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TABLE OF CONTENTS

ABSTRACT 1
PLAIN LANGUAGE SUMMARY 2
BACKGROUND 3
OBJECTIVES 3
METHODS 3
RESULTS 4
DISCUSSION 5
AUTHORS' CONCLUSIONS 6
ACKNOWLEDGEMENTS 6
REFERENCES 7
CHARACTERISTICS OF STUDIES 8
ADDITIONAL TABLES 12
WHAT'S NEW 13
HISTORY 13
CONTRIBUTIONS OF AUTHORS 13
DECLARATIONS OF INTEREST 13
INDEX TERMS 13

[Intervention Review]

Amantadine for dyskinesia in Parkinson's disease

Niall J Crosby[1], Katherine Deane[2], Carl E Clarke[3]

[1]Department of Neurology, University of Birmingham, Birmingham, UK. [2]Institute of Health & Society, Newcastle University, Newcastle-upon-Tyne, UK. [3]Department of Neurology, City Hospital, Sandwell and West Birmingham Hospitals NHS Trust, Birmingham, UK

Contact: Carl E Clarke, Department of Neurology, City Hospital, Sandwell and West Birmingham Hospitals NHS Trust, Dudley Road, Birmingham, West Midlands, B18 7QH, UK. c.e.clarke@bham.ac.uk.

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ABSTRACT

Background

Abnormal involuntary movements known as dyskinesias are amongst the most disabling side-effects of levodopa therapy. It is thought that amantadine, an NMDA-receptor antagonist, may reduce dyskinesias in patients with Parkinson's disease without worsening Parkinsonian symptoms.

Objectives

To compare the efficacy and safety of adjuvant amantadine therapy versus placebo in treating dyskinesia in patients with Parkinson's disease, already established on levodopa, and suffering from motor complications.

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 dyskinesia in 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

Three randomised controlled trials were found comparing amantadine with placebo in the treatment of dyskinesia in patients with idiopathic Parkinson's disease. Three trials were excluded on the basis that they had no control group and a further three did not state whether they randomised the treatment that participants received. The included trials were double-blind cross-over studies involving a total of 53 patients. All three studies failed to present data from the first arm, instead presenting results as combined data from both treatment arms and both placebo arms. Two trials had no wash-out interval between the treatment periods. In view of the risk of a carry-over effect into the second arm, the results of these trials were not analysed. The final trial had a one week wash-out interval but only

examined 11 participants. One study reported side-effects of amantadine in 8 of the 18 participants, including confusion and worsening of hallucinations. Another reported reversible edema of both feet in one of eleven participants.

Authors' conclusions

Due to lack of evidence it is impossible to determine whether amantadine is a safe and effective form of treatment for levodopa-induced dyskinesias in patients with Parkinson's disease.

PLAIN LANGUAGE SUMMARY

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

Levodopa is regarded as the most effective treatment for Parkinson's disease but in many patients it causes abnormal involuntary movements known as dyskinesias. It is thought that amantadine may be added to levodopa to reduce dyskinesias in patients with Parkinson's disease without worsening Parkinsonian symptoms. This review found that there is not enough evidence from trials about the effects of amantadine for people with dyskinesia in Parkinson's disease. Adverse effects in trials so far have included confusion, worsening of hallucinations, the re-emergence of palpitations, nausea, dry mouth, swelling of feet and constipation.

BACKGROUND

Levodopa remains the most commonly prescribed and effective drug treatment for symptomatic relief in Parkinson's disease (PD). However, it is associated with dose-limiting motor and psychiatric side-effects. The former include abnormal involuntary movements which are also known as dyskinesias. These are comprised of choreoathetoid writhing movements of the limbs, face and trunk and painful dystonic movements of the legs or rarely the hands. They usually occur at the peak effect of each dose but can return just before the effect of the dose wanes, so-called diphasic dyskinesia. Dyskinesias are usually associated with response fluctuations including a shortened response to each dose of levodopa (end-of-dose deterioration) and unpredictable switching between the on and relatively immobile off states. After 6 years of therapy these motor complications affect 50% of patients (Rajput 1984) and 100% of young onset patients (Quinn 1986).

The pathogenesis of dyskinesias remains unclear. Recent studies have implicated the glutamatergic projection from the subthalamic nucleus to the medial segment of the globus pallidus. Antagonists of N-methyl-D-aspartate (NMDA) receptors diminish levodopa-induced dyskinesias in both rat (Engber 1994) and primate (Papa 1996) models of Parkinson's disease. This has led to the view that levodopa-induced dyskinesias may in part be caused by over-activity of the glutamatergic subthalamo-pallidal pathway (Chase 1996).

Dyskinesias have traditionally been managed by:-

- Fractionating the dose of immediate-release levodopa (e.g. 200 mg three times daily becomes 100 mg taken six times daily)
- Introducing a modified-release levodopa preparation
- Introducing a dopamine agonist, selegiline or a catechol-O-methyltransferase (COMT) inhibitor such as entacapone.

However, these approaches are only effective in the management of mild to moderate dyskinesia. For severe disabling dyskinesia, changes in medical therapy are often futile and the only recourse is surgical intervention such as pallidotomy or subthalamic stimulation. There is an urgent need for an orally active agent which can reduce severe dyskinesia.

Amantadine hydrochloride, a member of the adamantanamine class, is known to act as a non-competitive antagonist at the phencyclidine (PCP) site within the NMDA-receptor at therapeutic concentrations (Kornhuber 1994). Small pilot studies have demonstrated that amantadine may reduce dyskinesias in people with Parkinson's disease without worsening Parkinsonian symptoms (Verhagen Metman 1998). Unfortunately not all patients respond to amantadine (Rajput 1997) and the drug is reported to be associated with a significant adverse event profile which has limited its use.

This systematic review examines all randomised controlled trials of adjuvant amantadine therapy versus placebo in patients with Parkinson's disease with levodopa-induced dyskinesias to examine its effectiveness in treating dyskinesia along with its tolerability. A separate review considers the efficacy of amantadine in the relief of Parkinsonian symptoms (Crosby 2002).

OBJECTIVES

To compare the efficacy and safety of adjuvant amantadine therapy versus placebo in treating dyskinesia in patients with Parkinson's disease already established on levodopa and suffering from motor complications.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised trials comparing amantadine with placebo in the treatment of dyskinesia were considered for inclusion in the study.

Types of participants

Patients with a clinical diagnosis of idiopathic Parkinson's disease (as defined by the trial report authors) who had developed long-term motor complications of dyskinesia with or without end-of-dose deterioration. All ages were included. Any duration of levodopa therapy was included.

Types of interventions

Oral amantadine therapy or placebo. Trial durations of greater than 4 weeks were included.

Types of outcome measures

1. Changes in dyskinesia rating scales and the prevalence of dyskinesia.

2. Improvement in the time patients spend in the off state.

3. Changes in Parkinsonian rating scales.

4. Levodopa dose.

5. Number of withdrawals due to 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), 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, 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.

RESULTS

Description of studies

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

Three trials were found that compared amantadine with placebo for the treatment of levodopa-induced dyskinesias in a total of 53 patients with idiopathic Parkinson's disease (Luginger 2000, Snow 2000 and Verhagen Metman 1998). A further six trials initially appeared to meet the criteria for inclusion. However, on more detailed scrutiny, three were found to contain no control group (Rajput 1997, Rajput 1998 and Ruzicka 2000) and a further two did not randomise the treatment that participants received (Cersosimo 2000 and Verhagen Metman1999). Kim 2000 did not state whether the patients were randomised and attempts to clarify this with the authors were unsuccessful. We have assumed that the study was not randomised until we receive evidence to the contrary.

TRIAL DESIGN
All three trials were placebo-controlled, randomised, double-blind cross-over studies, based in single centres. In Luginger 2000 the patients received treatment (active drug or placebo) over 2 weeks separated by a one week wash-out interval. In Snow 2000 and Verhagen Metman 1998 the patients received treatment (active drug or placebo) over 3 weeks with no wash-out interval between each treatment period.

PARTICIPANTS
Snow 2000 and Verhagen Metman 1998 did not provide data about the characteristics of the individual participants or of the two groups at baseline. Both gave characteristics of the entire study population. Luginger 2000 examined 11 participants (4 male) with a mean age of 63.5 years. On average they had had Parkinson's disease for 16.2 years, dyskinesias for 10.1 years and were taking 777 mg/day of levodopa. Snow 2000 examined 24 patients (10 male), with a mean age of 64 years. On average they had had Parkinson's disease for 10.6 years, dyskinesias for 3.1 years, and were taking 834 mg/day of levodopa. Verhagen Metman 1998 treated 18 patients (12 male) with a mean age of 60 years. On average they had had Parkinson's disease for 13 years, had a Hoehn and Yahr score of 3.5, and were taking 1074 mg/day of levodopa.

INTERVENTIONS
The regimen of treatment varied between the three studies. Luginger 2000 used amantadine 300mg/day titrated over 3 days with daily 100mg increments. Snow 2000 used amantadine 100 mg/d for the first week, followed by 200 mg/d for the remaining two weeks. Verhagen Metman 1998 titrated participants up to 300 or 400 mg/d (depending on age, renal function and tolerance) over the first 4 to 6 days of the 3 week treatment arm, with patients remaining at this dose until the 3 weeks was complete.

Patients in all studies continued their previous medication. Luginger 2000 performed oral levodopa challenges before the first and on the last day of each treatment period. Antiparkinsonian medications were withheld overnight (12 hours) and on the following morning patients were challenged with 100/25 or 200/50 mg of levodopa depending on their regularly scheduled levodopa morning dose. Snow 2000 halted antiparkinsonian medications on the morning of assessments which came at the end of each 3 week arm and challenged patients with 1.5 times their regular morning dose of levodopa in the form of standard release tablets in order to assess the severity of dyskinesias. Verhagen Metman 1998 discontinued levodopa at 11pm on the nights before evaluations which were also at the end of the 3 week arms and withheld dopamine agonists and selegiline on assessment days until after the completion of testing. Patients then received a 7 hour intravenous infusion of levodopa. This was at the lowest rate that produced the greatest antiparkinsonian response and was determined individually for each patient before the test day and remained constant for the remaining arms.

OUTCOME MEASURES
Luginger 2000 measured dyskinesias using the 'Marconi dyskinesia rating scale', a 0 to 4 point rating scale for dyskinesias affecting the extremities, trunk and neck and during finger tapping (maximum score of 72). The Unified Parkinson's Disease Rating Scale (UPDRS) part IV questions 1 to 4 were also used to assess the degree of dyskinesia. The severity of parkinsonism in both "on" and "off " states was rated using the UPDRS III motor scale. Snow 2000 measured dyskinesias using a 0 to 4 point rating scale for each limb, the trunk, head, neck and face. The Unified Parkinson's Disease Rating Scale (UPDRS) part IV questions 1 to 4 were also used to assess the degree of dyskinesia. The severity of parkinsonism in both "on" and "off " states was rated using the UPDRS III motor scale. Verhagen Metman 1998 employed an abbreviated UPDRS part III scale and a revised version of the Abnormal Involuntary Movement Scale (AIMS) to evaluate dyskinesias. Secondary outcome measures comprised the UPDRS part IV and patient diaries in which patients used a scale from -3 (very bradykinetic) to + 3 (very dyskinetic) with 0 representing an optimum score. The UPDRS part II was also used to assess the patients' abilities to perform activities of daily living.

Risk of bias in included studies

See Table: Additional Table 1.

RANDOMISATION METHOD AND CONCEALMENT OF ALLOCATION
Luginger 2000 randomised patients using random number tables, numbers 1 and 2 were allocated in blocks of four. The allocation was kept concealed in consecutively numbered opaque envelopes. Snow 2000 randomised patients by computer and ensured that equal numbers were included in each treatment group. There was no information regarding the concealment of allocation, so

detection bias cannot be ruled out. Verhagen Metman 1998 did not describe the method of randomisation, so selection bias cannot be excluded. However, the allocation of patients to treatment groups was determined by a safety officer not involved in patient assessment and was therefore concealed from the assessors.

ELIGIBILITY CRITERIA
All patients suffered from idiopathic Parkinson's disease (IPD). Snow 2000 maintained that all 24 participants met the UK Brain Bank Criteria for diagnosis of Parkinson's disease (Hughes 1992). Luginger 2000 and Verhagen Metman 1998 did not state the criteria used to distinguish between patients with IPD and other forms of parkinsonism.

PATIENT NUMBERS AND BASELINE CHARACTERISTICS
Only 53 patients were studied. The small number of participants means that the results may not be applicable to the entire population of Parkinson's disease patients.

27 of the patients (51%) were female. This is representative of the Parkinson's disease population as a whole.

The baseline characteristics in Snow 2000 and Verhagen Metman 1998 were given for both study populations but not for individual patients or the particular treatment groups. Snow 2000 did not state the mean Hoehn and Yahr score of the study population at baseline, which means that the severity of disease of patients in this study cannot be judged.

BLINDING OF ASSESSORS
All three trials were double-blinded which should reduce performance and attrition bias.

OUTCOME MEASURES
The 'Marconi dyskinesia rating scale' used by Luginger 2000 did not appear to have been examined for reliability and validity (Marconi 1994).

DATA ANALYSIS
All three trials were of the cross-over design. None of the trials gave the results of the first arms, only presenting combined data from both active treatment arms and both placebo arms. Since a wash-out period was not incorporated into Snow 2000 or Verhagen Metman 1998 there is a strong possibility of a carry-over effect. Furthermore, both studies analysed data on a per protocol basis (withdrawals were not included in the analysis). For these reasons we were unable to use data from these trials. The policy of the Cochrane Collaboration is not to analyse combined data from both active treatment arms and both placebo arms. However we recognise that with a wash-out period of one week the results from Luginger 2000 are unlikely to suffer from carry-over effect. We have contacted the authors of all three trials for the data from the end of the first part of the cross-over protocol but have been unsuccessful so far.

Effects of interventions

All three included studies were cross-over trials. Data were presented in the form of the combined results of both active treatment arms and both placebo arms in Luginger 2000, Snow 2000 and Verhagen Metman 1998. Since Snow 2000 and Verhagen Metman 1998 did not have a wash-out period there is a significant risk of a carry-over effect of the active treatment into the second arms.

One patient (9%) withdrew from the Luginger 2000 trial as a result of dizziness whilst on placebo. Two (8%) patients withdrew from Snow 2000 after the first period. One because he felt he had had benefit from the medication (which was found to be amantadine) and did not wish to cross-over, the other because of poor compliance in taking the placebo. Four (22%) patients withdrew from Verhagen Metman 1998 because of mild and transient adverse events (two with confusion or hallucinations, one with nausea and one with recurrance of pre-existing palpitations). This large withdrawal rate in this trial could be due to chance but may have led to attrition bias. All the trials also analysed patients on a per-protocol basis (withdrawals were not included in the analysis), which could have led to attrition bias.

Luginger 2000 had a wash-out period so the risk of carry-over effect was reduced, and they stated that there were no differences between patients receiving amantadine in the first or second treatment period. Dyskinesia severity following the levodopa challenge was reduced after oral amantadine treatment by 6.4 points (41%) when compared to the placebo arm.

One patient experienced reversible oedema of both feet during active amantadine treatment in Luginger 2000, and one patient withdrew whilst on placebo due to dizziness. Snow 2000 maintained that none of the 24 participants complained of any adverse effects. Verhagen Metman 1998 reported a range of adverse events. The four patients who withdrew did so as a result of confusion (at an amantadine dose of 200 mg), worsening of hallucinations (on 300 mg of amantadine), the reappearance of palpitations (on 100 mg of amantadine) and nausea (on 100 mg of amantadine). Of the remaining patients, one complained of an exacerbation of hallucinations (on 300 mg of amantadine), another of a slightly worsened dry mouth and constipation and two reported confusion on 400 mg of amantadine which resolved when the dose was reduced to 300 mg.

Nine studies were excluded from this review. Three studies did not randomly allocate the patients to the treatment groups (Cersosimo 2000, Verhagen 1999, Verhagen Metman1999), three studies had no control group (Rajput 1997, Rajput 1998 and Ruzicka 2000), two studies examined intravenous infusion of amantadine (Del Dotto 2001, Verhagen Metman1998), one study was only published as an abstract and it did not state whether the patients were randomly allocated to the treatment groups (Kim 2000). The full papers had to be assessed as it was usually not possible to determine the details of the studies that met our exclusion criteria from the titles and/or abstracts available to us from the various databases searched.

DISCUSSION

Three trials comparing the efficacy and safety of oral amantadine therapy against placebo met our inclusion criteria. A total of 53 patients were studied. All three trials were short, so the long term effects of amantadine cannot be determined.

All three trials used a cross-over design and only presented the combined results of both treatment and both placebo arms. Since neither Snow 2000 or Verhagen Metman 1998 included a washout period there is a possibility of a carry-over effect into the second arm of the trial. Therefore data from neither trial could be used. Luginger 2000 had a wash-out period and did show some positive results in the combined results of both treatment and both placebo

arms i.e. a 41% reduction in dyskinesia subsequent to levodopa challenge. However it was difficult to determine if any reduction in the dyskinesias was of any benefits from the patient's point of view as none of the trials assessed quality of life. Also none carried out an economic analysis, despite dyskinesias being responsible for an increase in the healthcare costs of Parkinson's disease (Pechevis 2001).

The impact of dyskinesia is hard to measure. All of the trials used components of UPDRS (part IV) scores which assess duration and disability caused by the dyskinesia. Although the 'Marconi dyskinesia rating scale' was reported in Luginger 2000 to perform a more detailed description of the dyskinesia we were unable to find details about the scale, and whether it had been tested for validity and reliability (Marconi 1994).

Amantadine has a reputation for inducing severe psychiatric side-effects. However none of the patients in Snow 2000 reported any adverse events on 200mg of amantadine. Only one patient in Luginger 2000 had an adverse event associated with active treatment (reversible feet oedema). Eight patients who participated in the Verhagen Metman 1998 trial suffered adverse effects from amantadine. However only two patients had to withdraw from the trial as a result of psychiatric side-effects (confusion and worsened hallucinations). Three other patients suffered psychiatric side-effects (worsened hallucinations and confusion), however the two patients with confusion found that this resolved when the dosage of amantadine was reduced from 400 to 300 mg/day. This suggests that patients with pre-existing hallucinations may not be suitable candidates for amantadine therapy and that if confusion does occur a reduction in the dosage should be attempted before taking the patient off the drug. However, due to the small size of both trials, it is not possible to make any definitive conclusions about the safety of amantadine in the general Parkinson's disease population.

Three trials were excluded on the basis that they had no control group (Rajput 1997, Rajput 1998 and Ruzicka 2000). A further two did not randomise the treatment that participants received (Cersosimo 2000 and Verhagen Metman1999), meaning that selection bias may have been introduced. Kim 2000 did not state whether the patients were randomised. In future trials must be reported according to CONSORT guidelines (CONSORT 2001) to avoid many of these reporting problems. Del Dotto 2001 used intravenous amantadine which is not part of usual clinical practice and breached our inclusion criteria.

AUTHORS' CONCLUSIONS

Implications for practice

In view of the lack of evidence it is impossible to determine whether amantadine is a safe and effective treatment for levodopa-induced dyskinesias in patients with Parkinson's disease.

Implications for research

Further trials involving larger numbers of patients are needed to judge 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 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.
- Use validated scales to assess the severity of the dyskinesia and the impact it has upon the patient's quality of life.
- 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 a 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.

ACKNOWLEDGEMENTS

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Luginger 2000

Methods	Randomised double-blind cross-over study with two treatmement periods of 2 weeks each separated by a 1 week wash-out interval. Random number tables were used, numbers 1 and 2 were assigned in blocks of four. The assignment was concealed using sequentially numbered opaque envelopes. Results presented as combined data from both active treatment arms and both placebo arms. Per protocol analysis. Location: One centre in Austria. Duration: 5 weeks.
Participants	11 patients with 1 withdrawal. 4 patients were male, 7 female. Mean age 63.5 years old (SD 8.2 years). Mean disease duration 16.2 years (SD 6.2 years) Mean dyskinesia duration 10.1 years (SD 5.1 years). Mean Hoehn and Yahr stage 'On': 2.8 (SD1.2), 'Off': 3.8 (SD 0.9). Mean levodopa dose 777 mg/day (range 450-1300 mg/day). Inclusion criteria: Advanced Parkinson's disease complicated by motor fluctuations and dyskinesias. Exclusion criteria: Dementia, renal hepatic or cardiac failure.
Interventions	Amantadine was titrated to 100mg three times per day over three days with daily 100mg increments. Remaining antiparkinsonian medication unchanged during trial. In addition oral levodopa challenges were performed before the first and last day of each treatment period. Antiparkinsonian medication was withheld overnight (12 hours) and the following morning patients were challenged with 100/25 or 200/50 mg of levodopa depending on their regularly scheduled levodopa morning dose.
Outcomes	Primary: Marconi dyskinesia rating scale Secondary: Part IV UPDRS and ADL Part II UPDRS in 'Off' state. Parkinsonian symptoms in 'On' and 'Off' states scored using UPDRS part III
Notes	Cross-over trial - data presented as combined results of all treatment arms and all placebo arms.

Luginger 2000 *(Continued)*

Risk of bias

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

Snow 2000

Methods	Randomised, double-blind, cross-over study. Computerised randomisation. Results presented as combined data from both active treatment arms and both placebo arms. Per protocol analysis. Location: One centre in New Zealand. Duration: 6 weeks.
Participants	24 patients. 2 withdrawals. 10 patients were male and 14 were female. Mean age: 64.2 years (SD: 8.90 y) Mean symptom duration: 10.6 years (SD: 3.6 y) Mean dyskinesia duration: 3.1 years (SD: 1.5 y) Mean levodopa dose: 834 mg/day (range: 200-3000mg). Inclusion criteria: Parkinson's disease as defined by the Brain Bank Criteria with daily levodopa-induced dyskinesias. Folstein Mini-Mental status examination score greater than 26. Stable medication for one month prior to trial. No previous experience of amantadine. Normal serum creatinine. Exclusion criteria: none stated.
Interventions	Amantadine 100 mg/day for one week, then 100 mg twice daily for two weeks. Remaining antiparkinsonian medication unchanged during trial.
Outcomes	Primary: dyskinesia score (0-4 point rating scale) Unified Parkinson's Disease Rating Scale (UPDRS) part IV questions 1-4. Secondary: UPDRS part III motor score. Adverse events.
Notes	Cross-over trial - data presented as combined results of all treatment arms and all placebo arms.

Risk of bias

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

Verhagen Metman 1998

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. Per protocol analysis. Location: One centre in the USA. Duration: 6 weeks.

Verhagen Metman 1998 *(Continued)*

Participants	18 patients with 4 withdrawals. 12 patients were male and 6 were female. Mean age: 60 years (range: 35 to 78 years). Symptom duration: 13 years (range: 4 to 31 years). Mean Hoehn and Yahr score: 3.5 (two stage II, nine stage III, three stage IV, four stage V) Mean levodopa treatment duration: 12 years (range: 3 to 28 years). Daily levodopa dose at baseline: 1074 mg (range: 450 to 2800 mg) Inclusion criteria: Parkinson's disease with motor fluctuations and peak-dose dyskinesias. Exclusion criteria: none stated.
Interventions	Amantadine 300 - 400 mg/day (depending on age, renal function and tolerance) for 3 weeks. Oral levodopa withheld from 11pm on nights prior to testing with intravenous levodopa infusions. Dopamine agonists and seleginine withheld on assessment days until testing completed.
Outcomes	Primary: abbreviated Unified Parkinson's Disease Rating Scale (UPDRS, part III). Abnormal Involuntary Movement Scale (AIMS). Secondary: UPDRS part IV. Patient diaries. UPDRS part II.
Notes	Cross-over trial - data presented as combined results of all treatment arms and all placebo arms.

Risk of bias

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

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

Study	Reason for exclusion
Cersosimo 2000	Non-randomised study.
Del Dotto 2001	Used intravenous amantadine which is not part of usual clinical practice and breached our inclusion criteria.
Kim 2000	Trial published in the form of an abstract and does not state whether patients were randomised to amantadine or placebo. We are attempting to contact the authors to determine this.
Rajput 1997	No control group.
Rajput 1998	No control group.
Ruzicka 2000	No control group. Amantadine given as an oral and an infusion treatment.
Verhagen 1999	Non-randomised study
Verhagen Metman1998	Amantadine given as intravenous infusion.
Verhagen Metman1999	Non-randomised study.

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
Snow 2000	A	A	B	B	A	A	A	A	C
Verhagen Metman 98	A	B	B	B	C	B	B	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	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 2, 2003

Date	Event	Description
7 January 2003	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. N Crosby was the primary author.

DECLARATIONS OF INTEREST

None.

INDEX TERMS

Medical Subject Headings (MeSH)

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

MeSH check words

Humans