dosages for respective agents were similar; lecithin containing phosphatidyl choline 20-35 g/day, deanol 1000-2000 mg/day and meclofenoxate 900 mg/day. Lecithin was used because one of its main components, phosphatidyl choline, is a theoretical precursor of acetylcholine. It was thought that high levels of choline in the blood (which phosphatidyl choline converts into after digestion)

would enhance acetylcholine synthesis in neurons by making the precursor more available. Deanol, a synthetic substance, is also thought to be a precursor of acetylcholine, but this is unproven, and deanol might be an acetylcholine agonist or even a suppressor of ACh synthesis.

4.4 Outcomes

4.4.1 Global outcome measures

We were able to extract the outcome of death from all but one study. Assessments of treatment effect on true global measures were scarce. It should be noted that the term 'global' is used in the literature, and in this review, in two different contexts. In the following paragraph the term 'global' refers to the patient's life as a whole (level of functioning, quality of life, employment, being an inpatient or outpatient, death etc.). However, the term 'global assessment' is also used later in the context of 'global assessment of symptoms of tardive dyskinesia' which refers to assessment of the specific symptom or syndrome investigated. Only Yagi 1990 reported a global assessment in the form of global usefulness rating. This was defined as a combined assessment of the outcomes' final global improvement rating, an assessment of tardive dyskinesia symptom severity in categories of 'improved' and 'aggravated', and 'Overall safety rating' which was an assessment of severity of adverse effects. The global usefulness rating was then divided into categories useful and harmful.

4.4.2 Tardive dyskinesia measures

The movements of tardive dyskinesia are influenced by a person's emotional state. Therefore, arrangements for observation under standardised conditions were an issue in most trials. Another issue was to ensure the blinding of raters. Usually raters observed tardive dyskinesia or videotaped participants under standard conditions to familiarise patients with the rating situation. To ensure consistent rating, most trials used at least two independent raters. Yagi 1990 carried out an extensive evaluation of the correlation between live and video ratings.

George 1981, Kocher 1980 and Lucius 1976 all used locally developed scales to measure severity of tardive dyskinesia. For reasons explained above (see Methods), scores from such scales were not used. Dichotomous outcomes, such as 'any improvement' or 'deterioration' were, however, extracted by comparing baseline and endpoint scores on local scales, since dichotomous outcome measures are a cruder estimate of symptom development.

Only Price 1982 reported participants' self-assessment of treatment effects. Beckham 1981, Gelenberg 1990, and Lucius 1976 all stated that this was an outcome of interest, but did not report their findings. One study, de Montigny 1979, rated tardivey dyskinesia on Extrapyramidal Symptom Rating Scale, but it was impossible to use these data as they reported no standard deviations. On the whole, the assessment of tardive dyskinesia was well thought out, but the reporting of raw data was poor.

Tardive dyskinesia scales from which data were available to use in this review:

i. Abnormal Involuntary Movement Scale (AIMS) (Guy 1976a)

The rating procedure of this 12-item scale begins with a standardised examination. Following the examination items are scored. Seven items evaluate orofacial, extremity and trunk movements and three evaluate global measurements. These 10 items can be scored from 0 (none) to 4 (severe). Two additional items assess dental status and are scored 0 (absent) or 1 (present). The scale ranges from 0-42 points with higher scores indicating greater severity. For the trials analysed in this review, results from the global severity item of the AIMS scale only were reported. This item is rated from 0 to 4. The score on this item, however, reflects the score on the scale as a whole. Gelenberg 1990, Jackson 1978, Jackson 1979 and Yagi 1990 all used the AIMS.

ii. Rockland (Simpson) Tardive Dyskinesia Rating Scale (TDRS) (Simpson 1979)

This scale consists of 34 items, evaluating movements around the orofacial region, neck, trunk and extremities, and holokinetic movements. Nine write-in items are provided for use if necessary. Each item is scored from 1 (absent) to 6 (very severe). The scale ranges from 34-204 with higher scores indicating greater severity. Price 1982 and Tarsy 1977 employed the Simpson Rating Scale, but it was impossible to extract these data from Price 1982 (see included studies table).

iii. Global outcome scale: Clinical Global Impressions scale (CGI) (Guy 1976b)

This scale is used to assess both severity of illness and clinical improvement by comparing the conditions of the person standardised against other people with the same diagnosis. A seven point scoring system is usually used with low scores showing decreased severity and/or overall improvement. Only Beckham 1981 used the CGI to assess severity of tardive dyskinesia symptoms.

4.4.3 General mental state changes

Many trials recorded changes in general mental state, and many different ways were employed to rate these changes. No scores, however, were reported in sufficient detail (number of people, mean and SD) to be used in analysis. Only the outcome of 'deterioration of mental state' could be found and used.

4.4.4 Acceptability of treatment

Possible worsening of acute extrapyramidal symptoms due to cholinergic medication was assessed in some trials, however, trialists did not report scores in detail. All trials assessed general adverse effects, but, again, we often found it impossible to extract useful data (see included studies table).

Risk of bias in included studies

1. Randomisation

Lucius 1976 and Yagi 1990 both described adequate allocation concealment, and for the Gelenberg 1990 study, the authors were able to confirm that allocation was well undertaken. We classified these three studies as category A for allocation concealment (see Methods). In all three the randomisation procedure was conducted by an independent member of the group, preventing trial-

ists from being able to influence the allocation of participants to intervention groups. The rest of the trials are of category B.

2. Blinding

All studies were double blind. Blinding protects against performance bias (systematic differences in care provided apart from the intervention being evaluated) and detection bias (systematic differences in outcome assessment). Five trials (Beckham 1981, George 1981, Jackson 1978, Jackson 1979, Yagi 1990) carried out ratings using videotapes presented in random order.

3. Follow up

All trials reported that some people left before completion of the study, or how many participants finished the trial. The reasons for withdrawal and the group from which the person left are important as it makes evaluating attrition bias (systematic differences in withdrawals from the trial) possible. Only one study, Beckham 1981, gave explicit reasons for early withdrawal. We could extract the outcome of 'leaving the study early' from all but one trial (Gelenberg 1990). This trial did not report dichotomous outcomes in such a way that reviewers could extract them as group sizes at the beginning of the trial were unclear.

Effects of interventions

1. The search

The search identified 60 studies, (11 included, 44 excluded, 4 awaiting assessment, 1 ongoing). There is clearly an under-representation of other than Anglo-American and German literature.

2. COMPARISON: CHOLINERGIC DRUGS versus PLACEBO

2.1 Death

No deaths were reported in any of the studies (10 trials, 240 people). For crossover trials we counted only the first period before the crossover. However, in one crossover study, Tarsy 1977, one person died suddenly at home due to acute aspiration in the second crossover period, his placebo period. By this time he had completed eight weeks of deanol treatment and four weeks of placebo treatment.

2.2 Global outcome: Intervention not useful as assessed by the Global Usefulness Rating (GUR)

Yagi 1990 assessed global usefulness of meclofenoxate on the categorical scale described above. Meclofenoxate was neither clearly helpful nor harmful (60 people, RR 0.89 CI 0.59 to 1.32).

2.3 Tardive dyskinesia symptoms

2.3.1 No clinically important improvement in tardive dyskinesia (50% on any validated TD scale)

We could extract data from only three trials, often because studies did not use validated scales. The sample is small and the result inconclusive (17 people, RR 0.71 CI 0.43 to 1.16).

2.3.2 Not any improvement in tardive dyskinesia symptoms (as rated by independent rater)

We could extract data from most studies (8/11) for this rather crude dichotomous outcome. The pooled result, however, is inconclusive. There is no difference in effect between drug and placebo groups (8 RCTs, 170 people, RR 0.84 CI 0.68 to 1.04).

2.3.3 Not any improvement in tardive dyskinesia symptoms (self rated)

Only Price 1982 reported this outcome. There was no clear difference between lecithin and placebo (30 people, RR 0.92 CI 0.62 to 1.36).

2.3.4 Deterioration of tardive dyskinesia symptoms (as rated by independent rater)

The definition for this outcome was also wide (deterioration of tardive dyskinesia symptoms by any means of assessment). The pooled result shows no clear difference between drug and placebo groups (7 RCTs, 137 people, RR 1.17 CI 0.55 to 2.50).

2.3.5 Deterioration of tardive dyskinesia symptoms (self rated)

Again, only Price 1982 reported this outcome. There was no clear difference between groups (30 people, RR 3.00 CI 0.13 to 68).

2.3.6 Average endpoint score on AIMS

Four studies reported useful data. Pooled summary result does not show a beneficial effect of cholinergic drugs when compared with placebo (86 people, WMD -0.19 CI -0.53 to 0.14).

2.3.7 Average endpoint score on modified Simpson TDRS

One study (Tarsy 1977, n=5) used this scale. The confidence interval of mean difference was not estimable because the placebo group only had one participant. Mean (SD) for deanol 10.00 (5.48), for placebo 10.00 (0.00, not estimable).

2.3.8 Average endpoint score on CGI for tardive dyskinesia

Beckham 1981 used this means of rating. There was no clear difference in effect between groups (31 people, WMD -0.43 CI -1.36 to 0.50).

2.4 General mental state (deterioration)

The pooled result does not show a difference between drug and placebo groups (5 RCTs, 77 people, RR 0.50 CI 0.10 to 2.61).

2.5 Adverse effects

The results on adverse effects are not pooled between compounds and reporting was so unclear that interpretation was very difficult. For lecithin, the risk for adverse effects was impossible to estimate as only two studies reported numerical data and these trials identified no adverse effects (2 RCTs, n=36, 0/18 and 0/18 for drug and placebo group respectively).

Denol may cause gastric adverse effects (5 RCTs, 61 people, RR 9.00 CI 0.55-148) and other adverse effects such as sedation, peripheral cholinergic effects and undesirable body odour (6 RCTs, 94 people, RR 6.83 CI 0.99-47). None of these results, however, are statistically significant. For meclofenoxate there is also no clear difference between groups (1 trial, 60 people, RR 0.56 CI 0.15-2.14).

2.6 Leaving the study early

We found no difference between people allocated cholinergics and those given placebo for the outcome of leaving the study before completion (10 RCTs, 240 people, RR 0.52 CI 0.21 to 1.33).

3. Heterogeneity

Data are homogenous. We calculated all pooled results with the

fixed effects model. There was one incidence of heterogeneity. This was in the subgroup 'Deanol - over 6 weeks' in the outcome 2.3.2 (Not any improvement in tardive dyskinesia symptoms as rated by independent rater) and involved two studies. The heterogeneity between these two studies' results (Chi-square 2.77, df=1, p= 0.096), was judged to be due to the very small sample sizes (6 and 5 people). Using the random effects model or removing these studies did not change the statistical significance of the pooled result (2 RCTs, 11 people, RR random effects model 0.72 CI 0.06-8.49).

4. Sensitivity analyses

In the graphical presentation, data are divided into five subgroups: 1. lecithin - over 6 weeks, 2. lecithin - less than 6 weeks, 3. deanol - over 6 weeks, 4. deanol - less than 6 weeks and 5. meclofenoxate - over 6 weeks. Not one result from these subtotals reach statistically significant values. The predefined sensitivity analyses could not be undertaken because of the small sample size.

5. Publication bias

The reviewers were able to enter data into funnel plots for three outcomes (2.3.2 Not any improvement in tardive dyskinesia symptoms as rated by independent rater; 2.3.4 Deterioration of tardive dyskinesia symptoms (as rated by independent rater); 2.3.5 Average endpoint score on AIMS). There was no suggestion of asymmetry.

DISCUSSION

1. General

The most important finding of this review is that a systematic search of the literature, still results in a review that is considerably underpowered to really investigate the clinical efficacy of cholinergic agents in tardive dyskinesia. All data are inconclusive. We were unable to detect any effect, good or bad of these drugs for tardive dyskinesia.

With the advent of new CNS-active cholinergic agents for treatment of Alzheimer's disease, the theoretical base for this review is strengthened. However, the actual central cholinergic transmission enhancing effect of old cholinergic drugs, such as lecithin and especially deanol remains unclear. Even if any of these old compounds had an effect on cholinergic transmission, the impact would probably be limited. Modern cholinergic drugs use a different mode of action and would be worthy of investigation.

2. Strengths and weaknesses of the review

It remains possible that we did not identify existing randomised controlled trials of cholinergic agents other than lecithin, deanol and meclofenoxate by our search. Judging from internal referencing in the articles identified, the search has seemed to find all relevant trials on these compounds. One randomised controlled trial investigating the effects of 7-methoxytacrine was identified (Marsalek 1997) and further information from authors is awaited. One ongoing randomised controlled trial with galantamine was identified (Caroff 2002). The results are not yet available. It is probable, however, that the effect of modern cholinergic agents for tardive dyskinesia has not been comprehensively investigated within randomised trials.

A weakness affecting the meta-analysis is the fact that a large portion of the data produced in these trials could not be used. Poor reporting of primary data, combined with problems with trial design limit the power of this review. The use of validated scales and good reporting of scores, varied enormously. Overall, sample sizes were small, and studies with small sample sizes risk producing beta-errors (the error of not finding an existing difference between treatments), if treatment effects are themselves small.

3. COMPARISON: CHOLINERGIC DRUGS versus PLACEBO

3.1 Global outcomes

Few global outcomes were measured. Nothing can be concluded about effects of treatment on the level of functioning or quality of life of people with schizophrenia. Trials investigating cholinergic treatment effects for tardive dyskinesia are at an exploratory stage, and global well-being was not a primary aim of these studies.

3.2 Tardive dyskinesia symptoms

Data provide no evidence to support the use of the cholinergic agents lecithin, deanol or meclofenoxate for treatment of neuroleptic-induced tardive dyskinesia and there may be some evidence to refute their use (see adverse effects, below). There were no apparent differences in treatment effects between these drugs and placebo. There were some suggestions of benefit for cholinergic compounds, but none were convincing. . However, none of these outcomes reach statistically significant values and this could be explained by the several biases that are likely be operating within and upon this small group of underpowered studies.

Early studies suggested that cholinergic compounds may worsen tardive dyskinesia symptoms. This is not supported by the results of this review.

3.3 General mental state

There are no apparent differences for outcomes of mental state for people allocated to cholinergic drugs compared with those given placebo. This would be expected with such small samples. One trial, however, reported a "significant" increase in the Brief Psychiatric Rating Scale schizophrenia score for people given deanol but primary data are not available (de Montigny 1979).

3.4 Acceptability of the treatment

No adverse effects could be estimated from the lecithin trials as reporting was so poor. The adverse effect profiles for deanol and meclofenoxate seem different from each other. Because adverse

effects do seem to occur, with little support for a positive clinical effect of cholinergic agents, this would be inhibiting of routine use of these compounds.

3.5 Leaving the study early

The duration of all studies was short and the opportunity for leaving early, therefore, was limited. According to existing data, cholinergic compounds were well tolerated.

AUTHORS' CONCLUSIONS

Implications for practice

1. For the person with tardive dyskinesia

Given the absence of evidence for efficacy, and some evidence of adverse effects, it would be understandable if a person with tardive dyskinesia would rather avoid these additional treatments. Should the tardive dyskinesia be serious and warrant intervention, the person with the movement disorder or their family may wish to ask for use of one of the more modern cholinergics, within a well designed, conducted and reported randomised trial.

2. For clinicians

The available data on the efficacy of cholinergic medications for the treatment of neuroleptic-induced tardive dyskinesia are insufficient to recommend their use. The adverse effects associated with some of these compounds are burdensome. For the compounds reviewed, adverse effects outweigh benefits.

3. For policy makers and funders of studies

There is no evidence to support recommendations for cholinergic agents as a routine treatment for tardive dyskinesia. New cholinergic drugs have been synthesised in the past ten years for the treatment of Alzheimer's disease. It would be interesting to see if these drugs could have meaningful effects for people with the distressing and disfiguring syndrome of tardive dyskinesia. As yet, however, the effects of these drugs for this condition are unknown.

Implications for research

1. General

If cholinergic agents are to be investigated, their effects should be demonstrated in well designed, conducted and reported randomised controlled clinical trials (Moher 2001).

2. Specific

It is possible that cholinergic agents have a small to moderate effect (positive or negative) that has not, as yet, been detected. The results of this review do not support further investigation of the effects of lecithin and deanol. However, there is a need for well designed, conducted and reported randomised trials to evaluate the effects of modern cholinergic agents for the treatment of neuroleptic-induced tardive dyskinesia.

Research findings in the field of neuropathology might bring new implications for the use of more cholinergic drugs for tardive dyskinesia. If modern cholinergic agents are to be investigated in the treatment of tardive dyskinesia, it is important to assess their influence on mental state and adverse effects. Specific implications for tardive dyskinesia research, addressing design issues of trials, are discussed in another review in this series of reviews (Soares 2001d).

We identified one ongoing randomised placebo-controlled trial of a new cholinesterase inhibitor (Caroff 2002). The results are eagerly awaited.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Beckham 1981

Methods	Allocation: randomised, no details. Blindness: double, described and adequate. Duration: 11 days. Design: parallel. Raters: 1 blinded rater, frequency of dyskinesia count rated from videotapes presented in random order. Jadad: 4/5.
Participants	Diagnosis: schizophrenia (21), affective disorder (3), OBS (7), neurosis (2). History: TD present and stable >6 months, antipsychotic dose stable >4 months, mean duration psychiatric ill ~17 years (range 1-45), CPE dose (mg/day) mean ~420, SD 430. N=50. Sex: all male. Age: mean 55 yrs, range 23-77. Setting: mostly inpatients, some outpatients.
Interventions	1. Lecithin: dose 60 g/day containing phosphatidylcholine 33 g/day. N=25. 2. Placebo. N=25. Effort made to keep antipsychotic medication stable during study, 7 received anticholinergic (-parkinsonian) medication
Outcomes	TD symptoms: CGI. Leaving the study early. Unable to use - Frequency of dyskinetic movement count (frequency of one selected movement/minute in 4 body areas counted visually from videotapes) (validation unsure, no SD). Adverse effects (reporting unspecific). Patient's subjective assessments (not reported).
Notes	Intention-to-treat analysis not performed for continuous outcomes (CGI), results reported only for N= 31 who completed study (lecithin group 15, control group 16). Sample attrition well reported. Author contacted 2002, awaiting further information.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

de Montigny 1979

Methods	Allocation: randomised, no details. Blindness: double, no details. Duration: 3 weeks. Design: parallel. Raters: ESRS rated independently by 2 psychiatrists. Jadad: 3/5.
Participants	Diagnosis: chronic schizophrenia. History: TD moderate to severe, maintenance antipsychotic treatment >6 yrs, CPE dose range 0-1850 mg/day. N=20. Sex: female 10, male 10. Age: range 34-73 yrs. Setting: from long-term wards.
Interventions	1. Deanol: dose increased from 600 to 1500 mg/day during first week, constant thereafter. N=10. 2. Placebo. N=10. Antipsychotic dose stable during study, no other psychotropics permitted
Outcomes	Adverse effects. Leaving the study early. Unable to use - TD symptom scores: ESRS (no SD). Mental state scores: BPRS (no SD).
Notes	Analysis of ESRS scores in publication did not detect significant treatment effect. No difference between treatments regarding parkinsonism. There was significant increase in mean schizophrenic subscore of BPRS in deanol treated group. Authors contacted - no reply.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Unclear risk	B - Unclear

Gelenberg 1990

Methods	Allocation: randomised, procedure conducted independently by trial statistician, stratified by maintenance antipsychotic drug therapy. Blindness: double, adequate. 1 blind rater assessed TD and psychopathology. 1 open rater assessed side-effects and distributed medication. Duration: 8 weeks (preceded by 4 wks pre-entry period). Design: crossover. Jadad: 4/5.
Participants	Diagnosis: schizophrenia (9), bipolar (6), major depression (3), generalized anxiety disorder (1), brief reactive psychosis (1), no psychiatric diagnosis (1). TD diagnosed by psychiatrist and neurologist using

Gelenberg 1990 (*Continued*)

	criteria. History: TD present 6 months - 17 yrs (median 1.5 yrs). N=21. Sex: female 11, male 10. Age: median 47 yrs, range 19-70. Setting: screened at area mental health centers or referred by private physicians
Interventions	1. Lecithin: containing PC 20 g/day. N=5 of completers of trial. 2. Placebo. N=9 of completers. No information given on how many were originally allocated to each group. 14 of 21 completed trial. Antipsychotics stable during trial. No anticholinergics permitted
Outcomes	TD symptoms: AIMS. Unable to use - Global impression: CGI (not reported). Movement disorders: TAKE (reported only final summary scores from both segments, after cross-over). Mental state: BPRS, HAM-D (reported only final summary scores from both segments, after cross-over). Adverse effects (reported only final summary scores from both segments, after cross-over). Leaving study early (reported only final summary scores from both segments, after cross-over)
Notes	Intention-to-treat analysis not performed for AIMS scores (results reported only for completers). Physiology (lab-tests, ECG, serum choline) monitored during trial. No clinically important changes in lab variables or vital signs during study. Serum choline levels doubled during lecithin treatm. Authors contacted, awaiting further information. Details of allocation procedure from authors

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	A - Adequate

George 1981

Methods	Allocation: randomised, no details, stratified by severity of TD. Blindness: double. Duration: 4 weeks. Design: parallel. Raters: Videotapes presented in random order and rated independently by 2 raters. Jadad: 3/5.
Participants	Diagnosis: oral TD. History: All received antipsychotics, 7 on antipsychotics during trial, CPE range 50-800 mg/day. N=33. Sex: female 25, male 8. Age: range 49 - 89 yrs, mean ~ 70. Setting: chronic psychiatric hospital residents.

George 1981 (*Continued*)

Interventions	1. Deanol: dose 2000 mg/day. N=11. 2. Deanol: dose 1000 mg/day. N=11. 3. Placebo. N=11.
Outcomes	TD symptoms. Adverse effects. Leaving study early. Unable to use - TD symptom scores: local scale (not validated).
Notes	No information about medication status and dose prior to study, or duration of TD. In review the two deanol groups are analysed as one group. Authors contacted - no reply.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Unclear risk	B - Unclear

Jackson 1978

Methods	Allocation: randomised, no details. Blindness: double. Duration: 12 weeks, preceded by 4 wks pre-entry period. Design: crossover. Raters: videotapes presented in random temporal sequence and rated independently by 4 psychiatrists using AIMS. Jadad: 3/5.
Participants	Diagnosis: schizophrenia + TD (Global AIMS rating of moderate to severe). History: mean duration ill ~22 yrs (range 18-30), high dose antipsychotic drugs over extended periods of time. N=6. Sex: all female. Age: mean 48 yrs, range 34-59. Setting: long-term inpatients.
Interventions	1. Deanol: dose gradually increased to 1500 mg/day over 4 weeks. N=4. 2. Placebo. N=2. Maintained on single, stable antipsychotic dose during study. No other psychotropics or anticholinergics permitted
Outcomes	TD symptoms: AIMS. Mental state. Adverse effects. Leaving study early. Unable to use -

Jackson 1978 (*Continued*)

	Mental state scores: MIBS (not reported). Parkinsonism scores: Simpson and Angus scale (not reported).
Notes	No participants developed clinical parkinsonism. People leaving the study early may not have been reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Jackson 1979

Methods	Allocation: randomised, no details. Blindness: double, described and adequate. Duration: 2 weeks (preceded by 2-4 wks pre-entry). Design: crossover. Raters: videotapes presented in random temporal sequence and rated blind and independently by 2 psychiatrists using AIMS. Jadad: 4/5.
Participants	Diagnosis: long-term schizophrenia + TD (moderate or severe on AIMS global rating). History: antipsychotics continuously >4 yrs (range 4-23). N=6. Sex: 5 female, 1 male. Age: mean 57 yrs, range 49-60. Setting: long-term inpatients.
Interventions	1. Lecithin: dose 50 g/day containing PC 35 g/day. N=3. 2. Placebo. N=3. Antipsychotics stable during study. No other psychotropics or anticholinergics permitted
Outcomes	TD symptoms: AIMS. Mental state. Adverse effects. Leaving study early. Unable to use - Mental state scores: BPRS, MIBS (not reported).
Notes	One person withdrawn early due to nausea and vomiting on a lecithin/water/orange flavour mix. Protocol changed to lecithin/ice cream/chocolate mix - well tolerated! Physiology (blood pressure, serum choline) monitored. Serum choline increased substantially during lecithin. Physiological assessment showed no evidence of adverse effects

Risk of bias

Jackson 1979 (*Continued*)

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Kocher 1980

Methods	Allocation: randomised, no details. Blindness: double, described and adequate. Duration: 4 weeks. Design: crossover. Raters: two independent raters. Jadad: 4/5.
Participants	Diagnosis: schizophrenia (17), senile dementia (3) + TD (diagnosed by 2 physicians). History: antipsychotic medication >5 yrs. N=20. Sex: female 10, male 10. Age: average 67 yrs, range 42-82. Setting: long-term inpatients.
Interventions	1. Deanol: dose gradually increased to 1500 mg/day. N=10. 2. Placebo. N=10. Antipsychotic dose stable during trial, antiparkinsonian (-cholinergic) medication used by some
Outcomes	TD symptoms. Adverse effects. Leaving study early. Unable to use - TD symptom scores: local scale (not validated).
Notes	Deanol well tolerated. Authors contacted - no reply.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Lucius 1976

Methods	Allocation: matched pairs were randomised. Allocation procedure conducted independently by hospital pharmacist and not reported to trialists. Blindness: double, described and adequate. Duration: 5 weeks, preceded by pre-entry period 1 week. Design: crossover. Raters: two independent raters under standardised conditions. Jadad: 5/5.
Participants	Diagnosis: schizophrenia (8), bipolar (1), cerebralsclerosis (1) + TD (diagnosed by 3 physicians using criteria). History: mean duration antipsychotic drugs ~12 yrs (range 2-19), mean CPE dose ~177 mg/day (100-225). N=20 (please see notes). Sex: female 8, male 2. Age: mean 62 yrs (28-75). Setting: longterm inpatients.
Interventions	1. Deanol: dose gradually increased to 1500 mg/day. N=5. 2. Placebo. N=5. Antiparkinsonians cessated 8 days before trial.
Outcomes	TD symptoms. Mental state. Adverse effects. Leaving study early. Unable to use - TD symptom scores: local scale (not validated).
Notes	Original study N=20. Due to information about toxic effects of Clozapine in July 1975, antipsychotic medication abruptly changed. In dissertation, detailed individual patient data supplied. Data extracted for 10 participants whose antipsychotic medication was stable during study

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	A - Adequate

Price 1982

Methods	Allocation: randomised, no details. Blindness: double, described and adequate. Duration: 9-11 days. Design: parallel. Raters: one blinded rater. Jadad: 4/5.

Price 1982 (*Continued*)

Participants	Diagnosis: schizophrenia (69%), OBS (29%), bipolar (2%) + TD (diagnosed by criteria), thorough evaluation to rule out differential diagnostic categories. History: mean duration ill ~17 yrs (range 2-26). N=45. Sex: all male. Age: mean 56 yrs, range 26-77. Setting: inpatients.
Interventions	1. Lecithin: dose 60 g/day containing PC dose of 33 g/day. N=15. 2. Placebo. N=15. 3. No-treatment control group. N=15. Antipsychotics stable, anticholinergics used by 7 participants
Outcomes	TD symptoms. Adverse effects. Leaving study early. Unable to use - TD symptom scores: Simpson TDRS, SRTDRS (reported in ANCOVA tables, unable to extract data)
Notes	Review uses data only from lecithin and placebo groups for whom blinding adequate and reporting consistent. (N=15+15=30). Author contacted to confirm lack of additional data. 60% of participants overlapped with Beckham 1981 study. Extensive neuropsychological and motor tests performed

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Tarsy 1977

Methods	Allocation: randomised, by table of random numbers, concealment unclear. Blindness: double. Duration: 8 weeks. Design: crossover. Raters: one rater. Jadad: 3/5.
Participants	Diagnosis: psychiatric disorder. History: mean duration of TD ~13 months, none chronically institutionalised, phenothiazines discontinued in 4 people 1-11 months before trial. N=5. Sex: all male. Age: mean 54.8 yrs. Setting: outpatients and inpatients.

Tarsy 1977 (*Continued*)

Interventions	1. Deanol: dose 1000 mg/day for 4 weeks, then 2000 mg/day for next 4 weeks. N=4. 2. Placebo. N=1.
Outcomes	TD symptoms: modified Simpson TDRS. Mental state. Adverse effects. Leaving study early.
Notes	No parkinsonian adverse effects or mood changes observed. One person died suddenly at home due to acute aspiration in second crossover period (which is not included in review analysis), by which time he had completed 8 weeks of deanol treatm and 4 weeks of placebo treatm - e.g. 4 weeks after cessation of deanol

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Unclear risk	B - Unclear

Yagi 1990

Methods	Allocation: randomised, blocks of 4. Blindness: double, described and adequate. Duration: 8 weeks preceded by 2 wks pre-entry period. Design: parallel, multicenter study. Raters: blinded raters assessed AIMS live, additional videotapes rated independently. Jadad: 5/5.
Participants	Diagnosis: schizophrenia (90%), other (10%). History: TD >3 months, stable during 2 weeks pre-entry period, mean duration of TD for 97% >1 year, for 63% >5 yrs, mean duration of antipsychotic drugs 77% >10 yrs. N=60. Sex: female 33, male 27. Age: range 30-79 yrs. Setting: 97% longterm inpatients.
Interventions	1. Meclofenoxate hydrochloride (MF): dose 900 mg/day. N=31. 2. Placebo. N=29. Antipsychotics stable, antidepressants, minor tranquilisers, antiparkinsonian drugs were used but doses stable
Outcomes	TD symptoms: AIMS, FGIR. Global improvement: GUR. Adverse effects. Leaving study early. Unable to use - Mental state scores: BPRS (hypochondriasis item scored only, not all participants assessed)

Yagi 1990 (*Continued*)

Notes	For physiological monitoring no differences between MF and placebo groups. According to Overall Safety Rating MF caused no severe adverse effects, as did not placebo. Assistance with translation provided by Prof Toshiaki Furukawa, Nagoya, Japan

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Note: For crossover trials, the duration of trial indicates only length of first treatment period (before crossover), e.g. the period used in review analysis.
Scales:
AIMS = Abnormal Involuntary Movement Scale
BPRS = Brief Psychiatric Rating Scale
CGI = Clinical Global Impressions
ESRS = Extrapyramidal Symptom Rating Scale
HAM-D = Hamilton Rating Scale for Depression
MIBS = Missouri In-Patient Behavior Scale
SRTDRS = Self-Report Tardive Dyskinesia Rating Scale
STDRS = Simpson (Rockland) Tardive Dyskinesia Rating Scale
TAKE = Target Abnormal Kinetic Effects
Other abbreviations:
ANCOVA = Analysis of covariance
CPE = Chlorpromazine equivalent
ECG = Electrocardiogram
GI = gastrointestinal
OBS = Organic Brain Syndrome
PC = Phosphatidylcholine
TD = Tardive dyskinesia

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Anderson 1982	Allocation: publication does not specify if trial was randomised. One of authors contacted to confirm lack of additional data
Branchey 1979	Allocation: no mention of randomisation. Authors contacted twice, no reply
Caroff 2001	Allocation: not randomised.
Casey 1975	Allocation: not randomised, case study.

(*Continued*)

Casey 1977	Allocation: not randomised, ABAB design.
Casey 1979	Allocation: not randomised, clinical trial.
Chien 1978	Allocation: randomised. Interventions: deanol versus oxypertine versus sodium valproate, no placebo group
Crane 1975	Allocation: not randomised, case series.
Curran 1975	Allocation: not randomised, case study.
Davis 1975	Allocation: not randomised, case study.
Davis 1976	Allocation: not randomised, cohort study, AB(A).
Davis 1977	Allocation: not randomised, AB design.
Davis 1978	Allocation: not randomised, cohort study, AB.
De Silva 1975	Allocation: not randomised, case reports.
Domino 1985	Allocation: randomised. Participants: people with TD (not all had mental illness). N=19. Intervention: phosphatidylcholine (lecithin) versus placebo. Outcomes: AIMS, Physician′ s Global Impression of Patient′ s Mental Illness, Nurse′ s Global Impression of Patient′ s Mental Illness, ESS and mouth movements frequency count. Plasma and RBC choline concentration. Trial used crossover design. Unable to extract results from the first segment before crossover. Author contacted to confirm lack of additional data
Escobar 1975	Allocation: not randomised, case studies.
Fann 1974	Allocation: not randomised, clinical trial.
Fann 1975	Allocation: not randomised, cohort study.
Fann 1976	Allocation: not randomised, case series.
Gelenberg 1979	Allocation: not randomised, cohort study.
Granacher 1975	Allocation: not randomised, case series.
Growdon 1977	Allocation: not randomised.
Hanus 1993	Allocation: not randomised, open clinical study.
Ingram 1983	Allocation: not randomised, open clinical study.
Izumi 1986	Allocation: not randomised, open study.

(*Continued*)

Jus 1978	Allocation: randomised. Participants: people with TD. N=29. Interventions: deanol versus lithium carbonate versus placebo. Outcomes: AIMS, TD symptom rating scale, CGI, BPRS, NOSIE, vital signs, lab values. Trial used crossover design. Impossible to extract data. One of authors contacted to confirm lack of additional data
Klawans 1974	Allocation: not randomised, case series.
Kumar 1976	Allocation: not randomised, case study.
Laterre 1975	Allocation: not randomised, case study.
Lieberman 1988	Allocation: randomised. Participants: people with TD. N=15. Intervention: bromocriptine versus benztropine IV versus haloperidol IV versus physostigmine IV, no placebo
Lonowski 1979	Allocation: not randomised, controlled clinical trial.
Marsalek 1994	Allocation: not randomised, open trial.
Mehta 1976	Allocation: not randomised, case reports.
Moore 1980	Allocation: randomised. Interventions: challenge drugs given IV, not regarding subsequent deanol administration
Nasrallah 1984	Allocation: not randomised, cohort study, ABA.
Nasrallah 1986	Allocation: randomised. Participants: people with TD. N=10. Intervention: choline chloride versus AMPT versus L-Dopa versus valproic acid versus 5-hydroxytryptophan (5-HTP), not randomised to placebo
Noring 1984	Allocation: not randomised, controlled single-dose trials.
Penovich 1978	Allocation: randomised. Participants: people with TD. N=14. Interventions: deanol versus placebo. Outcomes: locally developed TD severity scale. Crossover design. impossible to extract results from segment before crossover. Author contacted to confirm lack of additional data
Ray 1982	Allocation: not randomised, case series.
Rektor 1988	Allocation: not randomised.
Simpson 1977	Allocation: randomised. Participants: excluded because neuroleptic medication for some participants abruptly stopped 4 weeks before start of trial

(*Continued)*

Tamminga 1977	Allocation: not randomised, ABA design.
Volavka 1986	Allocation: no description of randomisation,. Participants: people with TD. N=18. Intervention: lithium versus lithium + lecithin, no placebo, no lecithin only group
Zapletalek 1989	Allocation: not randomised, open study.

Abbreviations:
AIMS - Abnormal Involuntary Movement Scale
BPRS - Brief Psychiatric Rating Scale
ESS - Emergent Symptom Scale (adverse effects)
HD - Huntington´ s Disease
NOSIE - Nurses´ Observation Scale for Inpatient Evaluation
RBC - Red blood cell
TD - Tardive dyskinesia

Characteristics of ongoing studies *[ordered by study ID]*

Caroff 2002

Trial name or title	Treatment of tardive dyskinesia with galantamine
Methods	
Participants	Diagnosis: people with tardive dyskinesia.
Interventions	1. Galantamine. 2. Placebo.
Outcomes	No details available.
Starting date	1/1/2002
Contact information	Investigators: Stanley N. Caroff, M.D.(Caroff.Stanley_N+@philadelphia.VA.gov), E. Cabrina Campbell, M. D., Patricia Walker, Joan Havey, Stephan C. Mann, M.D., Kenneth A. Sullivan, Ph.D Location: Department of Veterans Affairs Medical Center and the University of Pennsylvania, Philadelphia, Pennsylvania, USA
Notes	Allocation: randomised. Blindness: double. Design: crossover. Sponsor: Janssen Pharmaceutica.

DATA AND ANALYSES

Comparison 1. CHOLINERGIC DRUGS versus PLACEBO

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death for any reason	10	240	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.1 lecithin - less than 6 weeks	3	86	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 deanol - over 6 weeks	2	11	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 deanol - less than 6 weeks	4	83	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.4 meclofenoxate - over 6 weeks	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Global outcome: Intervention not useful as assessed by Global Usefulness Rating (GUR)	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.59, 1.32]
2.1 meclofenoxate - over 6 weeks	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.59, 1.32]
3 Tardive dyskinesia: 1. No clinically important improvement (50% or more change on any validated TD scale)	3	17	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.44, 1.37]
3.1 lecithin - less than 6 weeks	1	6	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.31, 1.66]
3.2 deanol - over 6 weeks	2	11	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.39, 1.81]
4 Tardive dyskinesia: 2a. Not any improvement (as assessed by rater)	8	170	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.68, 1.04]
4.1 lecithin - less than 6 weeks	2	36	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.63, 1.21]
4.2 deanol - over 6 weeks	2	11	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.26, 2.57]
4.3 deanol - less than 6 weeks	3	63	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.58, 1.18]
4.4 meclofenoxate - over 6 weeks	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.55, 1.27]
5 Tardive dyskinesia: 2b. Not any improvement (as assessed by self report)	1	30	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.62, 1.36]
5.1 lecithin - less than 6 weeks	1	30	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.62, 1.36]
6 Tardive dyskinesia: 3a. Deterioration (as assessed by rater)	7	137	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.56, 2.43]
6.1 lecithin - less than 6 weeks	2	36	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.16, 6.31]
6.2 deanol - over 6 weeks	2	11	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.20, 2.18]
6.3 deanol - less than 6 weeks	2	30	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [0.48, 5.76]
6.4 meclofenoxate - over 6 weeks	1	60	Risk Ratio (M-H, Fixed, 95% CI)	1.87 [0.18, 19.55]
7 Tardive dyskinesia: 3b. Deterioration (as assessed by self report)	1	30	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.13, 68.26]
7.1 lecithin - less than 6 weeks	1	30	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.13, 68.26]

8 Tardive dyskinesia: 4a. Average endpoint score on AIMS (low score = better)	4	86	Mean Difference (IV, Fixed, 95% CI)	-0.19 [-0.53, 0.14]
8.1 lecithin - over 6 weeks	1	14	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-1.04, 0.84]
8.2 lecithin - less than 6 weeks	1	6	Mean Difference (IV, Fixed, 95% CI)	-1.07 [-2.21, 0.07]
8.3 deanol - over 6 weeks	1	6	Mean Difference (IV, Fixed, 95% CI)	1.42 [-0.29, 3.13]
8.4 meclofenoxate - over 6 weeks	1	60	Mean Difference (IV, Fixed, 95% CI)	-0.19 [-0.58, 0.20]
9 Tardive dyskinesia: 4b. Average endpoint score on modified Simpson TDRS (low score = better)	1	5	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.1 deanol - over 6 weeks	1	5	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
10 Tardive dyskinesia: 4c. Average endpoint score on CGI (low score = better)	1	31	Mean Difference (IV, Fixed, 95% CI)	-0.43 [-1.36, 0.50]
10.1 lecithin - less than 6 weeks	1	31	Mean Difference (IV, Fixed, 95% CI)	-0.43 [-1.36, 0.50]
11 Mental state: Deterioration	5	77	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.10, 2.61]
11.1 lecithin - less than 6 weeks	2	56	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.81]
11.2 deanol - over 6 weeks	2	11	Risk Ratio (M-H, Fixed, 95% CI)	1.2 [0.08, 18.75]
11.3 deanol - less than 6 weeks	1	10	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.02, 6.65]
12 Adverse effects: Various	9		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
12.1 lecithin - GI adverse effects	2	36	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12.2 lecithin - any other adverse effects, undesirable body odour, sedation	2	36	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12.3 deanol - gastric adverse effects	5	61	Risk Ratio (M-H, Fixed, 95% CI)	9.0 [0.55, 147.95]
12.4 deanol - sedation, periferal cholinergic effects, undesirable body odour	6	94	Risk Ratio (M-H, Fixed, 95% CI)	6.83 [0.99, 47.25]
12.5 meclofenoxate - any adverse effects	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.15, 2.14]
13 Leaving the study early	10	240	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.21, 1.33]
13.1 lecithin - less than 6 weeks	3	86	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.17, 1.45]
13.2 deanol - over 6 weeks	2	11	Risk Ratio (M-H, Fixed, 95% CI)	1.2 [0.08, 18.75]
13.3 deanol - less than 6 weeks	4	83	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.02, 6.65]
13.4 meclofenoxate - over 6 weeks	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

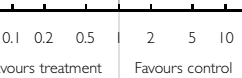
Analysis 1.1. Comparison 1 CHOLINERGIC DRUGS versus PLACEBO, Outcome 1 Death for any reason.

Review: Cholinergic medication for neuroleptic-induced tardive dyskinesia

Comparison: 1 CHOLINERGIC DRUGS versus PLACEBO

Outcome: 1 Death for any reason

Study or subgroup	Cholinergic drug n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 lecithin - less than 6 weeks				
Beckham 1981	0/25	0/25		0.0 [0.0, 0.0]
Jackson 1979	0/3	0/3		0.0 [0.0, 0.0]
Price 1982	0/15	0/15		0.0 [0.0, 0.0]
Subtotal (95% CI)	**43**	**43**		**0.0 [0.0, 0.0]**
Total events: 0 (Cholinergic drug), 0 (Control)				
Heterogeneity: Chi^2 = 0.0, df = 0 (P<0.00001); I^2 =0.0%				
Test for overall effect: Z = 0.0 (P < 0.00001)				
2 deanol - over 6 weeks				
Jackson 1978	0/4	0/2		0.0 [0.0, 0.0]
Tarsy 1977	0/4	0/1		0.0 [0.0, 0.0]
Subtotal (95% CI)	**8**	**3**		**0.0 [0.0, 0.0]**
Total events: 0 (Cholinergic drug), 0 (Control)				
Heterogeneity: Chi^2 = 0.0, df = 0 (P<0.00001); I^2 =0.0%				
Test for overall effect: Z = 0.0 (P < 0.00001)				
3 deanol - less than 6 weeks				
de Montigny 1979	0/10	0/10		0.0 [0.0, 0.0]
George 1981	0/22	0/11		0.0 [0.0, 0.0]
Kocher 1980	0/10	0/10		0.0 [0.0, 0.0]
Lucius 1976	0/5	0/5		0.0 [0.0, 0.0]
Subtotal (95% CI)	**47**	**36**		**0.0 [0.0, 0.0]**
Total events: 0 (Cholinergic drug), 0 (Control)				
Heterogeneity: Chi^2 = 0.0, df = 0 (P<0.00001); I^2 =0.0%				
Test for overall effect: Z = 0.0 (P < 0.00001)				
4 meclofenoxate - over 6 weeks				
Yagi 1990	0/31	0/29		0.0 [0.0, 0.0]
Subtotal (95% CI)	**31**	**29**		**0.0 [0.0, 0.0]**
Total events: 0 (Cholinergic drug), 0 (Control)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Total (95% CI)	**129**	**111**		**0.0 [0.0, 0.0]**
Total events: 0 (Cholinergic drug), 0 (Control)				
Heterogeneity: Chi^2 = 0.0, df = 0 (P<0.00001); I^2 =0.0%				
Test for overall effect: Z = 0.0 (P < 0.00001)				



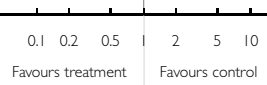
Analysis 1.2. Comparison 1 CHOLINERGIC DRUGS versus PLACEBO, Outcome 2 Global outcome: Intervention not useful as assessed by Global Usefulness Rating (GUR).

Review: Cholinergic medication for neuroleptic-induced tardive dyskinesia

Comparison: 1 CHOLINERGIC DRUGS versus PLACEBO

Outcome: 2 Global outcome: Intervention not useful as assessed by Global Usefulness Rating (GUR)

Study or subgroup	Cholinergic agent n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 meclofenoxate - over 6 weeks					
Yagi 1990	18/31	19/29		100.0 %	0.89 [0.59, 1.32]
Total (95% CI)	**31**	**29**		**100.0 %**	**0.89 [0.59, 1.32]**
Total events: 18 (Cholinergic agent), 19 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.59 (P = 0.55)					



Analysis 1.3. Comparison 1 CHOLINERGIC DRUGS versus PLACEBO, Outcome 3 Tardive dyskinesia: 1. No clinically important improvement (50% or more change on any validated TD scale).

Review: Cholinergic medication for neuroleptic-induced tardive dyskinesia

Comparison: 1 CHOLINERGIC DRUGS versus PLACEBO

Outcome: 3 Tardive dyskinesia: 1. No clinically important improvement (50% or more change on any validated TD scale)

Study or subgroup	Cholinergic drug n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 lecithin - less than 6 weeks				
Jackson 1979	2/3	3/3		0.71 [0.31, 1.66]
Subtotal (95% CI)	**3**	**3**		**0.71 [0.31, 1.66]**
Total events: 2 (Cholinergic drug), 3 (Control)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.78 (P = 0.43)				
2 deanol - over 6 weeks				
Jackson 1978	3/4	2/2		0.84 [0.39, 1.81]
Tarsy 1977	4/4	1/1		0.0 [0.0, 0.0]
Subtotal (95% CI)	**8**	**3**		**0.84 [0.39, 1.81]**
Total events: 7 (Cholinergic drug), 3 (Control)				
Heterogeneity: Chi^2 = 0.0, df = 0 (P = 1.00); I^2 =0.0%				
Test for overall effect: Z = 0.45 (P = 0.66)				
Total (95% CI)	**11**	**6**		**0.77 [0.44, 1.37]**
Total events: 9 (Cholinergic drug), 6 (Control)				
Heterogeneity: Chi^2 = 0.08, df = 1 (P = 0.78); I^2 =0.0%				
Test for overall effect: Z = 0.88 (P = 0.38)				

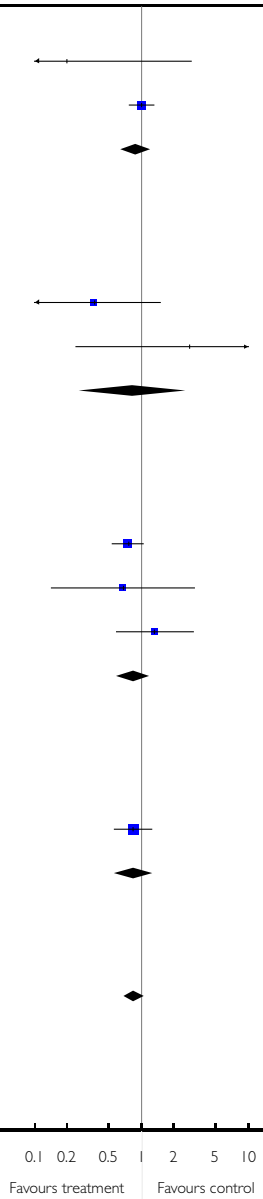
Analysis 1.4. Comparison 1 CHOLINERGIC DRUGS versus PLACEBO, Outcome 4 Tardive dyskinesia: 2a. Not any improvement (as assessed by rater).

Review: Cholinergic medication for neuroleptic-induced tardive dyskinesia

Comparison: 1 CHOLINERGIC DRUGS versus PLACEBO

Outcome: 4 Tardive dyskinesia: 2a. Not any improvement (as assessed by rater)

Study or subgroup	Cholinergic drug n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 lecithin - less than 6 weeks					
Jackson 1979	0/3	2/3		4.3 %	0.20 [0.01, 2.98]
Price 1982	13/15	13/15		22.3 %	1.00 [0.76, 1.32]
Subtotal (95% CI)	**18**	**18**		**26.6 %**	**0.87 [0.63, 1.21]**
Total events: 13 (Cholinergic drug), 15 (Control)					
Heterogeneity: Chi^2 = 2.07, df = 1 (P = 0.15); I^2 =52%					
Test for overall effect: Z = 0.83 (P = 0.41)					
2 deanol - over 6 weeks					
Jackson 1978	1/4	2/2		5.4 %	0.36 [0.09, 1.51]
Tarsy 1977	3/4	0/1		1.2 %	2.80 [0.24, 33.04]
Subtotal (95% CI)	**8**	**3**		**6.6 %**	**0.81 [0.26, 2.57]**
Total events: 4 (Cholinergic drug), 2 (Control)					
Heterogeneity: Chi^2 = 2.21, df = 1 (P = 0.14); I^2 =55%					
Test for overall effect: Z = 0.35 (P = 0.73)					
3 deanol - less than 6 weeks					
George 1981	15/22	10/11		22.9 %	0.75 [0.53, 1.05]
Kocher 1980	2/10	3/10		5.1 %	0.67 [0.14, 3.17]
Lucius 1976	4/5	3/5		5.1 %	1.33 [0.58, 3.09]
Subtotal (95% CI)	**37**	**26**		**33.2 %**	**0.83 [0.58, 1.18]**
Total events: 21 (Cholinergic drug), 16 (Control)					
Heterogeneity: Chi^2 = 1.63, df = 2 (P = 0.44); I^2 =0.0%					
Test for overall effect: Z = 1.05 (P = 0.29)					
4 meclofenoxate - over 6 weeks					
Yagi 1990	17/31	19/29		33.7 %	0.84 [0.55, 1.27]
Subtotal (95% CI)	**31**	**29**		**33.7 %**	**0.84 [0.55, 1.27]**
Total events: 17 (Cholinergic drug), 19 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.84 (P = 0.40)					
Total (95% CI)	**94**	**76**		**100.0 %**	**0.84 [0.68, 1.04]**
Total events: 55 (Cholinergic drug), 52 (Control)					
Heterogeneity: Chi^2 = 6.48, df = 7 (P = 0.48); I^2 =0.0%					
Test for overall effect: Z = 1.57 (P = 0.12)					

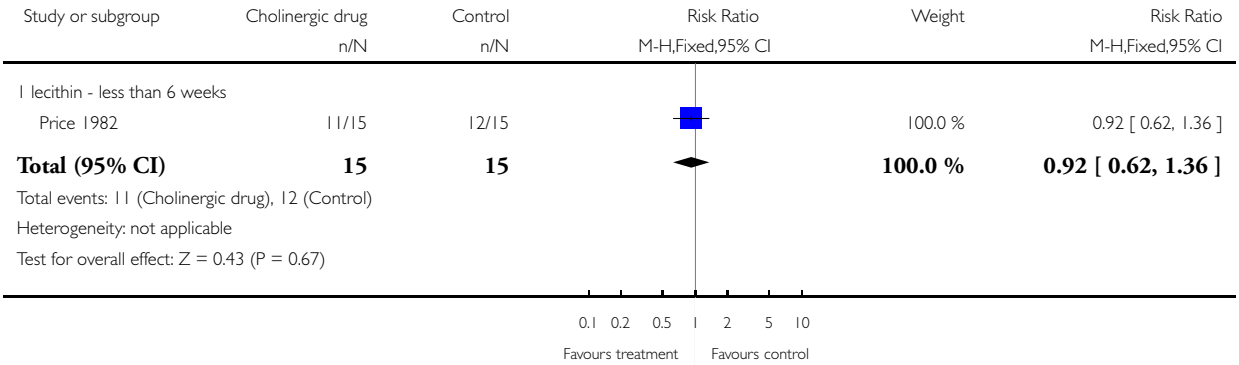


Analysis 1.5. Comparison 1 CHOLINERGIC DRUGS versus PLACEBO, Outcome 5 Tardive dyskinesia: 2b. Not any improvement (as assessed by self report).

Review: Cholinergic medication for neuroleptic-induced tardive dyskinesia

Comparison: 1 CHOLINERGIC DRUGS versus PLACEBO

Outcome: 5 Tardive dyskinesia: 2b. Not any improvement (as assessed by self report)



Analysis 1.6. Comparison 1 CHOLINERGIC DRUGS versus PLACEBO, Outcome 6 Tardive dyskinesia: 3a. Deterioration (as assessed by rater).

Review: Cholinergic medication for neuroleptic-induced tardive dyskinesia

Comparison: 1 CHOLINERGIC DRUGS versus PLACEBO

Outcome: 6 Tardive dyskinesia: 3a. Deterioration (as assessed by rater)

Study or subgroup	Cholinergic drug n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 lecithin - less than 6 weeks					
Jackson 1979	0/3	1/3		15.2 %	0.33 [0.02, 5.97]
Price 1982	1/15	0/15		5.1 %	3.00 [0.13, 68.26]
Subtotal (95% CI)	**18**	**18**		**20.3 %**	**1.00 [0.16, 6.31]**
Total events: 1 (Cholinergic drug), 1 (Control)					
Heterogeneity: Chi^2 = 1.03, df = 1 (P = 0.31); I^2 =3%					
Test for overall effect: Z = 0.0 (P = 1.0)					
2 deanol - over 6 weeks					
Jackson 1978	1/4	2/2		31.7 %	0.36 [0.09, 1.51]
Tarsy 1977	2/4	0/1		7.2 %	2.00 [0.16, 25.75]
Subtotal (95% CI)	**8**	**3**		**38.9 %**	**0.67 [0.20, 2.18]**
Total events: 3 (Cholinergic drug), 2 (Control)					
Heterogeneity: Chi^2 = 1.42, df = 1 (P = 0.23); I^2 =30%					
Test for overall effect: Z = 0.67 (P = 0.50)					
3 deanol - less than 6 weeks					
Kocher 1980	2/10	2/10		20.3 %	1.00 [0.17, 5.77]
Lucius 1976	3/5	1/5		10.1 %	3.00 [0.45, 19.93]
Subtotal (95% CI)	**15**	**15**		**30.4 %**	**1.67 [0.48, 5.76]**
Total events: 5 (Cholinergic drug), 3 (Control)					
Heterogeneity: Chi^2 = 0.70, df = 1 (P = 0.40); I^2 =0.0%					
Test for overall effect: Z = 0.81 (P = 0.42)					
4 meclofenoxate - over 6 weeks					
Yagi 1990	2/31	1/29		10.5 %	1.87 [0.18, 19.55]
Subtotal (95% CI)	**31**	**29**		**10.5 %**	**1.87 [0.18, 19.55]**
Total events: 2 (Cholinergic drug), 1 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.52 (P = 0.60)					
Total (95% CI)	**72**	**65**		**100.0 %**	**1.16 [0.56, 2.43]**
Total events: 11 (Cholinergic drug), 7 (Control)					
Heterogeneity: Chi^2 = 4.97, df = 6 (P = 0.55); I^2 =0.0%					
Test for overall effect: Z = 0.40 (P = 0.69)					

Analysis 1.7. Comparison 1 CHOLINERGIC DRUGS versus PLACEBO, Outcome 7 Tardive dyskinesia: 3b. Deterioration (as assessed by self report).

Review: Cholinergic medication for neuroleptic-induced tardive dyskinesia

Comparison: 1 CHOLINERGIC DRUGS versus PLACEBO

Outcome: 7 Tardive dyskinesia: 3b. Deterioration (as assessed by self report)

Study or subgroup	Cholinergic drug n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 lecithin - less than 6 weeks					
Price 1982	1/15	0/15		100.0 %	3.00 [0.13, 68.26]
Total (95% CI)	**15**	**15**		**100.0 %**	**3.00 [0.13, 68.26]**
Total events: 1 (Cholinergic drug), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.69 (P = 0.49)					

Analysis 1.8. Comparison 1 CHOLINERGIC DRUGS versus PLACEBO, Outcome 8 Tardive dyskinesia: 4a. Average endpoint score on AIMS (low score = better).

Review: Cholinergic medication for neuroleptic-induced tardive dyskinesia

Comparison: 1 CHOLINERGIC DRUGS versus PLACEBO

Outcome: 8 Tardive dyskinesia: 4a. Average endpoint score on AIMS (low score = better)

Study or subgroup	Cholinergic drug N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 lecithin - over 6 weeks							
Gelenberg 1990	5	2.3 (0.82)	9	2.4 (0.92)		12.7 %	-0.10 [-1.04, 0.84]
Subtotal (95% CI)	**5**		**9**			**12.7 %**	**-0.10 [-1.04, 0.84]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.21 (P = 0.83)							
2 lecithin - less than 6 weeks							
Jackson 1979	3	1.93 (0.12)	3	3 (1)		8.6 %	-1.07 [-2.21, 0.07]
Subtotal (95% CI)	**3**		**3**			**8.6 %**	**-1.07 [-2.21, 0.07]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.84 (P = 0.066)							
3 deanol - over 6 weeks							
Jackson 1978	4	2.82 (1.26)	2	1.4 (0.85)		3.8 %	1.42 [-0.29, 3.13]
Subtotal (95% CI)	**4**		**2**			**3.8 %**	**1.42 [-0.29, 3.13]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.63 (P = 0.10)							
4 meclofenoxate - over 6 weeks							
Yagi 1990	31	2.29 (0.74)	29	2.48 (0.78)		74.9 %	-0.19 [-0.58, 0.20]
Subtotal (95% CI)	**31**		**29**			**74.9 %**	**-0.19 [-0.58, 0.20]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.97 (P = 0.33)							
Total (95% CI)	**43**		**43**			**100.0 %**	**-0.19 [-0.53, 0.14]**
Heterogeneity: Chi^2 = 5.74, df = 3 (P = 0.12); I^2 =48%							
Test for overall effect: Z = 1.13 (P = 0.26)							
Test for subgroup differences: Chi^2 = 5.74, df = 3 (P = 0.12), I^2 =48%							

Analysis 1.9. Comparison 1 CHOLINERGIC DRUGS versus PLACEBO, Outcome 9 Tardive dyskinesia: 4b. Average endpoint score on modified Simpson TDRS (low score = better).

Review: Cholinergic medication for neuroleptic-induced tardive dyskinesia

Comparison: 1 CHOLINERGIC DRUGS versus PLACEBO

Outcome: 9 Tardive dyskinesia: 4b. Average endpoint score on modified Simpson TDRS (low score = better)

Study or subgroup	Cholinergic drug N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 deanol - over 6 weeks						
Tarsy 1977	4	10 (5.48)	1	10 (0)		0.0 [0.0, 0.0]
Total (95% CI)	**4**		**1**			**0.0 [0.0, 0.0]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.0 (P < 0.00001)

Test for subgroup differences: Chi^2 = 0.0, df = -1 (P = 0.0), I^2 =0.0%

Analysis 1.10. Comparison 1 CHOLINERGIC DRUGS versus PLACEBO, Outcome 10 Tardive dyskinesia: 4c. Average endpoint score on CGI (low score = better).

Review: Cholinergic medication for neuroleptic-induced tardive dyskinesia

Comparison: 1 CHOLINERGIC DRUGS versus PLACEBO

Outcome: 10 Tardive dyskinesia: 4c. Average endpoint score on CGI (low score = better)

Study or subgroup	Cholinergic drug N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 lecithin - less than 6 weeks							
Beckham 1981	15	3.2 (1.42)	16	3.63 (1.2)		100.0 %	-0.43 [-1.36, 0.50]
Total (95% CI)	**15**		**16**			**100.0 %**	**-0.43 [-1.36, 0.50]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.91 (P = 0.36)

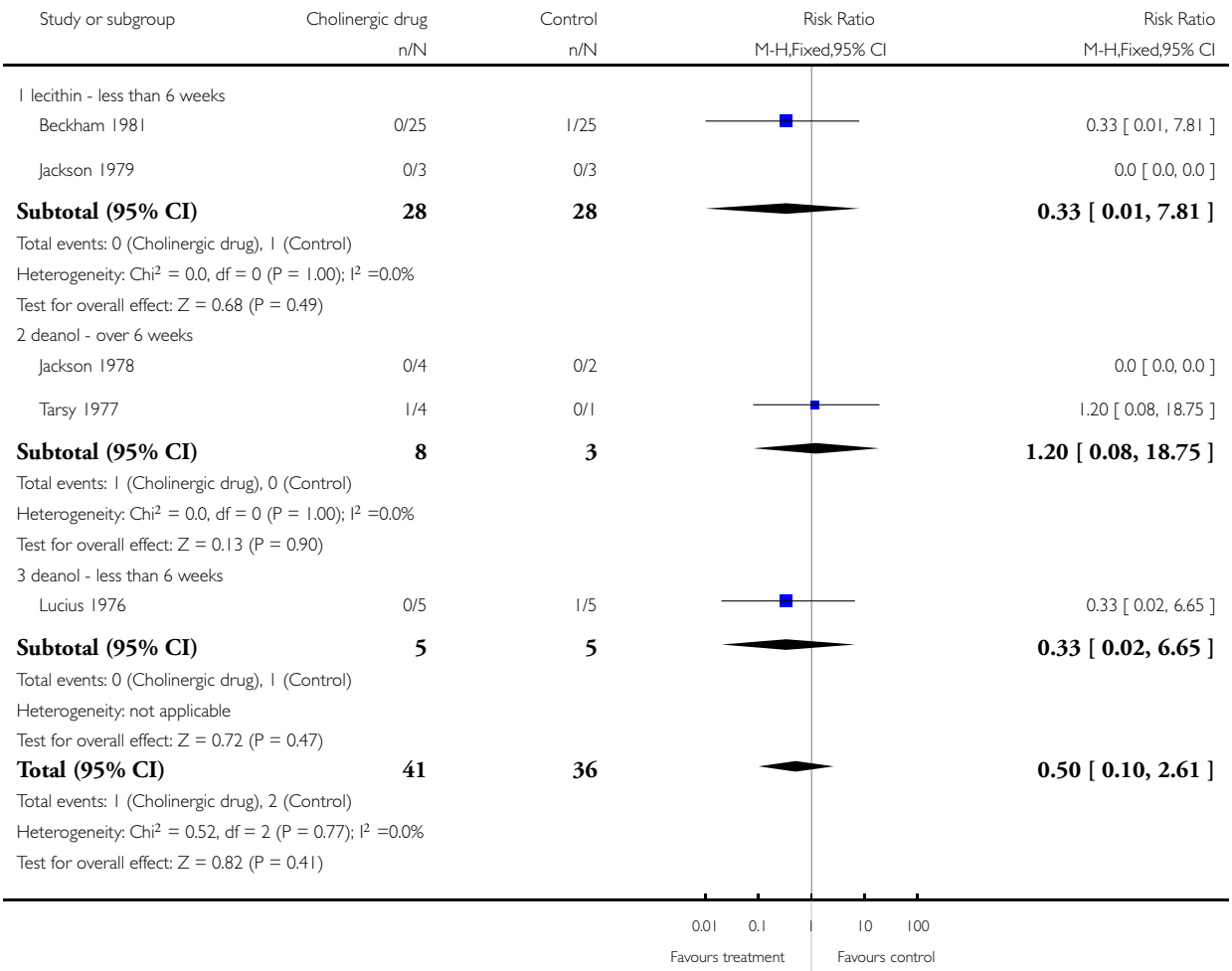
Test for subgroup differences: Not applicable

Analysis 1.11. Comparison 1 CHOLINERGIC DRUGS versus PLACEBO, Outcome 11 Mental state: Deterioration.

Review: Cholinergic medication for neuroleptic-induced tardive dyskinesia

Comparison: 1 CHOLINERGIC DRUGS versus PLACEBO

Outcome: 11 Mental state: Deterioration



Analysis 1.12. Comparison 1 CHOLINERGIC DRUGS versus PLACEBO, Outcome 12 Adverse effects: Various.

Review: Cholinergic medication for neuroleptic-induced tardive dyskinesia

Comparison: 1 CHOLINERGIC DRUGS versus PLACEBO

Outcome: 12 Adverse effects: Various

Study or subgroup	Cholinergic drug n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 lecithin - GI adverse effects				
Jackson 1979	0/3	0/3		0.0 [0.0, 0.0]
Price 1982	0/15	0/15		0.0 [0.0, 0.0]
Subtotal (95% CI)	**18**	**18**		**0.0 [0.0, 0.0]**
Total events: 0 (Cholinergic drug), 0 (Control)				
Heterogeneity: Chi² = 0.0, df = 0 (P<0.00001); I² =0.0%				
Test for overall effect: Z = 0.0 (P < 0.00001)				
2 lecithin - any other adverse effects, undesirable body odour, sedation				
Jackson 1979	0/3	0/3		0.0 [0.0, 0.0]
Price 1982	0/15	0/15		0.0 [0.0, 0.0]
Subtotal (95% CI)	**18**	**18**		**0.0 [0.0, 0.0]**
Total events: 0 (Cholinergic drug), 0 (Control)				
Heterogeneity: Chi² = 0.0, df = 0 (P<0.00001); I² =0.0%				
Test for overall effect: Z = 0.0 (P < 0.00001)				
3 deanol - gastric adverse effects				
de Montigny 1979	4/10	0/10		9.00 [0.55, 147.95]
Jackson 1978	0/4	0/2		0.0 [0.0, 0.0]
Kocher 1980	0/10	0/10		0.0 [0.0, 0.0]
Lucius 1976	0/5	0/5		0.0 [0.0, 0.0]
Tarsy 1977	0/4	0/1		0.0 [0.0, 0.0]
Subtotal (95% CI)	**33**	**28**		**9.00 [0.55, 147.95]**
Total events: 4 (Cholinergic drug), 0 (Control)				
Heterogeneity: Chi² = 0.0, df = 0 (P = 1.00); I² =0.0%				
Test for overall effect: Z = 1.54 (P = 0.12)				
4 deanol - sedation, periferal cholinergic effects, undesirable body odour				
de Montigny 1979	5/10	0/10		11.00 [0.69, 175.86]
George 1981	3/22	0/11		3.65 [0.21, 65.05]
Jackson 1978	0/4	0/2		0.0 [0.0, 0.0]
Kocher 1980	0/10	0/10		0.0 [0.0, 0.0]
Lucius 1976	0/5	0/5		0.0 [0.0, 0.0]

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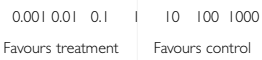
Study or subgroup	Cholinergic drug n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Tarsy 1977	0/4	0/1		0.0 [0.0, 0.0]
Subtotal (95% CI)	**55**	**39**		**6.83 [0.99, 47.25]**
Total events: 8 (Cholinergic drug), 0 (Control)				
Heterogeneity: Chi^2 = 0.30, df = 1 (P = 0.59); I^2 =0.0%				
Test for overall effect: Z = 1.95 (P = 0.052)				
5 meclofenoxate - any adverse effects				
Yagi 1990	3/31	5/29		0.56 [0.15, 2.14]
Subtotal (95% CI)	**31**	**29**		**0.56 [0.15, 2.14]**
Total events: 3 (Cholinergic drug), 5 (Control)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.85 (P = 0.40)				



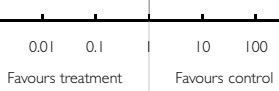
Analysis 1.13. Comparison 1 CHOLINERGIC DRUGS versus PLACEBO, Outcome 13 Leaving the study early.

Review: Cholinergic medication for neuroleptic-induced tardive dyskinesia

Comparison: 1 CHOLINERGIC DRUGS versus PLACEBO

Outcome: 13 Leaving the study early

Study or subgroup	Cholinergic drug n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 lecithin - less than 6 weeks				
Beckham 1981	4/25	8/25		0.50 [0.17, 1.45]
Jackson 1979	0/3	0/3		0.0 [0.0, 0.0]
Price 1982	0/15	0/15		0.0 [0.0, 0.0]
Subtotal (95% CI)	**43**	**43**		**0.50 [0.17, 1.45]**
Total events: 4 (Cholinergic drug), 8 (Control)				
Heterogeneity: Chi^2 = 0.0, df = 0 (P = 1.00); I^2 =0.0%				
Test for overall effect: Z = 1.28 (P = 0.20)				
2 deanol - over 6 weeks				
Jackson 1978	0/4	0/2		0.0 [0.0, 0.0]
Tarsy 1977	1/4	0/1		1.20 [0.08, 18.75]
Subtotal (95% CI)	**8**	**3**		**1.20 [0.08, 18.75]**
Total events: 1 (Cholinergic drug), 0 (Control)				
Heterogeneity: Chi^2 = 0.0, df = 0 (P = 1.00); I^2 =0.0%				
Test for overall effect: Z = 0.13 (P = 0.90)				
3 deanol - less than 6 weeks				
de Montigny 1979	0/10	0/10		0.0 [0.0, 0.0]
George 1981	0/22	0/11		0.0 [0.0, 0.0]
Kocher 1980	0/10	0/10		0.0 [0.0, 0.0]
Lucius 1976	0/5	1/5		0.33 [0.02, 6.65]
Subtotal (95% CI)	**47**	**36**		**0.33 [0.02, 6.65]**
Total events: 0 (Cholinergic drug), 1 (Control)				
Heterogeneity: Chi^2 = 0.0, df = 0 (P = 1.00); I^2 =0.0%				
Test for overall effect: Z = 0.72 (P = 0.47)				
4 meclofenoxate - over 6 weeks				
Yagi 1990	0/31	0/29		0.0 [0.0, 0.0]
Subtotal (95% CI)	**31**	**29**		**0.0 [0.0, 0.0]**
Total events: 0 (Cholinergic drug), 0 (Control)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Total (95% CI)	**129**	**111**		**0.52 [0.21, 1.33]**



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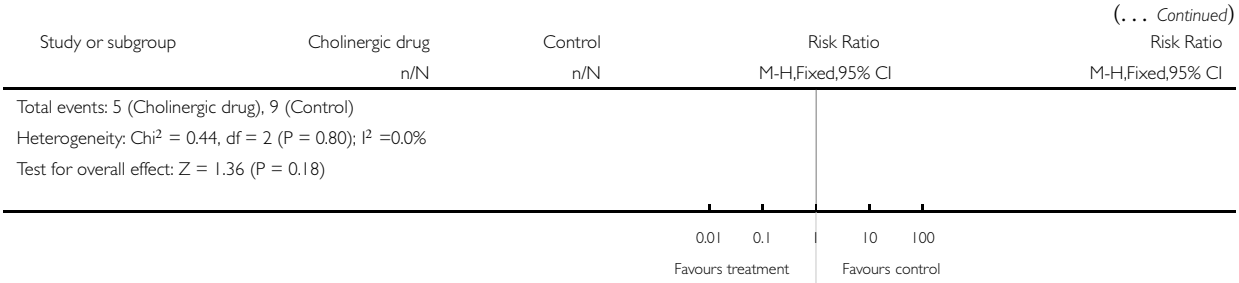

WHAT'S NEW

Last assessed as up-to-date: 17 May 2002.

Date	Event	Description
18 January 2012	Amended	Contact details updated.

HISTORY

Protocol first published: Issue 2, 1996

Review first published: Issue 2, 1997

Date	Event	Description
19 January 2011	Amended	Contact details updated.
10 November 2010	Amended	Contact details updated.
14 April 2010	Amended	Contact details updated.
16 January 2009	Amended	author correction
25 April 2008	Amended	Converted to new review format.
17 May 2002	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Irina Tammenmaa - searching for trials, evaluating trials, data extraction, analysis, writing of final report.

John McGrath - protocol development, author of first version of review, advisory.

Eila Sailas - evaluating trials.

Karla Soares-Weiser - protocol development, author of first version of review.

DECLARATIONS OF INTEREST

Irina Tammenmaa - None

John McGrath - None

Eila Sailas - None

Karla Soares-Weiser - None

SOURCES OF SUPPORT

Internal sources

- Queensland Health, Australia.
- CAPES - Ministry of Education, Brazil.
- Lapinlahti Hospital, Dept. of Psychiatry, University of Helsinki, Finland.

External sources

- Universidade Federal de Sao Paulo, Brazil.
- FinOHTA, STAKES, Finland.

NOTES

Cochrane Schizophrenia Group internal peer review complete (see Module).

External peer review complete.

INDEX TERMS

Medical Subject Headings (MeSH)

Antipsychotic Agents [adverse effects]; Cholinergic Agents [*therapeutic use]; Dyskinesia, Drug-Induced [*drug therapy; etiology]; Randomized Controlled Trials as Topic

MeSH check words

Humans