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[Intervention Review]

Anticholinergics for symptomatic management of Parkinson´s disease

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ABSTRACT

Background

Anticholinergics were the first drugs available for the symptomatic treatment of Parkinson´s disease and they are still widely used today, both as monotherapy and as part of combination regimes. They are commonly believed to be associated with a less favourable side effect profile than other antiparkinsonian drugs, in particular with respect to neuropsychiatric and cognitive adverse events. They have been claimed to exert a better effect on tremor than on other parkinsonian features.

Objectives

To determine the efficacy and tolerability of anticholinergics in the symptomatic treatment of Parkinson´s disease compared to placebo or no treatment.

Search methods

The literature search included electronic searches of the Cochrane Controlled Trials Register (The Cochrane Library, Issue 4, 2001), MEDLINE (1966 to 2001), Old Medline (1960-1965), Index Medicus (1927 - 1959), as well as handsearching the neurology literature including the reference lists of identified articles, other reviews and book chapters.

Selection criteria

Randomised controlled trials of anticholinergic drugs versus placebo or no treatment in de-novo or advanced Parkinson´s disease, either as monotherapy or as an add-on to other antiparkinsonian drugs were included. Trials of anticholinergic drugs that were never in general clinical use were excluded.

Data collection and analysis

Data was abstracted independently by two authors. Differences were settled by discussion among all authors. Data collected included patient characteristics, disease duration and severity, concomitant medication, interventions including duration and dose of anticholinergic treatment, outcome measures, rates of and reasons for withdrawals, and neuropsychiatric and cognitive adverse events.

Main results

The initial search yielded 14 potentially eligible studies, five of which were subsequently excluded. In three cases this was because they dealt with substances that had never been marketed or had not been licensed for as far as could be traced back. One trial had been published twice in different languages. One study was excluded based on the assessment of its methodological quality.
The remaining nine studies were all of double-blind cross-over design and included 221 patients. Trial duration was between five and 20 weeks and drugs investigated were benzhexol (mean doses: 8 to 20 mg/d), orphenadrine (mean dose not reported), benztropine (mean dose not reported), bornaprine (8 to 8.25 mg/d), benapryzine (200 mg/d), and methixine (45 mg/d). Only one study involved two

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anticholinergic drugs. Outcome measures varied widely across studies and in many cases, the scales applied were the authors´ own and were not defined in detail. Incomplete reporting of methodology and results was frequent. The heterogeneous study designs as well as incomplete reporting precluded combined statistical analysis.
Five studies used both tremor and other parkinsonian features as outcome measures. Outcome measures in these five studies were too different for a combined analysis and results varied widely, from a significant improvement in tremor only to significant improvement in other features but not in tremor.
All studies except one (dealing with methixine) found a significant improvement from baseline on the anticholinergic drug in at least one outcome measure. The difference between placebo and active drug was reported in four studies and was found to be significant in all cases. No study failed to show superiority of the anticholinergic over placebo.
The occurrence of neuropsychiatric and cognitive adverse events was reported in all but three studies (in 35 patients on active drug versus 13 on placebo). The most frequently reported reason for drop-outs from studies was in patients on placebo due to withdrawal from pre-trial anticholinergic treatment.

Authors' conclusions

As monotherapy or as an adjunct to other antiparkinsonian drugs, anticholinergics are more effective than placebo in improving motor function in Parkinson´s disease. Neuropsychiatric and cognitive adverse events occur more frequently on anticholinergics than on placebo and are a more common reason for withdrawal than lack of efficacy.
Results regarding a potentially better effect of the anticholinergic drug on tremor than on other outcome measures are conflicting and data do not strongly support a differential clinical effect on individual parkinsonian features.
Data is insufficient to allow comparisons in efficacy or tolerability between individual anticholinergic drugs.

PLAIN LANGUAGE SUMMARY

Anticholinergic drugs can improve movement symptoms of Parkinson's disease, but with adverse mental effects, and there is not enough evidence to compare the different drugs.

Anticholinergics were the first drugs available for Parkinson´s disease and they are still widely used. They are believed to work by counteracting an imbalance which exists in Parkinson´s disease between two chemicals in the brain which transmit messages between nerve cells. However, anticholinergic drugs have been associated with unfavourable side effects. They are used alone, or with other anti-Parkinson's drugs. The review of trials found that anticholinergics can improve movement problems in people with Parkinson's disease, but also cause adverse mental effects (such as confusion, memory problems, restlessness and hallucinations). There is not enough evidence to compare the different anticholinergic drugs.

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BACKGROUND

The antiparkinsonian effect of anticholinergics was discovered in 1867 (Ordenstein 1867), and for nearly a century, they remained the only drugs available for the symptomatic treatment of Parkinson´s disease. Initially, naturally occurring alkaloid extracts were used. These were increasingly replaced with synthetic anticholinergic agents from the 1940s on.

The exact mechanism of action of anticholinergic drugs in the relief of parkinsonian symptoms remains undetermined, although it is now clear that their antiparkinsonian effect is centrally mediated and that they work by counteracting the imbalance between striatal dopamine and acetylcholine activities caused by the degeneration of dopaminergic nigrostriatal neurons in Parkinson´s disease.

Clinical practice has shown that, compared with some other antiparkinsonian drugs, anticholinergics carry a greater risk of adverse effects. Due to their peripheral antimuscarinic action, they are contra-indicated in narrow-angle glaucoma, tachycardia, and prostatism. They may cause blurred vision due to accommodation impairment, urinary retention, nausea, and - more frequently - dry mucous membranes. Gingivitis and caries, rarely leading to loss of teeth, may occur (Lang 1989) and reduced sweating may interfere with body temperature regulation.

The most relevant limitation to their clinical use is however caused by their central anticholinergic effects, including acute confusion, hallucinations, and sedation. Their most important cognitive effect has been shown to be impairment of short-term verbal memory registration (Drachman 1977). They can also lead to an exacerbation of frontal lobe dysfunction in patients with Parkinson´s disease (Sadeh 1982;Syndulko 1981;Dubois 1987). Impaired neuro-psychiatric function has been demonstrated even in patients without cognitive impairment (Sadeh 1982;Syndulko 1981). These central effects are more likely to occur with advanced age and in patients with dementia (De Smet 1982).

There are a few reports of dyskinesias brought on (Birket-Smith 1974)or increased (Birket-Smith 1975) by the administration of anticholinergics, either as a monotherapy or in combination with L-dopa.

The abrupt withdrawal of anticholinergic drugs may lead to a rebound effect with marked deterioration of parkinsonism (Hughes 1971;Horrocks 1973;Goetz 1981).

With the introduction of L-dopa and the development of other classes of antiparkinsonian drugs with a more favourable side effect profile, the importance of anticholinergics in the management of Parkinson's disease has declined, although they are still widely prescribed.

There is a widespread belief among clinicians that anticholinergics have a more pronounced effect on tremor than on rigidity and bradykinesia.

It has not been established whether there are clinically relevant differences among the individual anticholinergics, either in terms of efficacy or tolerability.

OBJECTIVES

To determine the efficacy and tolerability of anticholinergics in the symptomatic management of Parkinson´s disease compared to placebo or no treatment.

The aim was to test the following hypotheses:

1. Improvement of parkinsonian symptoms and disability is greater in patients treated with anticholinergics than with placebo or in patients on no treatment.
2. Effect size on tremor exceeds that on rigidity and bradykinesia.
3. Withdrawal rates due to lack of efficacy or to side effects are higher than in patient groups on placebo or on no treatment.
4. Frequency of neuropsychiatric and cognitive adverse effects is higher than in patient groups on placebo or on no treatment.
5. There are no significant differences in efficacy compared to placebo or no treatment between individual anticholinergic drugs.

METHODS

Criteria for considering studies for this review

Types of studies

A trial was eligible for inclusion if all of the following applied:

1. It evaluated the efficacy of an anticholinergic drug.
2. It included a placebo or no treatment control group.
3. The allocation of patients was randomised.

Types of participants

Studies were considered where the majority of patients enrolled had a clinical diagnosis of idiopathic Parkinson´s disease.

Both trials dealing with de novo patients and with patients on other antiparkinsonian treatment were considered.

Types of interventions

Interventions considered were: any anticholinergic drug if marketed, compared to placebo or no treatment.

Types of outcome measures

1. Changes in global scores of impairment and disability scales.
2. Changes in scores for tremor, rigidity, and bradykinesia.
3. Numbers of withdrawals due to lack of efficacy.
4. Number of withdrawals due to adverse effects.
5. Rates of patients experiencing neuropsychiatric and cognitive adverse effects.

Search methods for identification of studies

The literature search included electronic searches of the Cochrane Controlled Trials Register (The Cochrane Library, Issue 4, 2001), MEDLINE (1966 to 2001), Old Medline (1960-1965), Index Medicus (1927 - 1959), as well as handsearching the neurology literature including the reference lists of identified articles, other reviews and book chapters.

In MEDLINE, the following search strategy was combined with the trial search strategy described in the Cochrane Reviewer's Handbook (Clarke MH 2001)

Reference lists of all relevant articles, of other reviews and of book chapters will be checked for other possible eligible studies.

Data collection and analysis

1)One reviewer (RK) checked the retrieval on two separate occasions for eligibility. Any doubts regarding eligibility were

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discussed with the other authors and decisions were made by consensus.

2)The methodological quality of the trials was assessed independently by two authors (RK, CS), using a published check list (Dixon RA) and the Global Introspection Method.

3)Eligible data was extracted from the included studies on standardised forms which were used independently by two authors (RK and CS), checked for accuracy and amalgamated.

4)The data collection of each trial included baseline characteristics of the participants: age and gender, inclusion and exclusion criteria, disease duration, disease severity (Hoehn & Yahr scale when provided), and when applicable, duration and dosage of concomitant antiparkinsonian treatment. Data collected also included interventions and outcomes. Data on all patients who were originally randomised was sought, whether or not they actually went on their trial medication and whether or not they completed the trial ("intention-to-treat" analysis). Neuropsychiatric and cognitive adverse events were evaluated. The number of drop-outs and reasons for dropping out were collected.

5)Because much of the literature on anticholinergics dates back up to several decades, no attempts were made to directly contact the authors of articles if required data was unavailable from the publications.

RESULTS

Description of studies

See also table: Characteristics of included studies.

Number of trials identified:

The search methods yielded 14 eligible studies published between 1954 and 1986. Of these, five were not included in the analysis: In three cases, this was because the studies dealt with substances that, to the best of our knowledge, had never been licensed or marketed: UCB 1549 (Strang 1966), dibenzazepnic hydrochloride (Couto 1976), and elantrine (Rix 1977). For the same reason, the two treatment arms dealing with panparnit and hyoscine in one included study (Kaplan 1954) were not considered.

One paper (Martin 1974) was excluded based on the assessment of its methodological quality. Although this was reported to be a randomised trial (of benzhexol versus placebo in patients on L-dopa), large differences in baseline characteristics between the two groups of patients exist: Disease duration was 16.9 years in the "control" and 7.9 years in the "treatment" group, disease severity was not stated. This difference appears to be incompatible with a direct and valid comparison; moreover, hardly any numerical results were reported and statistical analysis was not performed.
Finally, in one case (Iivainen 1974 b), the publication was the original Finnish language version of the identical English language study included in this review (Iivainen 1974).
The number of studies that eventually remained eligible was nine.

- Patient characteristics:

The overall number of patients randomised to an anticholinergic arm or a placebo / no treatment arm in the nine included trials was 221. The results reported in the publications are based on fewer patients as there were 12 drop-outs, and in addition, one study (Brumlik 1964) did not specify the number of drop-outs, and another (Kaplan 1954) states that not all patients were available for each assessment, without specifying the numbers.
Details on age and sex of the patients participating in the trials were given in all included publications.

- Interventions:

Of the nine studies included in this review, two dealt with benzhexol, three dealt with bornaprine, one with orphenadrine, one with benztropine, and one with methixene. The study by Vicary 1973 compared benzhexol and benapryzine with placebo.

All trials used a cross-over design comparing one or several anticholinergic drugs with placebo.

Mean doses ranged from 8 to 20 mg/day (not stated in Kaplan 1954) for benzhexol and from 8 to 8.25 mg/day for bornaprine. Mean benapryzine dose was 200 mg/day; mean methixene dose, 45 mg/day. Mean orphenadrine (Whyte 1971) and benztropine (Tourtelotte 1982) doses were not reported.

Seven studies investigated anticholinergics as add-on to other antiparkinsonian treatment regimes, which were kept stable during the trials. Anticholinergics were used as monotherapy in two studies: Kaplan 1954 and Brumlik 1964.
Most study designs included a titration period during which doses were increased; Vicary 1973 and Brumlik 1964 do not report having titrated the doses.

Risk of bias in included studies

See also table: Characteristics of included studies.

All studies meeting criteria for inclusion in this review are randomised controlled trials.

- Diagnosis

Almost all included studies were published before the general use of well defined clinical diagnostic criteria for idiopathic Parkinson´s disease. In five studies, some patients who were presumed by the authors to have parkinsonian disorders other than idiopathic Parkinson´s disease were included: six postencephalitic and two patients with parkinsonism of presumed vascular aetiology (of 35) in Kaplan 1954, six postencephalitic patients (of 32) in Brumlik 1964, "varied aetiology" but no drug-induced parkinsonism in Norris 1967, one postencephalitic patient (of 16) in Whyte 1971, one postencephalitic patient (of 26) in Vicary 1973, and one postencephalitic and one patient with parkinsonism of presumed vascular aetiology (of 20) in Iivainen 1974. By definition, any studies where more than half of the patient cohort was reported or presumed to have parkinsonism due to causes other than idiopathic Parkinson´s disease were excluded.

- Randomisation:

Although the authors of all the included studies stated or strongly implied to have allocated patients to treatment arms in a randomised fashion, only one publication (Iivainen 1974) attempts to describe the method of randomisation.

- Trial design:

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All studies were carried out under double-blind conditions, with the exception of Kaplan 1954, where blinding of the investigators is not specifically stated. This raises concerns that this may have been a single-blind study with the potential short-comings associated with this type of design, such as performance bias (bias while carrying out assessments), attrition bias (withdrawal of patients by investigators who are aware of allocation), and detection bias (analysing results while aware of allocation).

All studies were cross-over in design and patients therefore served as their own controls. However, in four studies (Whyte 1971; Vicary 1973; Iivainen 1974; Cantello 1986), no period for wash-out was allowed between different allocation periods. None of these four studies reported whether a potential carry-over effect had been looked for.

Two studies were specifically designed to investigate anticholinergics as add-on to L-dopa therapy.

- Study duration:

Most of the included studies were short-term. Duration of trials ranged from 5 weeks to 20 weeks, but the actual treatment periods were shorter (2 to 10 weeks).

- Assessors and centres:

In most cases, the number of assessors was not specified. All trials were carried out in single centres.

- Trial performance:

Outcome measures vary widely across studies. In almost all cases, the scales applied were the authors´ own (Brumlik 1964; Whyte 1971; Iivainen 1974; Tourtelotte 1982), or are no longer in current use. Only two studies (Piccirilli 1985; Cantello 1986) used the Webster scale (Webster 1968). Details on the scales and outcome measures are lacking in many of the studies.

There is also a lack of detailed numerical results reported in several studies.

- Sample size calculations:

Sample size calculations were not available for any of the included studies.

- Attrition characteristics:

Numbers of withdrawals and circumstances were reported incompletely in several cases: Numbers of patients who were withdrawn were not specified in two studies (Brumlik 1964; Kaplan 1954). Reasons for withdrawal are stated in all the other studies except in one patient in Norris 1967. Treatment allocation is not reported in three patients who dropped out from the study by Cantello 1986 and in one patient from the study by Vicary 1973.

- Data analysis and reporting of results:

None of the studies performed data analysis on an intention-to-treat basis.

Four studies did not report the statistical methods applied to analyse their data (Kaplan 1954; Norris 1967; Whyte 1971; Tourtelotte 1982). There is a lack of numerical details in reported results in several studies.

Effects of interventions

All the studies included in this review used different outcome measures. Primary outcome variables varied widely and ranged from tremor only to a whole range of disability scores. In several studies, tremor was not among the outcome measures at all. Moreover, there are considerable differences in baseline characteristics of the patients included in the studies, for instance with respect to disease duration and concomitant therapy. Inclusion and exclusion criteria were not usually listed in detail. Differences also exist in the duration of the studies, ranging from five weeks (Brumlik 1964) to 20 weeks (Kaplan 1954). Duration of periods on actual treatment range from two to 10 weeks.

For these reasons, a combined analysis of pooled data applying statistical methods was not possible.

- Motor function and disability:

All studies included outcome measures of motor function. Most studies were performed before the publication of generally accepted rating scales for motor function and disability in Parkinson´s disease, such as the Unified Parkinson´s Disease Rating Scale (UPDRS). Only the Webster scale (Webster 1968), which was used in two studies (Piccirilli 1985;Cantello 1986), is still in use as a research and clinical tool today.

Tremor was not an outcome variable in all studies: Tourtelotte 1982 did not investigate tremor, while the study by Vicary 1973 does not report results for tremor separately from other parkinsonian features. On the other hand, in the studies by Norris 1967 and Piccirilli 1985, tremor was the only outcome variable used.

Information on tremor as well as other parkinsonian features is available from five studies:

1. Kaplan 1954 used electromyography (EMG) to measure tremor amplitude: a deterioration occurred on placebo but not on benzhexol (or the two other anticholinergic agents investigated). The "overall picture" on neurological examination was improved by 6% on placebo and by 40% on benzhexol, while performance on the pegboard did not differ significantly.
2. In Brumlik 1964, a "tendency towards significant improvement" is reported in tremor duration (but not tremor amplitude), speech intensity and speaking rate. Results are presented as comparison with an "expected range of variation", defined as the difference between two measurements on placebo.
3. Whyte 1971used the authors´ own four-item rating scale to assess 12 physical signs and eight disabilities. A significant improvement from baseline was found on the active drug in a number of measures including rigidity, posture, walking and total physical signs, but not in tremor.
4. Iivainen 1974 applied the author´s own five-grade rating scale, without reporting exact definitions of the grades. A statistically significant reduction of resting and postural tremor was found, while no significant improvement was found in other features such as rigidity, hypokinesia, power, gait, pro/retropulsion, sweating, everyday activities (which were not further specified), and mental function.

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5. Cantello 1986 applied the Webster score: Tremor showed the most marked improvement, from 2.48 at baseline to 1.18 on bornaprine versus 2.00 on placebo. However, other features such as bradykinesia, rigidity, posture, and facial expression also showed a significant improvement on drug with a less marked but still significant improvement on placebo.

Eight of the nine studies reported a statistically significant improvement from baseline in at least one motor function or activity of daily living in patients on active drug. Results in the placebo arms were not always reported in the same detail and only four studies reported whether the difference of effect between drug and placebo was statistically significant: The improvement in the active drug arm was reported to be significantly better than in the placebo arm in Vicary 1973 (total disability score), Iivainen 1974 (tremor on a five-item scale), Piccirilli 1985 (Webster scale, handwriting, drawing, accelerometry), Cantello 1986 ("all-round assessment of efficacy" by investigators and patients), and Tourtelotte 1982 (investigators´ and patients´ overall impression and a number of poorly defined motor function tests including speed, coordination, gait and others).

Kaplan 1954 found a significant difference between the two arms in that tremor amplitude remained the same on benzhexol and deteriorated on placebo.

One study found no significant difference in tremor from baseline on methixene, measured by accelerometry (Norris 1967), but no study found placebo to be superior to the active drug.

- Neuropsychiatric and cognitive adverse events:

Two studies (Norris 1967; Piccirilli 1985) found no neuropsychiatric or cognitive adverse events; in one study (Kaplan 1954), this aspect was not reported. All other studies reported the occurrence of neuropsychiatric side effects: These were listed as: confusion (in 26 patients), disorientation (1), "altered perception" (1), "psychic disturbance" (1), insomnia (2), restlessness (1), tiredness (2), memory problems (1), poor concentration (1), irritability (1), and hallucinations (21). When excluding the study by Tourtelotte 1982, which did not report whether patients had experienced any adverse events while on placebo, the number of patients who experienced any neuropsychiatric adverse events while on active drug in all studies taken together was 31, as opposed to 13 patients on placebo.

Only one study (Tourtelotte 1982) performed objective measurement of cognitive adverse events: a 10% decrease was found in one of five cognitive tests used (a word list memory test). Vicary 1973 used their own score, which was not described in detail, to assess the severity of neuropsychiatric adverse events. This score was reported to be significantly higher on benzhexol than on placebo. There was less difference between benapryzine and placebo but the significance of this difference was not reported.

- Withdrawals:

Numbers of drop-outs vary from none in three studies to four in two studies.

In Whyte 1971, four patients dropped out from placebo allocation. In three cases, this was due to deterioration of parkinsonism following the withdrawal of orphenadrine after patients had switched to the placebo period; one patient stopped placebo because of subjective lack of benefit.

In Vicary 1973, two patients dropped out from active drug allocation because of acute confusional state while on benzhexol. One patient was withdrawn after fracturing an ankle; allocation was not stated in this case.

In Norris 1967, one patient dropped out due to unspecified adverse events while on placebo and one due to a randomisation error. Three patients in Cantello 1986 were withdrawn because of failure to attend; allocation was not reported.

Two studies failed to report drop-outs altogether (Kaplan 1954; Brumlik 1964).

- Comparison of different anticholinergic drugs:

Only one of the included studies (Vicary 1973) involved two different anticholinergic drugs, benzhexol (8 mg/d) and benapryzine (200 mg/d), in patients who were on stable levodopa therapy. The outcome measure was a total disability score based on assessments including functional disability, tremor, rigidity, akinesia, posture and autonomic dysfunction. No significantly better improvement compared to placebo was found on either drug. A subgroup analysis (which appears to have been done post-hoc) showed significantly more improvement on both drugs compared to placebo in those patients who had previously been on any anticholinergics (which had been withdrawn before entry into the study).

The study by Kaplan 1954 involves benzhexol and two anticholinergic agents which are not in clinical use any longer, hyoscine and panparnit, and which have therefore not been considered in this review.

DISCUSSION

There are particular difficulties in summarising data on anticholinergic drugs in the treatment of Parkinson´s disease. Most studies investigating this class of drugs were carried out decades ago, most even before randomised controlled trials were introduced into therapeutics. This means that many of the aspects of conducting and reporting clinical trials that seem obvious and indispensable today are lacking. Methodological problems exist in all the studies included in this review. These were often related to the performance of the studies, such as the application of unvalidated and apparently largely subjective scales to assess outcome measures. One major shortcoming of four studies was the lack of a wash-out period between the two treatment periods, and a possible carry-over effect was not checked for in any study. Given the observed deterioration of parkinsonism following withdrawal of the anticholinergic drug in one study, which led to patient drop-out in three cases, carry-over effects might be particularly relevant with this class of drugs. The included studies do not provide sufficient individual patient data from each treatment period to rule out or confirm this possibility. Problems were also encountered with reporting methods and results. In several cases, the lack of reported details precludes an evaluation of the quality of study performance itself.

The heterogeneous nature of the nine included studies made it impossible to apply statistical methods for a combined analysis. Important differences were present in patient population, end

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points and assessments as well as the way results were analysed and presented.

No attempt was made to obtain additional data from the authors of the included studies because of the time that has elapsed since publication in almost all cases. Therefore, conclusions had to be drawn from the available data.

All nine included studies were rather small. The total number of patients involved was 221, of which at least 12 were withdrawn. The exact number of drop-outs cannot be determined because two studies failed to report withdrawals (Kaplan 1954;Brumlik 1964).

Despite these methodological difficulties, the data extracted from the studies included in this review is sufficient to provide evidence for an antiparkinsonian effect of anticholinergic agents as a group, and for a better effect than placebo. Data is however only available for short term application.

Data is insufficient to allow comparisons in efficacy of tolerability between individual anticholinergic drugs.

Only five studies used both tremor and other parkinsonian motor manifestations as outcome measures. However, features investigated vary across those five studies, ranging from performance on the pegboard (Kaplan 1954) to the Webster scale (Cantello 1986), thus precluding direct comparisons. Results are conflicting: While one study reported a significant improvement in tremor but not in the other features (Iivainen 1974), one reported a significant improvement in both (Cantello 1986), one reported no significant changes but a tendency towards improvement in tremor and other features (Brumlik 1964), and one study found a significant improvement in several measures but not in tremor.

In the study by Kaplan et al (Kaplan 1954), a significant deterioration in tremor occurred on placebo but not on active treatment. This may be explained by the cross-over design of the study investigating three anticholinergic agents and placebo, so that three out of four placebo periods coincided with the withdrawal from an anticholinergic drug. Other measures in that study did not show a significant improvement on the anticholinergics tested compared to placebo.

The results available from the studies included in this review do not argue in favour of a preferential effect of anticholinergics on tremor, but data is not sufficient to draw firm conclusions.

Neuropsychiatric side effects were commonly reported and led to withdrawal in at least two patients. However, most of the studies included patients with advanced Parkinson's disease, and results on efficacy or on tolerability were not reported separately for different age groups or stages of disease. Moreover, the reported rate of withdrawals due to neuropsychiatric adverse events cannot reliably be put into the context of all reasons for withdrawal as other reasons were not always stated, and the authors of two studies failed to report whether there had been any withdrawals at all. However, lack of efficacy while on active drug was not stated as the reason for withdrawal in any patients. Worsening of parkinsonism on withdrawal of an anticholinergic drug was a more frequently reported reason for dropping out, and this supports the current dogma that anticholinergics should be discontinued slowly and with caution.

Data on safety can never be complete from a systematic review of clinical trials, which are set up to address specific issues and are limited to a defined subgroup of the literature on a drug or a class of drugs, such as randomised controlled studies fulfilling certain inclusion criteria. Data on safety needs to be collected from a far wider range of sources including post-marketing surveillance and observational studies. Accordingly, comprehensiveness was not attempted with respect to the safety of anticholinergics. Nevertheless, the data on neuropsychiatric adverse effects from the studies included in this review add to the existing evidence for a negative effect of anticholinergics on cognitive and mental function in Parkinson´s disease.

AUTHORS' CONCLUSIONS

Implications for practice

As monotherapy or as an adjunct to other antiparkinsonian drugs, anticholinergics are more effective than placebo in improving motor function in Parkinson´s disease in short-term use.

The clinical usefulness of anticholinergics may be limited by adverse events. Neuropsychiatric adverse events occur considerably more often in patients on anticholinergics than on placebo and they lead to withdrawal from trials. Withdrawal of an anticholinergic drug can lead to worsening of parkinsonism and should be carried out with caution.
Data in the literature surveyed for this review is conflicting with respect to a possible preferential effect of anticholinergics on tremor compared with other parkinsonian features such as rigidity and bradykinesia.

There is insufficient data to draw conclusions on differences between individual anticholinergic drugs, either in efficacy or in safety.

Implications for research

Despite the problems with quality in performance and reporting in much of the existing literature, as outlined in this review, the existing data provide evidence of a superior antiparkinsonian effect of anticholinergics compared to placebo in short-term application. Efficacy as well as tolerability in long-term use should be investigated both in early stage and in advanced disease.
Comparison of individual drugs from this class might be of interest.
Addressing the issue of a potentially better effect on tremor than on other parkinsonian features would also be of interest, especially in comparison with other antiparkinsonian agents such as dopamine agonists.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Brumlik 1964

Methods	Randomised, controlled, double-blind cross-over study of benzhexol vs placebo. Randomisation method not stated. Setting: 1 centre (U.S.). Duration: 5 weeks, each period: 2 weeks.
Participants	32 patients: 2 female, 30 male. Age: 39-81 (mean: 62) years. Disease duration: 5.25 years, range not stated. Disease severity not specified. 6 patients presumed postencephalitic ("definite history of flu or encephalitis").
Interventions	Cross-over design: 2 weeks drug / placebo - 1 week wash-out - 2 weeks placebo / drug. Dose: 20 mg benzhexol (5 mg 4 times daily), reduced in 2 patients due to side effects.. Apparently no titration period. No other antiparkinsonian medication.
Outcomes	Outcome measures: 41 items, including muscle tone, accelerometry, recorded speech, bradykinesia and psychometry. "Tendency towards significant improvement" on drug in 3 parameters: tremor duration, speech intensity, and speaking rate. Results reported as better or worse than "expected range of variation" defined as 2 measurements on placebo. Neuropsychiatric AE: Drug: confusion in 4 patients, disorientation in 1, "altered perception" in 1; placebo: confusion in 3, behaviour disturbance in 2. Drop-outs: unclear.

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Brumlik 1964 *(Continued)*

Notes	Treatment results expressed qualitatively, no numeric results reported other than baseline measures.

Risk of bias

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

Cantello 1986

Methods	Randomised, double-blind cross-over study of bornaprine vs placebo. Randomisation method not stated. Setting: 1 site (Italy). Duration: 2 months, each period: 30 days.
Participants	30 patients: 17 female, 13 male. Age: 50-70 (mean: 65) years. Disease duration: not stated. Disease severity: 14 patients H&Y II, 13: III, 2: IV, 1: V. Inclusion criteria: IPD with tremor; age 35-70; stable dose of L-dopa or bromocriptine "without adequate control of symptoms". Exclusion criteria: Glaucoma, gastrointestinal stenosis, myocardial infarction in previous year, hyperkinetic cardiac arrhythmias, mental deterioration.
Interventions	Cross-over design: 30 days drug / placebo - 30 days placebo / drug. No wash-out period. Drug titrated to maximum of 12 mg/day if tolerated. Length of titration period not stated. Mean dose: 8.25 mg/day (SD 2.8). L-dopa and /or bromocriptine kept stable, doses not stated. Other antiparkinsonian drugs allowed, not specified.
Outcomes	Webster scale: - Tremor: most marked improvement: from 2.48 baseline to 1.18 on drug and 2.00 on placebo; both: $p<0.01$. -Bradykinesia, rigidity, posture, facial expression, seborrhea, coping ability: all significantly ($p<0.05$) improved on drug; on placebo: less marked, but significant. Subjective assessment by patients and investigators: -Efficacy: significant ($p<0.01$) difference in favour of bornaprine. -Tolerability: no significant difference. Neuropsychiatric AE: -Drug: "psychic disturbance" in 1 patient, insomnia in 2. Placebo: none. Drop-outs: 3, failure to attend; allocation not stated.
Notes	Not intention-to-treat.

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Cantello 1986 *(Continued)*

	No wash-out period.

Risk of bias

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

Iivainen 1974

Methods	Randomised, double-blind cross-over study of bornaprine vs placebo. Randomisation by ballot, incompletely described. 1 site (Finland). Duration: 12 weeks, each period: 6 weeks.
Participants	20 patients: 9 female, 11 male. Age: 48-76 (mean: 61) years. Disease duration: 0-17 years (mean: 6). Disease severity: "majority mild to moderate symptoms", mild in 5, moderate in 11, severe in 4 patients. Diagnoses: IPD except postencephalitic parkinsonism in 1 patients, presumed vascular aetiology in 1. Exclusion criteria not stated.
Interventions	Cross-over design: 6 weeks on drug and placebo, no wash-out period. Dosage increased over 4 days to 8 mg/day (4mg twice/day). Mean dose apparently 8 mg in all patients. Other antiparkinsonian drugs remained unchanged: L-dopa in 12 patients (2-5 g/day, no decarboxylase inhibitor), amantadine ib 9 and unspecified other anticholinergic drugs in 14. Two patients not previously treated.
Outcomes	Author´s own 5-item rating scale (1=normal, 5="severe disturbance") for: - Tremor: statistically significant reduction of resting and postural tremor. - Rigidity, hypokinesia, power, trophic changes, gait, accompanying movements, pro/retropulsion, starting, stopping, getting up, saliva, sweating, "waxen face", some autonomic functions and everyday activities, mental function: No statistically significant effect. Neuropsychiatric AE: restlessness in 1 patient, tiredness in 2 on active drug. Drop-outs: none.
Notes	No wash-out period. Results not reported in more detail than listed here.

Risk of bias

Bias	Authors' judgement	Support for judgement

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Iivainen 1974 *(Continued)*

Allocation concealment?	Unclear risk	B - Unclear

Kaplan 1954

Methods	Randomised, presumably single-blind (patients blinded) cross-over study of benzhexol, panparnit, hyoscine and placebo. Randomisation method not stated. One site (U.S.) Duration: 20 weeks, each period: 4 weeks.
Participants	35 patients: 11 female, 24 male. Age: 32-63 Disease duration: not stated. Disease severity: not stated. Diagnoses: 6 patients postencephalitic, 2 "vascular etiology".
Interventions	Cross-over design: 4 weeks on each drug - 1 week on reduced dose after each treatment period. "Build up" of dosage, but titration method or doses not stated. Mean dose: not stated. Concomitant therapy: not stated.
Outcomes	- "Overall picture" on neurological examination: improvement by 6% on placebo vs 40% on benzhexol; worsening by 42.4% on placebo (= withdrawal from previous anticholinergic treatment period in 3 of 4 cases) vs 6.2% on benzhexol. - EMG: tremor amplitude: benzhexol significantly ($p<0.01$) better than placebo, but: worsening on placebo, no improvement on drug. - Dynamometer (grip strength): improvement on drug and placebo, no significant difference. - Purdue peg board (timed performance): benzhexol slightly more effective than placebo; difference not significant. Neuropsychiatric AE: not reported. Drop-outs: not specified, but not all patients available for each assessment.
Notes	Review includes benzhexol data vs placebo only. Unclear whether investigators were blinded. Number of patients available for each assessment not reported.

Risk of bias

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

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Norris 1967

Methods	Randomised, double-blind cross-over study of methixene vs placebo. Randomisation method not stated. 1 site (U.K.) Duration: 7 weeks, each period: 3 weeks.
Participants	16 patients: 2 drop-outs not included in report, 7 female, 7 male. Age: 47-89 (mean: 67) years. Disease duration: not stated. Disease severity: not specified. Inclusion criteria: Persistent and marked tremor. "Aetiology varied", but not drug-induced.
Interventions	Cross-over design: 3 weeks active drug / placebo - 1 week wash-out - 3 weeks placebo / active drug. Dose increased over 1 week to maximum 3 times 15 mg = 45 mg. Mean dose: apparently 45 mg in all patients. Other antiparkinsonian drugs continued, kept stable.
Outcomes	Tremor activity, measured with own accelerometer, measure: percentage of change. Trend in favour of mehixene, not statistically significant (p>0.1). No definite subjective difference. Neuropsychiatric AE: none. Drop-outs: 1 unspecified AE on placebo, 1 error in randomisation.
Notes	Tremor only parkinsonian feature studied.

Risk of bias

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

Piccirilli 1985

Methods	Randomised, double-blind cross-over study of bornaprine vs placebo. Randomisation method not stated. 1 site (Italy). Duration: 67 days, each period: 30 days.
Participants	17 patients: 5 female, 12 male. Age: only mean age provided: 61 years. Disease duration: 3-11 (mean 6.8) years. Disease severity: not specified.

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Piccirilli 1985 *(Continued)*

	Inclusion criteria: Parkinsonian patients (exact aetiology not stated) with persistent tremor on stable dopaminergic treatment. Exclusion criteria not stated.
Interventions	Cross-over design: 30 days on drug / placebo - 1 week wash-out - 30 days placebo / drug. Dose increased over 8 days from 2 to 8 mg/day (4 mg twice/day). 8 mg/day in all patients but one (6 mg/day due to blurred vision). Other antiparkinsonian drugs not specified, but "on stable treatment".
Outcomes	- Webster scale: tremor score only: Reduction by 14% on placebo / 47% on bornaprine. - Handwriting: Speed increase: 14% on placebo / 42% on bornaprine. - Drawing a spiral: Speed and accuracy under specified conditions: improved by 5% on placebo / 19% on bornaprine. - Accelerometry in upper limbs: improved by 13% on placebo / 33% on bornaprine. Significantly better improvement ($p<0.01$) on drug than placebo: Webster, handwriting, drawing, accelerometry. Neuropsychiatric AE: none. Drop-outs: none.
Notes	Parkinsonian signs other than tremor not reported.

Risk of bias

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

Tourtelotte 1982

Methods	Randomised, double-blind cross-over study of benztropine vs placebo. Randomisation method not stated. Location: 1 site. (U.S). Duration: 30 weeks, each period: 10 weeks.
Participants	29 male patients. Age: 47-79 (mean: 62.5) years. Disease duration: not stated. Disease severity: "mild to moderate". Inclusion criteria: - IPD for a minimum of 1 year - Disability status 2-5 on own 7-item scale -Stable on L-dopa. Exclusion criteria: - Prior neurosurgery - Major diseases of central or peripheral NS

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Tourtelotte 1982 *(Continued)*

	- "Limited psycho-neurological function" - Concurrent medication.
Interventions	Cross-over design: -10 weeks active drug / placebo - 5 weeks wash-out - 10 weeks placebo / active drug. Therapy titrated over 5 weeks, then optimal dose maintained for rest of 10-week period: 2-4 times 0.5 mg/day. Mean benztropine dose not stated. L-dopa doses maintained stable: 500-1750 mg / day.
Outcomes	- Patients' and investigators' global impression: significantly in favour of benztropine ($p<0.05$ for patients). - Disability rating (own scale): no detailed results given. Improvement in only 6 patients. - Small (10%) but statistically significant improvement on benztropine in - rigidity ($p<0.01$) -activities of daily living (not specified) ($p<0.01$) -finger tapping ($p<0.001$). Improvements on placebo not significant. - Quantitative assessments included tandem gait and upper extremity strength: "significant improvement" ($p<0.05$), numeric results not given. Patients' choice at end of trial: 16 drug, 4 placebo. Drop-outs: none. Neuropsychiatric AE: Drug: all AE mild, remitted with dose reduction: Subjective memory problems, poor concentration, irritability, confusion in 2 patients, hallucinations in 2. Objective cognitive measure: 10% decrease in 1 of 5 tests (word list memory test). Placebo: AE not stated.
Notes	Lack of detailed outcome results. Tremor was not an outcome measure.

Risk of bias

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

Vicary 1973

Methods	Randomised, double-blind cross-over study of benzhexol and benapryzine vs placebo. Randomisation method not stated. 1 site (U.K.) Duration: 10 weeks, periods: 2-4 weeks.
Participants	26 patients: 16 female, 10 male. Age: 41-77 years, mean age not stated. Disease duration: not reported.

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Vicary 1973 *(Continued)*

	Disease severity: not specified. Diagnoses: IPD in 25, postencephalitic parkinsonism in 1. Exclusion criteria: not stated.
Interventions	Cross-over design: 2 groups. A: 4 weeks placebo - 2 weeks one of the active drugs - 4 weeks other drug. B: 6 weeks placebo - 2 weeks one active drug - 2 weeks other drug. No wash-out periods. Apparently no titration period. Doses: benapryzine 200 mg/day, benzhexol: 8 mg/day. Other antiparkinsonian medication kept stable: -L-dopa in all patients (mean dose 2.5 g/day, no decarboxylase inhibitor) -Amantadine in 18 patients. Any anticholinergics withdrawn before entry.
Outcomes	-Patients´ impression: no significant preference of drugs over placebo. -Total disability score (including tremor, rigidity, akinesia): significant improvement from baseline on both drugs (p<0.05 for benapryzine, <0.02 for benzhexol) and significant difference from placebo in those 14 patients who had previously been on anticholinergics; no significant improvement for all patients. Significant difference between benzhexol and benapryzine (p<0.02 in favour of benzhexol). Neuropsychiatric AE: Hallucinations and confusion in 8 patients on placebo, 11 on benzhexol, 7 on benapryzine. Severity scores (not described in detail) significantly worse on benzhexol (score 27) than benypryzine (9); placebo: score 6.5. Drop-outs: 3: acute confusional state in 2 on benzhexol, fractured ankle in 1 (allocation not stated).
Notes	No wash-out between periods. Analysis not intention-to-treat. Results for tremor and other parkinsonian features not reported separately.

Risk of bias

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

Whyte 1971

Methods	Randomised, cross-over study of orphenadrine vs placebo. "Randomly divided into 2 groups". Setting: 1 site (U.K.) Duration: 11 weeks, each period: 2 weeks. Investigators blinded, patients unblinded during weeks 1-3 and 10-11, but blinded during period comparing drug and placebo.
Participants	16 patients: 9 female, 6 male, 1 drop-out of unspecified gender.

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Whyte 1971 *(Continued)*

	Age: 51-71 (mean: 59) years. Disease duration: 2-29 (mean: 10) years. Disease severity not specified. Diagnoses: 14 IPD, 1 postencephalitic patient. Exclusion criteria: not stated.
Interventions	Cross-over design: -3 weeks withdrawal from previous anticholinergics. - Weeks 4-5: Group 1 placebo, group 2 drug, titrated to 300 mg/day if tolerated. -Weeks 6-7: reverse. No wash-out. -Weeks 8-9: Group 1 only: back to drug, without wash-out. -Weeks 10-11: gradual decrease. Mean dose: not stated. Other antiparkinsonian drugs: "on maximum L-dopa dose tolerated", kept stable, dose not stated.
Outcomes	Outcome measures: 12 physical signs and 8 disabilities rated on authors´ own 4-item scale. Significant improvement from baseline on drug: Balance, posture, walking, rigidity, sweating, handwriting, household tasks, turning over, dressing, feeding, washing, and total physical signs and disabilities. Changes on placebo reported but not statistically analysed. Neuropsychiatric AE: Visual hallucinations in 1 patient, resolved on dose reduction. Drop-outs: 1 patient due to marked deterioration during initial withdrawal period. 3 patients withdrawn from placebo arm due to deterioration of parkinsonism.
Notes	Not intention-to-treat. No wash-out. Results discussed in this review from first part of the study only; second part deals with withdrawal effects. Tremor: no significant improvement.

Risk of bias

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

AE = adverse events
H&Y = Hoehn & Yahr stage
IPD = Idiopathic Parkinson´s disease
SD = standard deviation

APPENDICES

Appendix 1. MEDLINE search strategy

MEDLINE

1.Parkinson disease/

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2.Parkinsonian disorders/
3.Parkinson*.tw
4.Or/1-3
5.Cholinergic antagonists/
6.Muscarinic antagonists/
7.Anticholinergic*.tw
8.trihexyphenidyl/
9.trihexyphenidy.tw
10.benzhexol.tw
11.biperiden/
12.biperiden.tw
13.orphenadrine/
14.orphenadrine.tw
15.procyclidine/
16.procyclidine.tw
17.benztropine/
18.benztropine.tw
19.bornaprine.tw
20.ethopropazine.tw
21.scopolamine/
22.scopolamine.tw
23.propantheline/
24.propantheline.tw
25.benapryzine.tw
26.cycrimine.tw
27.elantrine.tw
28.histamine antagonists/
29.Antihistamin*.tw
30.diphenhydramine/
31.diphenhydramine.tw
32.Or/5-31
33.4 and 32

WHAT'S NEW

Date	Event	Description
21 October 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 4, 2002
Review first published: Issue 2, 2003

Date	Event	Description
5 May 2002	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Regina Katzenschlager, Cristina Sampaio and Andrew J Lees conceived and designed the review.
Regina Katzenschlager undertook the literature search, screened the search results, organised retrieval of papers, screened the retrieved papers against inclusion criteria.
Regina Katzenschlager and Cristina Sampaio developed the search strategy, appraised quality of papers.

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Regina Katzenschlager, João Costa and Cristina Sampaio abstracted data from papers, entered data into RevMan, analysed and interpreted data.
Cristina Sampaio provided a methodological perspective.
Regina Katzenschlager, Cristina Sampaio and Andrew J Lees wrote the review.

DECLARATIONS OF INTEREST

None.

INDEX TERMS

Medical Subject Headings (MeSH)

Cholinergic Antagonists [*therapeutic use]; Muscarinic Antagonists [therapeutic use]; Parkinson Disease [*drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Humans

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