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[Intervention Review]

Amantadine in Parkinson's disease

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ABSTRACT

Background

Although levodopa is the most common drug prescribed to relieve the symptoms of Parkinson's disease it is associated with motor and psychiatric side-effects. Consequently, interest has turned to alternative drugs with improved side-effect profiles to replace or augment levodopa. Amantadine, originally used as an antiviral drug, has been shown to improve the symptoms of Parkinson's disease.

Objectives

To compare the efficacy and safety of amantadine therapy (monotherapy or adjuvant therapy) versus placebo in treating people with Parkinson's disease.

Search methods

Electronic searches of The Cochrane Controlled Trials Register (The Cochrane Library Issue 3, 2001), MEDLINE (1966-2001), EMBASE (1974-2001), SCISEARCH (1974-2001), BIOSIS (1993-2001), GEROLIT (1979-2001), OLDMEDLINE (1957-1965), LILACS (1982-2001), MedCarib (17th Century - 2001), PASCAL (1973-2001), JICST-EPLUS (1985-2001), RUSSMED (1973-2001), DISSERTATION ABSTRACTS (2000-2001), SIGLE (1980-2001), ISI-ISTP (1990-2001), Aslib Index to Theses (2001), Clinicaltrials.gov (2001), metaRegister of Controlled Trials (2001), NIDRR (2001) and NRR (2001) were conducted. Grey literature was hand searched and the reference lists of identified studies and reviews examined. The manufacturers of amantadine were contacted.

Selection criteria

Randomised controlled trials comparing amantadine with placebo in the treatment of patients with a clinical diagnosis of idiopathic Parkinson's disease.

Data collection and analysis

Data was abstracted independently by NC and KD onto standardised forms and disagreements were resolved by discussion.

Main results

Six randomised controlled trials were found comparing amantadine monotherapy or adjuvant therapy with placebo in the treatment of idiopathic Parkinson's disease. Five examined amantadine as adjuvant therapy with optimal levels of levodopa or anticholinergics and one examined amantadine as an adjuvant therapy with minimum tolerated levels of anticholinergics or as a monotherapy. Five were double-blind cross-over studies and one was a double-blind parallel group study. In total they examined 215 patients. The parallel group study allowed the randomisation codes to be broken and allowed patients in the placebo group to then receive amantadine. This could have led to bias. One study did not present the results of the placebo arm of the trial, hence we could not determine the difference between the two treatment groups. Two cross-over studies presented the results of the combined data from both treatment and placebo arms. The risk of

carry-over effect into the second arm meant that these results could not be analysed. The final two studies presented at least some of their data from the end of the first arm of the trials. However only means were given, without standard deviations, so we could not determine the statistical significance of any difference between the amantadine and placebo groups. Although the authors did report on the side-effects from amantadine (such as livido recticularis, dry mouth and blurred vision), they state that none of them were severe.

Authors' conclusions

A considerable amount of evidence on the effectiveness of amantadine has accrued from non-controlled trials, often in patients with Parkinsonian conditions other than idiopathic Parkinson's disease. However, rigorous analysis of the six randomised controlled trials of amantadine reveals insufficient evidence of its efficacy and safety in the treatment of idiopathic Parkinson's disease.

PLAIN LANGUAGE SUMMARY

There is not enough evidence about the safety and effectiveness of amantadine for people with Parkinson's disease.

Parkinson's disease causes progressive muscle rigidity, tremors and other symptoms. The most common drug used to try and relieve these symptoms is levodopa, but serious physical and psychiatric adverse effects are common. Amantadine is another option, used alone or with levodopa. Amantadine can have serious adverse effects (including psychiatric problems), and people can become resistant to the drug. The review found that there is not enough evidence from trials about the effects of amantadine for people with Parkinson's disease. Adverse effects in trials so far have not been severe, and included skin rash, dry mouth and blurred vision.

BACKGROUND

Levodopa remains the most commonly prescribed and effective drug treatment for symptomatic relief in Parkinson's disease. However, it is associated with dose-limiting motor and psychiatric side-effects. After 6 years of therapy these affect 50% of patients (Rajput 1984) and 100% of young onset patients (Quinn 1986). Consequently, interest has turned to alternative drugs with improved side-effect profiles to replace or augment levodopa.

Amantadine hydrochloride is a member of the adamantanamine class of drugs. It was originally used as an antiviral for the treatment of influenza, but was coincidentally found to improve the symptoms of Parkinson's disease. Although its precise mechanism of action is uncertain, amantadine is known to function as a non-competitive antagonist at the phencyclidine (PCP) site within the NMDA-receptor at therapeutic concentrations (Kornhuber 1994). Amantadine is also known to augment the release of dopamine from nerve terminals and delay its re-uptake (Takahashi 1996, Mizoguchi 1994).

Amantadine has been used to control Parkinsonian symptoms in a large number of patients since the 1970's. Early clinical trials demonstrated the antiparkinsonian effects of amantadine both as an adjuvant with levodopa and when used alone (Fahn 1975; Butzer 1975). Unfortunately, not all patients respond to amantadine and tolerance to its effects can develop, although it has been suggested that such tolerance is less pronounced when it is combined with levodopa (Zeldowicz 1973). These problems combined with its significant adverse event profile have led to decreasing use of the drug in recent years.

This systematic review examines all randomised controlled trials of amantadine therapy versus placebo as both monotherapy and as an adjuvant treatment in patients with Parkinson's disease to examine its effectiveness and tolerability. A separate review considers the efficacy of amantadine in the treatment of levodopa-induced dyskinesias (Crosby 2002).

OBJECTIVES

To compare the efficacy and safety of monotherapy and adjuvant amantadine therapy against placebo for the treatment of Parkinson's disease.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials comparing monotherapy and adjuvant oral amantadine therapy with placebo were considered for inclusion in the study.

Types of participants

Patients with a clinical diagnosis of idiopathic Parkinson's disease as defined by the authors of the trial reports. All ages were included.

Types of interventions

Oral amantadine or placebo. Any trial duration was accepted.

Types of outcome measures

Outcomes were recorded where they were available in the trial reports:-
a. Quality of life and health economics assessments.
b. Parkinson's disease activities of daily living rating scales.
c. Parkinson's disease motor impairment rating scales.
d. Tests of individual motor impairments.
e. Patient self-evaluation rating scales.
f. Reduction in levodopa dose
g. Adverse event frequency.
h. Number of withdrawals as a result of lack of efficacy and/or side-effects.

Search methods for identification of studies

1. The review was based on the search strategy of the Movement Disorders Group. In general the search cross-referenced amantadine and its proprietary names with Parkinson's disease and its derivations, all as MeSH headings and as text words. The following databases were searched:

- Clinical trial databases: The Cochrane Controlled Trials Register (The Cochrane Library Issue 3, 2001), Clinicaltrials.gov (2001), metaRegister of Controlled Trials (2001), NIDRR (2001) and NRR (2001).
- General biomedical and science databases: MEDLINE (1966-2001), EMBASE (1974-2001), SCISEARCH (1974-2001), BIOSIS (1993-2001), GEROLIT (1979-2001) and OLDMEDLINE (1957-1965).
- English language databases of foreign language research and third world publications: LILACS (1982-2001), MedCarib (17th Century - 2001), PASCAL (1973-2001), JICST-EPLUS (1985-2001), RUSSMED (1973-2001).

2. The reference lists of located trials and review articles were searched.

3. Hand searching of appropriate journals was performed.

4. The following grey literature was searched: DISSERTATION ABSTRACTS (2000-2001), SIGLE (1980-2001), ISI-ISTP (1990-2001), Aslib Index to Theses (2001), Abstracts of the International Congress of Movement Disorders (1990-2000) and Abstracts of the XIII International Congress on Parkinson's Disease (1999).

Further details on this search strategy are available in the Group's module within the Cochrane library (www.cochrane.org). This includes explanations of the acronyms, sources and web sites.

Data collection and analysis

The identified trials were assessed by NC and KD. Disagreements about inclusions were resolved by discussion. The methodological quality of the studies was evaluated in a qualitative fashion by assessing the methods of randomisation and concealment of allocation, whether studies were blinded, whether an intention-to-treat evaluation was presented and the number of patients lost to follow up.

Eligible data was abstracted onto standardised forms by the authors independently, checked for accuracy and amalgamated.

RESULTS

Description of studies

See Tables: Characteristics of Included Studies and Characteristics of Excluded Studies.

Six trials were found that compared amantadine, as either monotherapy or adjuvant therapy, with placebo in a total of 215 patients. From the initial search strategy a further 70 studies appeared to be eligible from the descriptions available in their titles or abstracts. However they were later excluded on the basis that:

- the trials included patients suffering from non-idiopathic forms of parkinsonism
- the trials included patients who had undergone stereotactic operations to relieve their parkinsonism
- the studies were uncontrolled
- the patients received the placebo therapy and amantadine in a non-randomised order
- the amantadine was delivered parentally
- other drugs from the adamantanamine class were examined.

TRIAL DESIGN
All six trials were randomised double-blind studies. Five were cross-over design, and one was a parallel group study (Silver 1971). All were performed in single centres. A total of 215 patients received amantadine or placebo (with or without levodopa or anticholinergic drugs) over 6 to 64 weeks.

PARTICIPANTS
The mean ages of patients in the six studies ranged from 61 to 66 years. The overall age of participants ranged from 29 to 82 years. The means of the length of time since participants' Parkinson's disease had been diagnosed was not given in Savery 1977 or Silver 1971. In the other studies this varied from a mean of 7.2 to 9.25 years. For individual subjects, this ranged from 1 to 35 years. Silver 1971 and Walker 1972a did not give the baseline Hoehn and Yahr scores for their subjects. For the remaining four trials, the mean Hoehn and Yahr scores of participants ranged from 2.5 (Fahn 1975) to 3.2 (Fehling 1973).

INTERVENTIONS
The dose and frequency of amantadine used varied between studies. Fahn 1975, Silver 1971, Walker 1972a and Walker 1972b used 100 mg of amantadine twice daily. Fehling 1973 initiated patients on 50 mg of amantadine per day, and increased the dose to 100 mg/day within the first 2 weeks of the trial. Savery 1977 used 100 mg of amantadine per day for the first 3 weeks, then increased the dose to 200 mg/day for the second 3 weeks. For the final three weeks patients themselves were allowed to choose whether to take 100 mg or 200 mg/day.

LEVODOPA
Two studies stated the mean daily levodopa dose of their subjects: in Fehling 1973 this was 3.43 grams (ranging from 2.0 to 6.0 grams) and in Walker 1972b this was 3.58 grams. Only one study (Savery 1977) used levodopa in combination with a peripheral decarboxylase inhibitor (carbidopa). Fahn 1975 used patients who had not previously received levodopa therapy. Patients were initiated on slowly increasing doses of levodopa until optimal benefit or side effects occurred. They were then maintained on this dose of levodopa through all the arms of the trial. Those patients in Fehling 1973 and Silver 1971 who had been on levodopa at the start of the trial were maintained on stable doses during the study. All patients in Savery 1977 were placed on a stable dose of levodopa & carbidopa for 3 weeks prior to and throughout trial. Walker 1972a stopped levodopa in all subjects during the study. Walker 1972b continued patients on the maximal tolerable dose of levodopa from 6 weeks prior to trial until its completion.

ANTICHOLINERGICS
Both Fahn 1975 and Fehling 1973 stated that patients who had been taking anticholinergics prior to the study continued to take them. Savery 1977 discontinued subjects' remaining anti-Parkinsonian medication for 3 weeks before and also during the trial. Silver 1971 maintained subjects on stable doses of their concurrent anti-parkinsonian medication during the study. Subjects in Walker 1972a discontinued all other anti-parkinsonian medication with the exception of 6 patients who were not able to discontinue their anticholinergic therapy; this was maintained at the lowest tolerable dose. Walker 1972b did not appear to use any other anti-Parkinsonian medication other than the levodopa and amantadine.

OUTCOME MEASURES
The outcome measures used differed between trials. Fahn 1975 used subjective patient reports, neurological examination and timed tasks to assess the effect of amantadine on patients' Parkinsonian disability. The remaining trials each scored patients for various Parkinsonian motor signs. Fehling 1973 counted the number of pronation-supination movements of the hand that the patients could perform in 30 seconds. Silver 1971 used timed tasks and subjective patient reports. Walker 1972a scored patients' functional disability (walking, dressing, hygiene, eating, feeding and speech), activities of daily living, subjective patient reports, neurologists' global impression scoring and other motor, sensory and neuropsychological tests. Walker 1972b scored activities of daily living, neuropsychological tests and pulse and blood pressure.

Risk of bias in included studies

See Table: Additional Table 1.

RANDOMISATION METHOD AND CONCEALMENT OF ALLOCATION
None of the six trials provided details of the method of randomisation. Consequently selection bias cannot be ruled out. Five trials also failed to describe the concealment of allocation of patients treatment groups. The exception was Fehling 1973 which stated that the order in which treatment was allocated was unknown to the examiner.

ELIGIBILITY CRITERIA
Fahn 1975, Savery 1977 and Silver 1971 stated that the trials' participants had Parkinson's disease. Savery 1977 described participants as having Parkinson's syndrome. Subjects in Walker 1972a were described as 'consecutive patients applying for anti-Parkinsonian therapy'. Patients in Walker 1972b were selected from amongst those in Walker 1972a. No trials defined the criteria used to distinguish idiopathic Parkinson's disease from other forms of parkinsonism.

PATIENT NUMBERS AND BASELINE CHARACTERISTICS
Only 215 patients were studied. This relatively small number of patients means that the results may not be applicable to the entire population of Parkinson's disease patients.

Of the 156 patients whose gender was given, 106 (68%) were male and 50 (32%) were female. Since the prevalence of Parkinson's disease in the community is approximately equal in both sexes, this adds to the difficulty of generalising these results to the female population.

Certain baseline characteristics of the groups of patients were given, although data was not provided on individual patients. The mean Hoehn and Yahr scores of participants ranged from 2.5 (Fahn 1975) to 3.2 (Fehling 1973), indicating that patients in the latter group were more severely affected. In all other respects the studies contained a similar distribution of patients.

BLINDING OF ASSESSORS

All six trials were initially double blind which should exclude performance and attrition bias. However Silver 1971 allowed the code to be broken and patients to change to the alternative medication if they felt they were not improving. This could introduce performance and detection bias.

DATA ANALYSIS

Savery 1977 and Walker 1972a were cross-over trials which presented some of their data after each arm of the trial, although the statistical analyses were performed on the combined data from both treatment and placebo arms.

Fehling 1973 and Walker 1972b were cross-over trials, but did not give the results of the first arms, only presenting combined data from both active treatment and both placebo arms. Since a washout period was not incorporated there is a strong possibility of a carry-over effect from the previous arm. Furthermore, both trials analysed data on a per protocol basis. For this reason we were unable to use data from either of these two trials. The first cross-over of the complex trial designed by Fahn et al (Fahn 1975) was the only portion of the study examined in this review because of the possibility of carry-over effects and selection bias in the remainder of the trial. The combined data from both active treatment arms was presented, divided into responders and non-responders to amantadine. No data from the placebo control arms were presented. For this reason we were unable to use the data from this trial.

The study by Silver 1971 allowed the code to be broken. If the patient found they were on placebo they could be changed to amantadine if they felt they were not improving. As the number of patients who broke the code was not stated and the results were not analysed on an intention-to-treat basis, none of the results could be examined as the randomisation had been compromised and bias could have been introduced.

Effects of interventions

Six trials were identified that examined amantadine for idiopathic Parkinson's disease. Two trials examined amantadine as an adjuvant to optimal levodopa therapy alone (Savery 1977 and Walker 1972b). One examined amantadine as an adjuvant to optimal levodopa therapy and anticholinergics (if the patients had been on them prior to the trial) (Fehling 1973). Silver 1971 and Fahn 1975 maintained patients on their previous medication during the trial, these were stated to be anticholinergics in Fahn 1975, but were not described in Silver 1971. Finally, Walker 1972a reduced the patients previous anticholinergic medication to nil or the lowest dose the patients could tolerate.

Fehling 1973, Walker 1972b and Fahn 1975 were cross-over trials and did not present data from the end of the first arms. Since there is a risk of a carry-over effect, data from these trials was not analysed. Also Fahn 1975 only presented data from the amantadine arms of the trial, so no comparison could be made to results of the placebo arms. Silver 1971 compromised the randomisation and did not analyse their results on an intention-to-treat basis so the results of this trial were not analysed because of the strong possibility of bias.

Savery 1977 measured Parkinsonian symptoms and impairments on an ad hoc assessment scale. After 9 weeks of treatment the group treated with amantadine were on average 15.0 points better than the placebo group (average baseline score of 21.4) in the Parkinsonian symptoms severity scale and 28.1 points better (average baseline score of 38.3) on the activity impairment scale. The statistical significance of these results is impossible to determine from the data provided by the authors. However the size of the improvements does suggest that they may have been clinically significant.

Walker 1972a measured 19 timed Simulated Activities of Daily Living such as putting on a shirt or using a fork. The mean scores at the end of the first treatment arm are available but no standard deviations or baseline scores are provided. The importance of these activities to the patients is unclear, as is their clinical significance. Walker 1972a also performed the Clinical Quantitative Neurological Examination (50 items). Only the mean scores at the end of the first treatment arm are available but no standard deviations or baseline scores are provided. The Examination is not aimed at Parkinsonian symptoms and does not measure items such as tremor or bradykinesia directly. The clinical significance of these results is therefore unclear.

ADVERSE EVENTS

Walker 1972a reports 16 different side-effects 10 of which presented in patients on amantadine. These included weight loss (4 patients), constipation (3 patients), unsteadiness, blurred vision, and urinary straining (2 patients each). Surprisingly 26 patients on amantadine reported no side-effects compared with only 18 patients on placebo. Walker 1972b used the same patients as in Walker 1972a and reported no new side effects.

Savery 1977 reports that amantadine only caused trivial side effects, one instance of mild livedo reticularis and two of mild blurred vision. The total difference in frequency of side effects between amantadine and placebo was not statistically significant.

Fahn 1975 reported six different side effects caused by the amantadine. These included insomnia (4 patients), anorexia (5 patients), dizziness, and nervousness (2 patients each).

Fehling 1973 reported 14 different side effects caused by amantadine. These included dryness of mouth (14 patients), tiredness (7 patients), abdominal discomfort (4 patients), blurred vision, and giddiness (3 patients each).

Silver 1971 reported that side effects were encountered by 47% of patients receiving amantadine. The most common side effect was livido recticularis which occurred in nine of 34 patients. Oedema was seen in four of these nine cases. 12% of the patients on placebo developed adverse events. None of the side effects due

to amantadine were considered serious and all disappeared after discontinuing the drug.

EXCLUDED STUDIES
Seventy studies were excluded from this review. The majority of them (36) were excluded because the study included patients suffering from non-idiopathic forms of Parkinsonism and/or had previously undergone stereotactic neurosurgery. The results in all of these studies were not stratified according to aetiology or whether they had had surgery. Therefore we could not determine the impact the amantadine had had on those patients with idiopathic Parkinson's disease who had not undergone neurosurgery. Sixteen trials were excluded because they were uncontrolled studies, nine because the patients were not randomly allocated to the treatment groups, three because the study compared amantadine to another active drug and had no placebo arm and one because the amantadine was administered parentally. A further five studies examined other drugs in the adamantanamine class of drugs.

We were unable to translate the Finnish study (Hakkarainen 1973) so this awaits assessment.

DISCUSSION

PRINCIPLE FINDINGS

- Six randomised controlled trials were found comparing amantadine to placebo for the treatment of idiopathic Parkinson's disease. Five examined amantadine as adjuvant therapy with optimal levels of levodopa or anticholinergics and one examined amantadine as an adjuvant therapy with minimum tolerated levels of anticholinergics or as a monotherapy.
- Seventy studies were excluded. Mostly on the basis that they included patients with Parkinsonism of multiple aetiology and the results were not stratified according to aetiology.
- All six trials claimed a positive effect of amantadine for Parkinson's disease. However the results were presented in such a poor manner, by present standards, that it was impossible to determine the statistical significance of any of the results.
- The poor reporting of the results in all of the studies and the small numbers in all the trials prevents drawing any firm conclusions regarding the efficacy of amantadine in the treatment of Parkinson's disease.
- Large well-designed randomised controlled trials are required to examine the efficacy and effectiveness of amantadine for Parkinson's disease.

METHODOLOGICAL QUALITY
None of the six included studies stated their method of randomisation and only one study (Fehling 1973) stated that allocation was concealed. If the method of randomisation was inadequate or the allocation not concealed it could have led to selection bias. Silver 1971 compromised the randomisation once the study was underway by allowing patients to break the code and change to amantadine if they found they were on placebo. As the results were not then analysed on an intention-to-treat basis this could easily have led to the introduction of bias from a number of sources.

The presentation and analysis of the results of all of the trials was very poor. This resulted in only two trials having data that could be examined (Savery 1977 and Walker 1972a), but because only the means of the data were given no statistical analysis of the significance of the changes due to the amantadine could be undertaken.

OUTCOME MEASURES AND RESULTS
Savery 1977 used a scale that measured Parkinsonian symptoms and impairments. Each item was scored on a four point scale. However this scale appeared to have been created by the authors for the study. There is no evidence that it has been validated or examined for reliability. As only the means of each treatment group were provided at the end of the first arm of the trial, statistical analysis of the results was impossible to perform. However the size of the improvements, 15.0 points on the Parkinsonian symptoms scale and 28.1 points on the activity impairment scale when compared to the baseline mean scores of 21.4 and 38.3 respectively suggest a clinically worthwhile improvement.

Walker 1972a measured 19 timed Simulated Activities of Daily Living. As only mean scores were provided no statistical analysis was possible. Although this was a validated assessment scale it is unclear what the importance of all of the activities would be to a patient. They also assessed patients using the Clinical Qualitative Neurological Examination which had 50 items. Again this scale was validated but as it was designed to assess general neurological function it is not very specific to Parkinson's disease and symptoms such as bradykinesia and tremor were not directly assessed.

None of the trials assessed quality of life or the economics of treating patients with amantadine. Both measures are required if patients and clinicians are to be able to make informed decisions as to the effectiveness of amantadine for the treatment of Parkinson's disease.

ADVERSE EVENTS
Amantadine has a reputation for causing severe psychiatric side effects. However this was not supported by the reported adverse events in these studies. It may be that amantadine has a worse safety profile with Parkinsonian syndromes other than idiopathic Parkinson's disease. Some of the studies excluded because they did not stratify their results according to disease aetiology may have had a worse adverse event profile as a result. It must also be noted that these studies were conducted before the reporting of adverse events was standardised, so there may have been under-reporting of such problems.

EXCLUDED STUDIES
Seventy studies were excluded from this review. The majority of these studies were excluded because they included patients that had non-idiopathic forms of Parkinsonism such as vascular Parkinsonism and post-encephalitic Parkinsonism. It is important to exclude these patients as their diseases have a different aetiology to idiopathic Parkinson's disease and a different clinical course. Studies that included patients that had undergone stereotactic brain surgery were also excluded as this sort of intervention may fundamentally and irreversibly change the neural mechanism of Parkinsonism in the basal ganglia. Potentially these patients could respond in a different manner to the amantadine than those who had not had the surgery.

The remainder of the studies were excluded because they were either not randomised, placebo controlled or did not examine oral amantadine. These studies were noted because it was often impossible to determine these exclusion criteria from the titles or available abstracts on the various databases searched.

AUTHORS' CONCLUSIONS

Implications for practice

A considerable amount of evidence on the effectiveness of amantadine has accrued from non-controlled trials, often in patients with Parkinsonian conditions other than idiopathic Parkinson's disease. All of the six randomised controlled trials analysed in this review reported a positive effect of amantadine in Parkinson's disease. However poor reporting of results and the small numbers in all of the trials prevents any firm conclusions regarding the efficacy and safety of amantadine in the treatment of Parkinson's disease.

Implications for research

Further trials involving larger numbers of patients are needed to evaluate the efficacy and safety of amantadine in the treatment of levodopa-induced dyskinesias in patients with Parkinson's disease.

There are several recommendations that can be made as a result of this review. In particular, future trials involving patients with Parkinson's disease should:

- Follow the CONSORT guidelines to improve reporting standards (CONSORT 2001)
- Use firm diagnostic criteria such as the UK PDS Brain Bank Criteria (Hughes 1992)
- Aim to enlist uniform cohorts of Parkinson's disease patients and ensure that inclusion and exclusion criteria are clear.
- Be of sufficient length to assess the long-term effects of the treatment.
- Include valid sample size calculations thereby reducing the chance of false negative results.
- Provide full data on outcome measures including the mean and standard deviation.
- Provide data at the end of the first arm of the trial if it is a crossover study.
- If they are crossover trials, include sufficient washout period between the two arms of the trial to reduce the likelihood of cross-over effects.
- The data must be analysed on an intention-to-treat basis and the change in outcome measures must be compared statistically across the two therapy groups.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Fahn 1975

Methods	Randomised, double-blind cross-over study. Method of randomisation not stated. Data presented from the amantadine group only after the first arm of the trial. Per protocol analysis. Location: One centre in the USA. Duration: The first cross-over lasted 4 weeks but the whole of this complex study lasted 13 months.
Participants	23 patients with 7 withdrawals (30%). 10 patients were male and 13 were female. Mean age: 66 years (range: 52 to 77 years). Mean number of years since diagnosis: 7.6 (range: 1 to 35). Ethnicity: 19 white and 4 black. Hoehn and Yahr scores: 3 patients in Stage I; 9 in Stage II; 8 in Stage III; 2 in Stage IV and 1 in Stage V. Mean = 2.5. Inclusion criteria: IPD; no previous levodopa or amantadine therapy; no severe medical illnesses. Exclusion criteria: none stated.
Interventions	Amantadine hydrochloride 100 mg twice daily or placebo for 2 weeks, followed by opposite treatment for 2 weeks. Patients maintained on most effective drug (or placebo if neither superior) for 5 months plus a slowly increasing dose of levodopa (until optimal benefit or side effects occurred). Followed by 2 weeks of amantadine or placebo (plus levodopa), then 2 weeks of opposite treatment. Most effective treatment (or placebo if neither superior) plus levodopa continued for next 5 months. Followed by amantadine or placebo (plus levodopa) for 2 weeks then 2 weeks of opposite treatment (plus levodopa). Anticholinergic drugs continued during trial but reduced to a single drug if more than one being taken.
Outcomes	1. Subjective patient reports. 2. Neurological examination with scoring of parkinsonian signs. 3. Timed tasks.
Notes	

Risk of bias

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

Fehling 1973

Methods	Randomised, double-blind cross-over study. Method of randomisation not stated. Results presented as combined data from both active treatment arms and both placebo arms. Data analysed on a per protocol basis. Location: One centre in Sweden. Duration: 2 months.

Fehling 1973 *(Continued)*

Participants	30 patients with 9 withdrawals (30%). 13 patients were male and 8 were female. Mean age: 64.7 years (range: 50-82 years) Mean number of years since diagnosis: 7.2 (range: 2-18) Mean daily dose of levodopa: 3.43 g (range: 2.0-6.0 g) Hoehn and Yahr scores: 1 patient in Stage I; 3 in Stage II; 7 in Stage III; 10 in Stage IV and none in Stage V. Mean = 3.2. Inclusion criteria: levodopa dosage and clinical status stable for 2 months prior to trial. Exclusion criteria: none stated.
Interventions	Amantadine hydrochloride for 28-31 days. Dose raised from 50-100 mg twice daily in first 2 weeks. Levodopa and anticholinergic drugs stable during trial.
Outcomes	1. Clinician's scoring for rigidity, tremor, hypokinesia of extremities, gait, postural reflexes, facial expression, speech, seborrhea and sialorrhea. 2. The number of pronation-supination movements of the hand that patients could perform in 30 seconds. 3. Side-effects graded by interviewing patients.
Notes	

Risk of bias

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

Savery 1977

Methods	Randomised, double-blind cross-over study. Method of randomisation not stated. Some data were presented after each arm of the trial, however the statistcal analyses were only performed on the combined data from both treatment and placebo arms, on an intention-to-treat basis. Location: One centre on the USA. Duration: 18 weeks.
Participants	42 patients. No withdrawals. 41 patients were male and 1 was female. Mean age: 64.5 years (range: 29 to 82 years). Hoehn and Yahr scores at baseline: 16 in Stage II; 24 in Stage III; 2 in Stage IV. Inclusion criteria: Parkinson's disease. Exclusion criteria: diabetes mellitus; alcoholism; narrow angle glaucoma; psychosis; sensitivity to levodopa, carbidopa or amantadine.
Interventions	Amantadine 100 mg/day for first 3 weeks, 200mg/day for second 3 weeks, then either 100 mg or 200 mg/day for final 3 weeks (patient's choice). All patients placed on a stable dose of levodopa for 3 weeks prior to and throughout trial. Other anti-parkinsonian medication discontinued for 3 weeks before and also during trial.
Outcomes	Clinician's scoring for 10 symptoms of Parkinson's disease and 11 activities.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Savery 1977 *(Continued)*

Allocation concealment?	Unclear risk	B - Unclear

Silver 1971

Methods	Randomised, double-blind parallel group study. Method of randomisation not stated. 10 patients requested to have code broken and changed from placebo to amantadine. Very limited data were presented in a per protocol manner. Location: one centre in the USA. Duration: Varied between patients. Up to 64 weeks.
Participants	50 patients. It is not stated whether any patients withdrew. Mean age: 61 years. Inclusion criteria: Parkinson's disease. Exclusion criteria: not stated.
Interventions	Amantadine hydrochloride 100 mg twice daily for between 1 day and 64 weeks (mean of 35 weeks). Anti-parkinsonian and other medication unchanged.
Outcomes	1. Clinician's scoring of tremor, rigidity, facial expression, character and volume of speech. 2. Timed tasks. 3. Subjective patient reports.
Notes	Patients could request for code to be broken and to change to the alternative medication if they felt they were not improving.

Risk of bias

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

Walker 1972a

Methods	Randomised, double-blind cross-over study. Method of randomisation not stated. Data presented after each arm of the trial, however the statistcal analyses were only performed on the combined data from both treatment and placebo arms, on an intention-to-treat basis. Location: One centre in the USA. Duration: 6 weeks.
Participants	42 patients. No withdrawals. 26 patients were male and 16 were female. Mean age: 65 years (range: 48 to 65 years) Mean number of years since diagnosis: 8. Inclusion criteria: Consecutive patients applying for anti-parkinsonian therapy. Exclusion criteria: Concurrent medical disorders; uncertain diagnoses; physical disability preventing patient from standing, transferring to/from a wheelchair or attending evaluation; stereotactic surgery.
Interventions	Amantadine 100 mg twice daily for 3 weeks. 36 patients discontinued concurrent anti-parkinsonian medication during trial. 6 were unable to stop medication and remained on the lowest tolerable dose of anticholinergics.
Outcomes	1. Subjective patient reports.

Walker 1972a *(Continued)*

	2. Neurologists' global impression. 3. Clinicians' scoring for functional disability (walking, dressing, hygiene, eating, feeding and speech) on an ad hoc scale. 4. Clinicians' scoring of tremor, rigidity, cogwheeling, weakness, finger dexterity, succession movements, bradykinesia, foot tapping, associated movements, rising, posture, stability and gait on an ad hoc scale (0 to 4 points). 5. Activities of daily living on a Simulated Activities of Daily Living Examination scale (SADLE) 6. Quantitative motor and sensory tests (Clinical Quantitative Neurological Examination (CQNE)). 7. Neuropsychological tests.
Notes	

Risk of bias

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

Walker 1972b

Methods	Randomised, double-blind cross-over study. Method of randomisation not stated. Results presented as combined data from both active treatment arms and both placebo arms. Data analysed on a per protocol basis. Location: One centre in the USA. Duration: 6 weeks.
Participants	28 patients (all participants in Walker 1972a). 2 withdrawals (7%, due to death). 16 patients were male and 12 female. Mean age: 65.6 years Mean number of years since diagnosis: 9.25. Mean Hoehn and Yahr classification: 2.9. Mean daily levodopa dose: 3.58 g. Inclusion criteria: not stated. Patients selected from previous trial (Walker 1972a). Exclusion criteria: Concurrent medical disorders; uncertain diagnoses; physical disability preventing patient from standing, transferring to/from a wheelchair or attending evaluation; stereotactic surgery.
Interventions	Amantadine 100 mg twice daily for 3 weeks. Patients tested on (1) amantadine alone (2) placebo alone (3) levodopa alone (4) levodopa plus amantadine and (5) levodopa plus placebo. All patients on levodopa for 6 minimum of months prior to trial. Levodopa dosage at maximal tolerable and stable for 6 weeks prior to trial. Other medication: not stated.
Outcomes	1. Side-effects of medication. 2. Pulse, blood pressure and disability (walking, dressing, hygiene, eating, feeding, speech). 3. Standard neurological examination (tremor, rigidity, finger coordination, bradykinesia, power, rising, posture, gait, associative movement). 4. Quantitative evaluation of neurological function. 5. Activities of daily living on a Simulated Activities of Daily Living Examination scale (SADLE) 6. Neuropsychological tests.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Walker 1972b *(Continued)*

Allocation concealment?	Unclear risk	B - Unclear

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

Study	Reason for exclusion
Appleton 1970	Includes patients suffering from non-idiopathic forms of Parkinsonism. Results are not stratified by aetiology, which would allow use of data from patients in the study with idiopathic Parkinson's disease.
Appleton 1971	No control group.
Barbeau 1971	Study includes patients who have previously undergone sterotactic brain surgery. Results do not separate operated from non-operated patients.
Bauer 1974	Includes patients suffering from non-idiopathic forms of Parkinsonism and does not stratify results by aetiology.
Bodis-Wollner 1997	No control group.
Boman 1970	Allocation to treatment not randomised.
Butzer 1975	Includes patients suffering from non-idiopathic forms of Parkinsonism and does not stratify results by aetiology.
Callaghan 1974a	Includes patients suffering from non-idiopathic forms of Parkinsonism and does not stratify results by aetiology.
Callaghan 1974b	Includes patients suffering from non-idiopathic forms of Parkinsonism and does not stratify results by aetiology.
Campbell 1972	Includes patients suffering from non-idiopathic forms of Parkinsonism and does not stratify results by aetiology.
Castaigne 1972	Includes patients suffering from non-idiopathic forms of Parkinsonism and does not stratify results by aetiology.
Dallos 1970	Includes patients suffering from non-idiopathic forms of Parkinsonism and does not stratify results by aetiology.
Dallos 1972	No control group.
Evidente 1999	No control group. Examined Rimantadine.
Fehling 1972	Allocation to treatment not randomised.
Fieschi 1970a	Allocation to treatment not randomised.
Fieschi 1970b	Allocation to treatment not randomised.
Fieschi 1970c	Includes patients suffering from non-idiopathic forms of Parkinsonism and does not stratify results by aetiology.
Fischer 1977	Examined intravenous memantine

Study	Reason for exclusion
Forssman 1972	Study includes patients who have previously undergone sterotactic brain surgery. Results do not separate operated from non-operated patients.
Freedman 1971	Includes patients suffering from non-idiopathic forms of Parkinsonism and does not stratify results by aetiology.
Funfgeld 1970	Study includes patients who have previously undergone sterotactic brain surgery. Results do not separate operated from non-operated patients.
Getz 1970	No control group.
Gilligan 1970	Includes patients suffering from non-idiopathic forms of Parkinsonism and does not stratify results by aetiology.
Godwin-Austen 1970	Includes patients suffering from non-idiopathic forms of Parkinsonism and does not stratify results by aetiology.
Griffiths 1971	No control group.
Hacohen 1972	No control group.
Hueber 1996	No control group.
Hunter 1970a	Includes patients suffering from non-idiopathic forms of Parkinsonism and does not stratify results by aetiology.
Hunter 1970b	Includes patients suffering from non-idiopathic forms of Parkinsonism and does not stratify results by aetiology.
Iivanainen 1974	Examines drug Kr339 not amantadine.
Iizuka 1986	No placebo control group. Compared budipin against amantadine.
Jorgensen 1971	Includes patients suffering from non-idiopathic forms of Parkinsonism and does not stratify results by aetiology.
Kiseleva 1973	Includes patients suffering from non-idiopathic forms of Parkinsonism and does not stratify results by aetiology.
Laitinen 1971	Includes patients suffering from non-idiopathic forms of Parkinsonism and does not stratify results by aetiology.
MacFadyen 1972	Includes patients suffering from non-idiopathic forms of Parkinsonism and patients who have previously undergone sterotactic brain surgery. Results separate operated from non-operated patients, and stratify patients by aetiology. However, it is not possible to separate both groups simultaneousy (i.e. to identify which patients with idiopathic Parkinson's disease have not undergone stereotactic brain surgery).
Malsch 2001	Study compares budipin with amantadine. No placebo group.
Mann 1971	Study includes patients who have previously undergone sterotactic brain surgery. Results do not separate operated from non-operated patients.
Matsumoto 1974	Allocation to treatment not randomised.

Study	Reason for exclusion
Mawdsley 1972	Includes patients suffering from non-idiopathic forms of Parkinsonism and does not stratify results by aetiology.
Merello 1999	Examines memantine.
Merrick 1973	Includes patients suffering from non-idiopathic forms of Parkinsonism and does not stratify results by aetiology.
Merry 1974	No control group.
Millac 1970	Includes patients suffering from non-idiopathic forms of Parkinsonism and does not stratify results by aetiology.
Muschard 1973	Parenteral administration of amantadine.
Parkes 1970a	Includes patients suffering from non-idiopathic forms of Parkinsonism and does not stratify results by aetiology.
Parkes 1970b	Includes patients suffering from non-idiopathic forms of Parkinsonism and does not stratify results by aetiology.
Parkes 1971a	Includes patients suffering from non-idiopathic forms of Parkinsonism and does not stratify results by aetiology.
Parkes 1971b	No control group.
Parkes 1974	Includes patients suffering from non-idiopathic forms of Parkinsonism and does not stratify results by aetiology.
Pendefunda 1975	Includes patients suffering from non-idiopathic forms of Parkinsonism and does not stratify results by aetiology.
Pollock 1972	Includes patients suffering from non-idiopathic forms of Parkinsonism and does not stratify results by aetiology.
Rao 1971	No control group.
Reveno 1971	No control group.
Rinne 1972	Includes patients suffering from non-idiopathic forms of Parkinsonism and does not stratify results by aetiology.
Sandyk 1981	Allocation to treatment not randomised.
Savery 1976	No control group.
Schneider 1984	Examines memantine.
Schwab 1969a	No control group.
Schwab 1969b	No control group.
Schwieger 1970	Study includes patients who have previously undergone sterotactic brain surgery. Results do not separate operated from non-operated patients.
Shiozawa 1974	Study compares amantadine with trihexyphenidyl. There is no placebo control group.

Study	Reason for exclusion
Shiozawa 1981	No control group.
Sigwald 1970	Includes patients suffering from non-idiopathic forms of Parkinsonism and does not stratify results by aetiology.
Sigwald 1972	Not randomised.
Timberlake 1978	Includes patients suffering from non-idiopathic forms of Parkinsonism and does not stratify results by aetiology.
Voller 1973	Includes patients suffering from non-idiopathic forms of Parkinsonism and does not stratify results by aetiology.
Webster 1984	Allocation to treatment not randomised.
Weeth 1969	No control group.
Zeldowicz 1973	Allocation to treatment not randomised.

ADDITIONAL TABLES

Table 1. Methodological Quality of Included Studies

Study	Specified Eligibility Criteria	Randomisation Method	Concealment of Allocation	Similarity at Baseline	Withdrawals Described	Missing Values	Cointerventions Constant (e.g. drugs)	Blinded Assessors	Data Analysis
Fahn 1975	A	B	B	B	C	C	A	A	C
Fehling 1973	A	B	A	B	C	C	A	A	C
Savery 1977	A	B	B	B	A	A	A	A	A
Silver 1971	A	B	B	B	B	B	B	A	C
Walker 1972a	A	B	B	B	A	A	A	A	A
Walker 1972b	A	B	B	B	A	A	A	A	C
	Key: A: Adequate B: Unclear (not stated) C: Inadequate	Key: A: Good B: Unclear (not stated) C: Weak (e.g. alternate allocation)	Key: A: Adequate B: Unclear (not stated) C: Inadequate	Key: A: Good B: Unclear (not stated) C: Poor	A: Good, <10% B: Unclear (not stated) C: Poor, >10%	A: Good, <10% B: Unclear (not stated) C: Poor, >10%	A: Constant B: Unclear (not stated) C: Variation allowed	Key: A: Adequate B: Unclear (not stated) C: Inadequate	Key: A: Adequate B: Unclear (not stated) C: No valid data

WHAT'S NEW

Date	Event	Description
12 November 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 1, 2002
Review first published: Issue 1, 2003

Date	Event	Description
10 September 2002	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

K H O Deane and N Crosby carried out the literature searches and established which studies were eligible for inclusion. All reviewers were involved in writing the review.

DECLARATIONS OF INTEREST

None.

INDEX TERMS

Medical Subject Headings (MeSH)

Amantadine [*therapeutic use]; Antiparkinson Agents [*therapeutic use]; Levodopa [therapeutic use]; Parkinson Disease [*drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Humans