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[Intervention Review]

Pramipexole for levodopa-induced complications in Parkinson's disease

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ABSTRACT

Background

The long-term use of levodopa in Parkinson's disease is associated with the development of motor complications including abnormal involuntary movements (dyskinesia) and a shortening response to each dose (wearing off phenomenon). It is thought that dopamine agonists can reduce the duration of immobile off periods and the need for levodopa therapy whilst maintaining or improving motor impairments and only minimally increasing dopaminergic adverse events.

Objectives

To compare the efficacy and safety of adjuvant pramipexole therapy versus inactive placebo in patients with Parkinson's disease, already established on levodopa.

Search methods

Electronic searches of MEDLINE, EMBASE and the Cochrane Controlled Trials Register. Handsearching of the neurology literature as part of the Cochrane Movement Disorders Group's strategy. Examination of the reference lists of identified studies and other reviews. Contact with Pharmacia Upjohn and Boehringer Ingelheim.

Selection criteria

Randomised controlled trials of pramipexole versus placebo in patients with a clinical diagnosis of idiopathic Parkinson's disease and long-term complications of levodopa therapy.

Data collection and analysis

Data was abstracted independently by the authors and differences settled by discussion. The outcome measures used included Parkinson's disease rating scales, levodopa dosage, 'off' time measurements and the frequency of drop outs and adverse events.

Main results

Four randomised controlled trials have compared pramipexole with placebo in 669 patients with later Parkinson's disease. Two phase III studies were medium term (24 weeks maintenance period) and 2 phase II studies were short term (4 weeks maintenance period). The reduction in off time was significantly greater with pramipexole compared with placebo (weighted mean difference 1.8 hours; 1.2, 2.3 95% CI). No significant changes were noted in a dyskinesia rating scale in any of the 4 studies, but dyskinesia as an adverse event was reported more frequently with pramipexole. A significant improvement occurred in UPDRS complication score (part IV) in 2 studies but not in the remaining trials. Statistically significant improvements in UPDRS ADL score occurred with pramipexole in all studies. Significant improvements in UPDRS motor scores in the on state were reported in 3 of the 4 studies. Levodopa dose reduction was allowed in 3 studies and meta-analysis shows a significant difference in favour of pramipexole (weighted mean difference 115 mg; 87, 143 95% CI). Trends

toward a higher incidence of dopaminergic adverse events with pramipexole only reached statistical significance regarding hallucinations. There were significantly fewer withdrawals from pramipexole.

Authors' conclusions

Pramipexole can be used to reduce off time, improve motor impairments and disability and reduce levodopa dose at the expense of increased dyskinetic adverse events. This conclusion is based on short and medium term trials (up to 24 weeks). Further trials are required to directly compare the newer with the older dopamine agonists.

PLAIN LANGUAGE SUMMARY

In the later stages of Parkinson's disease, side effects occur because of the use of levodopa in its treatment. These consist of involuntary writhing movements (dyskinesia), painful cramps in the legs and a shortened response to each dose referred to as 'end-of-dose deterioration' or the 'wearing-off effect'. Dopamine agonist drugs act by mimicking levodopa in the brain, but they do not cause these long-term treatment complications. For this reason, dopamine agonists have for some years been added once these problems develop in the hope of improving them. Pramipexole is a new dopamine agonist recently licensed in the UK for the treatment of later Parkinson's disease. In this review, we will examine the trials performed with this drug to see how effective it is and what side effects it causes.

Four trials have compared pramipexole with placebo in 669 patients with later Parkinson's disease. Two studies were medium term (24 weeks) and 2 studies were short term (4 weeks). Pramipexole significantly reduced the time patients spent in the immobile off state compared with placebo by an average of 1.8 hours. No changes occurred in a dyskinesia rating scale in any of the studies, but dyskinesia recorded as a side effect was reported more frequently with pramipexole. A significant improvement occurred in the Unified Parkinson's Disease Rating Scale (UPDRS) complication score in 2 studies but not in the remaining trials. Significant improvements in UPDRS activities of daily living score occurred with pramipexole in all studies. Significant improvements in UPDRS motor scores in the mobile on state were reported in 3 of the 4 studies. Levodopa dose reduction was allowed in 3 studies and meta-analysis showed a significant difference in favour of pramipexole. There was a suggestion of more side effects such as nausea, vomiting and dizziness with pramipexole and a definite increase in hallucinations in those given pramipexole. There were significantly fewer withdrawals from pramipexole.

In conclusion, pramipexole can be used to reduce off time, improve motor impairments and disability and reduce levodopa dose at the expense of increased dyskinetic side effects. This is based on short and medium term trials (up to 24 weeks). Further trials are required to directly compare the newer with the older dopamine agonists.

BACKGROUND

Levodopa remains the 'gold standard' therapy for Parkinson's disease in spite of recent therapeutic developments. However, management in advanced patients is complicated by the long-term motor and psychiatric side-effects of the treatment. Choreoathetoid dyskinesia (involuntary writhing movements), dystonia (painful cramps) and a shortened response to each dose referred to as 'end-of-dose deterioration' or the 'wearing-off effect' affect around 50% of patients after 6 years of therapy (Rajput 1984) and 100% of young onset patients after 6 years of treatment (Quinn 1986). In a more recent study with lower doses of levodopa, Block 1997 still found such side-effects in 16% of patients after 5 years of treatment with either immediate-release or controlled-release levodopa therapy. It is because of such long-term levodopa-induced complications that we are now more cautious in our use of the agent.

Dopamine agonists offer an alternative therapy, acting directly on post-synaptic dopamine receptors in the striatum and thus not requiring conversion into dopamine as does levodopa. Agonists have traditionally been used in a levodopa-sparing capacity, but the more recent trend has been to use them in de novo patients to delay the introduction of levodopa. While some studies suggest agonists may be of value in de novo Parkinson's patients, most have looked at efficacy as adjuvant therapy which is of crucial importance to patients who are suffering the disturbing side effects of levodopa therapy.

The first agonist to be introduced in the UK in 1976 was bromocriptine. A large scale study by the United Kingdom Parkinson's Disease Study Group showed that only 2% of 224 patients developed dyskinesias after 3 years of bromocriptine therapy compared with 27% of 213 who had received levodopa treatment (PDRG 1993). The high frequency of adverse events reported with bromocriptine led to a search for other better tolerated dopamine agonists. Lisuride was introduced in 1990, pergolide in 1991, ropinirole in 1996 and cabergoline in 1997 and the introduction of pramipexole is expected in 1999 in the United Kingdom. Pramipexole is a non-ergoline agonist which acts at the D2 and D3 receptor sub-types. Early clinical trials have assessed the safety and efficacy of pramipexole in early and late Parkinson's disease.

The questions that need to be addressed are whether the newer agonists such as pramipexole are effective in comparison with placebo and whether they are superior to bromocriptine. The present study is a systematic review of all randomised controlled trials of adjuvant pramipexole therapy compared with placebo in patients with idiopathic Parkinson's disease suffering from levodopa-induced motor complications. Separate reviews by the same authors compare adjuvant pramipexole versus bromocriptine. The use of bromocriptine therapy in newly diagnosed patients is the subject of another Cochrane review (Hilten 1998).

OBJECTIVES

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

METHODS

Criteria for considering studies for this review

Types of studies

All randomised trials comparing pramipexole with placebo were considered for inclusion in the study.

Types of participants

Patients with a clinical diagnosis of idiopathic Parkinson's disease who had developed long-term complications of dyskinesia and/or end-of-dose deterioration. All ages were included. Any duration of levodopa therapy was included.

Types of interventions

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

Types of outcome measures

1. Improvement in the time patients spend in the immobile 'off' state.

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

3. Changes in parkinsonian rating scales.

4. Reduction in levodopa dose.

5. Number of withdrawals due to lack of efficacy and/or side-effects.

Search methods for identification of studies

1. The review is based on the search strategy of the Movement Disorders Group. This includes computerised searches of MEDLINE and EMBASE and hand searching of appropriate journals. Relevant trials were included on the Group's specialised register of randomised controlled trials. Further details are available in the Group's module within the Cochrane Library.

2 The Cochrane Controlled Trials Register was also searched for relevant trials.

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

4. Additional assistance was provided by the drug manufacturer Boehringer Ingelheim.

Data collection and analysis

The authors independently assessed the studies identified by the search strategy. Disagreements about inclusions were resolved by discussion. The full papers were assessed for methodological quality by recording the method of randomisation and blinding, whether an intention-to-treat analysis was used 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. Since Review Manager version 3 does not support non-parametric methods for combining categorical variables, the results from parkinsonian rating scales were included as descriptions of results. A weighted estimate (fixed effect model) of the typical treatment

effect across trials (odds ratio) was calculated for ordinal and dichotomous variables such as 'off' time and prevalence of adverse events.

RESULTS

Description of studies

See also Characteristics of Included Studies.

Five trial reports meeting the inclusion criteria were located. The patients in one of these (Molho 95) were included in another report (Lieberman 1997), so the former was excluded from this review.

The remaining 4 publications all report the results of double-blind, parallel group, multicentre studies which randomised a total of 669 patients with later Parkinson's disease to pramipexole or placebo.

The 2 groups in each trial were well matched at baseline for age, sex, duration and severity of Parkinson's disease, except for Pinter 99 in which the proportion of women in the pramipexole group was higher (41%) than in the placebo arm (30%).

The mean pramipexole dose in the active treatment arm was given in 3 reports. This was comparable in 2 (3.36 mg/d in Guttman 97; 3.59 mg/d in Pinter 99) but higher in Wermuth 98 (4.59 mg/d). The maximum allowed doses of pramipexole were similar in all 4 trials (4.5 mg/d in 2 and 5.0 mg/d in 2). Reduction in levodopa dose was allowed in all but Pinter 99.

Risk of bias in included studies

See also Characteristics of Included Studies.

Details of randomisation method and concealment of allocation were poorly recorded in all 4 published trial reports. However, further details have been obtained from the manufacturers: All 4 studies used computer generated random numbers. Randomisation was performed centrally so investigators had no access to this procedure. In the 2 smaller phase II studies, telephone randomisation was used to stratify the patients according to their levodopa dose alone (Wermuth 98) or levodopa dose and the use or not of other antiparkinsonian medication (Pinter 99).

All 4 trials were double-blind, thus performance and attrition bias are unlikely.

Statistical analyses were performed by a blinded observer up to the point of release of the randomisation code by the 'organisation independent service group', so detection bias is unlikely.

The larger 2 studies were medium term phase III trials with maintenance periods of 24 weeks compared with the smaller short term phase II studies with maintenance periods of only 4 weeks.

Sample size calculations were appropriately not given for the 2 phase II trials. However, only 1 of the phase III trials (Lieberman 1997) gave details of the power calculation. That such a calculation was done in Guttman 97 is implied by the statement that the pramipexole v bromocriptine comparison had insufficient power to detect a difference in efficacy.

Effects of interventions

Pramipexole has been compared to placebo in 4 studies. These were all randomised controlled trials conducted on a double-blind, parallel group, multicentre basis, including a total of 669 patients with Parkinson's disease and motor complications. Two phase III studies were medium term (Lieberman 1997; Guttman 1997) and 2 phase II studies were short term (Wermuth 1998; Pinter 1999).

Using additional data obtained from the manufacturers, meta-analysis of the reduction in the time patients spent in the off state in all 4 trials is possible. This showed a highly significant benefit with pramipexole (weighted mean difference 1.8 hours; 1.2, 2.3 95% CI; Table 9). Considering individual trial reports, off time was significantly reduced in the larger 2 phase III trials (31% v 7% in Lieberman 1997; 15% v 3% in Guttman 1997). No statistical comparison is given in the other 2 studies, but there was a trend towards a greater reduction in off time with pramipexole (10% v 3% in Wermuth 1998; 12% v 2% in Pinter 1999).

Although no significant changes were noted in a dyskinesia rating scale in any of the 4 studies (Table 10), dyskinesia as an adverse event was reported more frequently with pramipexole (Table 15). A significant improvement occurred in UPDRS complication score (part IV) in 2 studies but not in the remaining trials (Table 3).

The method of recording and analysing the UPDRS ADL score varied between the studies; some reported this in the off state, some with the patient on and others an average of off and on (Table 1). However, statistically significant improvements occurred with pramipexole compared with placebo in all studies irrespective of the method of assessment. Statistically significant improvements in UPDRS motor scores in the on state were reported in 3 of the 4 studies (Table 2). Both the Hoehn and Yahr stage and the Schwab and England scale significantly improved in 1 of the 2 studies in which these were reported (Tables 5 and 6). In the single study using it (Pinter 99), the clinician's global impression scale showed a larger number of patients with a "satisfactory or good improvement" with pramipexole compared to placebo (Table 7).

Levodopa dose reduction was allowed in 3 studies. Statistical overview of the additional data provided by the manufacturers shows a significant difference in favour of pramipexole (weighted mean difference 115 mg; 87, 143 95% CI; Table 8).

Quality of life scales were used in Guttman 1997 only. These showed superiority of pramipexole over placebo for the Functional Status Questionnaire (FSQ) Basic ADL, Intermediate ADL, and Mental Health Scales and the European Quality of Life (EuroQol) scale.

Trends toward a higher incidence of dopaminergic adverse events (Tables 11 to 14) with pramipexole only reached statistical significance regarding hallucinations (Table 13). There was a significant difference in all cause withdrawal rate in favour of pramipexole (Table 16).

DISCUSSION

Pramipexole has been compared with placebo in 4 well designed and conducted randomised controlled trials in a population of 669 patients with later Parkinson's disease. The larger 2 phase III studies were medium term with maintenance periods of 24 weeks, whereas the smaller phase II studies were short term with maintenance periods of only 4 weeks.

The main aim of dopamine agonist therapy in later disease is to reduce the long-term complications of therapy, particularly the time patients spend in the immobile off state. This was reduced significantly more in the pramipexole arm of the 2 larger, medium term trials and by an amount that would prove clinically relevant (off time reduction of 31% v 7% in Lieberman 1997; 15% v 3% in Guttman 1997). In the smaller 2 studies, there was a trend towards a greater reduction in off time with pramipexole but this was not tested statistically (10% v 3% in Wermuth 1998; 12% v 2% in Pinter 1999). Meta-analysis of all 4 trials shows a highly significant benefit with pramipexole (weighted mean difference 1.8 hours; 1.2, 2.3 95% CI; Table 9). This was achieved at the expense of more dyskinetic adverse event reports in the pramipexole treated patients (Table 15), although no significant differences were noted in a dyskinesia rating scale (Table 10). The net effect on the UPDRS complication score (part IV) was an improvement in favour of pramipexole in 2 trials but no difference in the other 2 studies (Table 3). Improvements in off time were achieved in spite of significant reduction in levodopa dose according to a meta-analysis of the 3 trials in which dose reduction was allowed (weighted mean difference 115 mg; 87, 143 95% CI; Table 8).

Another aim of adjuvant therapy in Parkinson's disease is to improve motor impairments and disability. Pramipexole produced significant reduction in impairment measured by the UPDRS motor rating scale in 3 of the 4 studies (Table 2). Disability measured by the UPDRS ADL score improved significantly in all 4 studies (Table 1). The global effect of the disease in terms of handicap and quality of life was assessed in only 1 study (Guttman 97) in which there was a significant improvement in the EuroQol and items of the Functional Status Questionnaire.

There was a trend toward a higher incidence of dopaminergic adverse events, such as nausea, confusion and postural hypotension, with pramipexole, but this only reached significance with hallucinations (Tables 11-14). Domperidone usage was allowed to block these problems in at least 1 of the studies. This contrasts with previous trials with the older agonists bromocriptine and pergolide which were performed before the advent of domperidone. This may account for any reduction in adverse events in more recent trials.

Overall, the beneficial effects of pramipexole on off time and parkinsonian impairments and disability outweighed any increase in adverse events in terms of significantly more withdrawals from the placebo arms of the studies (Table 16).

A number of general points can be made about the conduct of the trials:
1. The standard of reporting in these recent studies was relatively good, but it is suggested that the CONSORT (Consolidated Standards of Reporting Trials) reporting standards are used in the future (CONSORT 1996) to improve the standard further. In particular, details of sample size calculations should be included in the statistical section of all phase III studies.

2. The impact of allowing levodopa dose reduction in 3 trials but not in the fourth (Pinter 99) cannot be quantified. Some allowance for this must be made when interpreting the results of the smaller phase II study.

3. Considerable debate still surrounds which dyskinesia rating scale should be used in this type of study. Once an appropriate scale has been accepted in terms of validity and reliability, it should be included in similar studies in the future.

4. It is potentially difficult to interpret the results of the UPDRS part IV (Complications of therapy) scores in these trials. It is possible for increases in dyskinesia scores to cancel out decreases in off time in this scale.

AUTHORS' CONCLUSIONS

Implications for practice

Pramipexole can be used over the medium term (up to 24 weeks) in patients with Parkinson's disease and motor complications to reduce off time, improve motor impairments and disability and reduce levodopa dose at the expense of increased dyskinetic adverse events.

Implications for research

Incomplete Reporting
Data on the variance of continuous variables was not available in several of the original reports. The standard deviation or standard error should be given for all means in trial reports. Information on randomisation and concealment of allocation must be increased in trial reports to allow judgements on whether bias was prevented.

It is suggested that the CONSORT (Consolidated Standards of Reporting Trials) reporting standards are used in the future (CONSORT 1996). These guidelines have been adopted by several leading general medical and neurology journals. They consist of a checklist of 21 items that include descriptions of the randomisation procedure and allocation concealment, the mechanisms of blinding/masking and the number of people lost to follow-up. The adoption of these guidelines would greatly assist in performing systematic reviews and would improve the quality of individual trial reports.

Further Trials
Previous Cochrane reviews have examined trials comparing bromocriptine with placebo, lisuride versus placebo and bromocriptine and pergolide versus placebo and bromocriptine. Other reviews will be performed to define the effects of the other new dopamine agonists ropinirole and cabergoline compared with placebo and bromocriptine and pramipexole versus bromocriptine.

However, trials directly comparing the newer and the older agonists have not been performed. Therefore, clinicians do not have any information on which, if any, of the available agonists is superior. Further large multicentre pragmatic studies are required to answer this question. Such trials must include cost benefit analysis in view of the expense of the new agonists in comparison with bromocriptine. Such trials must have adequate power based on a priori sample size calculations.

ACKNOWLEDGEMENTS

The authors would like to thank Pharmacia Upjohn and Boehringer-Ingelheim for their considerable assistance in obtaining further trial data.

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Guttman 1997 *{published data only}*

Guttman M and the International Pramipexole-Bromocriptine Study Group. Double-blind comparison of pramipexole and bromocriptine treatment with placebo in advanced Parkinson's disease. *Neurology* 1997;**49**(4):1060-5.

Lieberman 1997 *{published data only}*

Lieberman A, Ranhosky A, Korts D. Clinical evaluation of pramipexole in advanced Parkinson's disease: results of a double-blind, placebo-controlled, parallel-group study. *Neurology* 1997;**49**(1):162-8.

Pinter 1999 *{published data only}*

Pinter MM, Pogarell O, Oertel WH. Efficacy, safety and tolerance of the non-ergoline dopamine agonist pramipexole in the treatment of advanced Parkinson's disease: a double-blind, placebo-controlled, randomised, multicentre study. *Journal of Neurology Neurosurgery and Psychiatry* 1999;**66**:436-441.

Wermuth 1998 *{published data only}*

Wermuth L and the Danish Pramipexole Study Group. A double-blind, placebo-controlled, randomised, multi-center study of pramipexole in advanced Parkinson's disease. *European Journal of Neurology* 1998;**5**:235-242.

References to studies excluded from this review

Molho 1995 *{published data only}*

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Rajput 1984

Rajput AH, Stern W, Laverty WH. Chronic low-dose levodopa therapy in Parkinson's disease. *Neurology* 1984;**34**:991-996.

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Fahn S, Elton RL and members of the UPDRS development committee. Unified Parkinson's Disease Rating Scale. In: Recent developments in Parkinson's disease. Eds: Fahn S, Marsden CD, Calne D, Goldstein M. Publ: Macmillan, New Jersey. Macmillan, New Jersey. 1987.

CHARACTERISTICS OF STUDIES

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

Guttman 1997

Methods	Randomised, double-blind, parallel group design. Included a third arm for bromocriptine although the study was not powered to examine differences between pramipexole and bromocriptine (see Cochrane pramipexole v bromocriptine review). Randomisation by computer generated random numbers. Medication allocated consecutively in blocks of 3 in centres. Double-dummy system for pramipexole and bromocriptine. Location - 34 multinational centres. Intention-to-treat analysis using last observation carried forward method. Duration of therapy < or = 36 weeks.
Participants	Pramipexole - 79 patients with 16 drop outs (20%). Placebo - 83 patients with 33 drop outs (40%). Details of terminations given. Patients comparable for age, sex, duration of disease and severity of disease at baseline. Hoehn and Yahr scale at baseline not given.

Guttman 1997 *(Continued)*

	Mean baseline levodopa dose not given.
Interventions	Blind titration to maximum of 1.5 mg tds of pramipexole. Titration phase < or = 12 weeks. Maintenance = 24 weeks. Dose reduction = 1 week. Mean dose of pramipexole in active arm 3.36 mg/d. Changes in levodopa dose allowed.
Outcomes	Primary: UPDRS ADL (part II) as average of on and off scores and UPDRS motor (part III) in on phase only. Secondary: UPDRS ADL on phase. UPDRS ADL off phase. UPDRS parts I and IV. Off time. Schwab and England scale in on and off phase. Hoehn and Yahr in on and off phase. Dyskinesia scale - details not given. Timed walking test. Clinician's global impression scale. EuroQol and Functional Status Questionnaires. Adverse events.
Notes	

Risk of bias

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

Lieberman 1997

Methods	Randomised, double-blind, parallel group design. Randomisation by computer generated random numbers. Medication allocated consecutively in blocks of 4 in centres. Location - 26 North American centres. Intention-to-treat analysis on 351 of the 360 patients randomised (see author's Table 1). I-to-T defined as those randomised who received one or more doses of study medication and for whom at least one post-drug efficacy assessment was available. Duration of therapy < or = 31 weeks.
Participants	Pramipexole - 181 patients with 30 drop outs (17%). Placebo - 179 patients with 39 drop outs (22%). Details of terminations given. Patients comparable for age, sex, duration of disease and severity of disease at baseline. Mean Hoehn and Yahr scale in on phase at baseline 2.3 in both groups. Mean baseline levodopa dose not given.
Interventions	Blind titration to maximum of 1.5 mg tds of pramipexole. Titration phase < or = 7 weeks. Maintenance < or = 24 weeks. Dose reduction = 1 week. Mean dose of pramipexole in active arm not given. Changes in levodopa dose allowed.

Lieberman 1997 *(Continued)*

Outcomes	Primary: UPDRS ADL (part II) as average of on and off scores and UPDRS motor (part III) in on phase only. Secondary: UPDRS ADL on phase. UPDRS ADL off phase. UPDRS parts I and IV. Off time. Schwab and England scale in on and off phase. Hoehn and Yahr in on and off phase. Dyskinesia scale - details not given. Timed walking test. Adverse events.
Notes	

Risk of bias

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

Pinter 1999

Methods	Randomised, double-blind, parallel group design. Randomisation by computer generated random numbers. Prospective stratification for high (> 600 mg) versus low (<600 mg) daily levodopa dose and whether or not other medication for PD was being taken. Medication allocated consecutively in blocks of 4 in centres. Location - 9 centres in Austria, Germany and Switzerland. Intention-to-treat analysis using last observation carried forward method. Duration of therapy = 11 weeks.
Participants	Pramipexole - 34 patients with 5 drop outs (15%). Placebo - 44 patients with 6 drop outs (14%). Details of terminations given. Patients comparable for age, duration of disease and UPDRS total score at baseline. Note: higher frequency of women in pramipexole arm (41%) compared with placebo arm (30%). Hoehn and Yahr scale comparable between arms at baseline. Mean baseline levodopa dose: pramipexole arm = 538 (SD 314) mg/d; placebo arm = 593 (SD 264) mg/d.
Interventions	Blind titration to maximum of 5 mg/d of pramipexole. Titration phase < or = 7 weeks. Maintenance = 4 weeks. Dose reduction = 1 week. Mean dose of pramipexole in active arm 3.59 mg/d. NO change in levodopa dose allowed.
Outcomes	Primary: UPDRS total score. Secondary: UPDRS subscale scores. Off time. Schwab and England scale in on and off phase. Dyskinesia scale - details not given. Clinicians global impression scale. Adverse events.
Notes	

Pinter 1999 *(Continued)*

Risk of bias

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

Wermuth 1998

Methods	Randomised, double-blind, parallel group design. Randomisation by computer generated random numbers. Prospective stratification for high (> 600 mg) versus low (<600 mg) daily levodopa dose. Medication allocated consecutively in blocks of 4 in centres. Location - 8 Danish centres. Intention-to-treat analysis using last observation carried forward method and per protocol analysis. Duration of therapy = 11 weeks.
Participants	Pramipexole - 36 patients with 6 drop outs (17%). Placebo - 33 patients with 5 drop outs (15%). No details of terminations given. Patients comparable for age, sex and duration of disease at baseline. Hoehn and Yahr scale comparable between groups at baseline. Mean baseline levodopa dose not given.
Interventions	Blind titration to maximum of 5 mg/d of pramipexole. Titration phase < or = 7 weeks. Maintenance = 4 weeks. Dose reduction = 1 week. Mean dose of pramipexole in active arm 4.59 mg/d. Change in levodopa dose allowed.
Outcomes	Primary: UPDRS total score. Secondary: UPDRS subscale scores. Off time. Schwab and England scale in on and off phase. Hoehn and Yahr score. Dyskinesia scale - 0 (normal) to 4 (incapacitating) scale applied to head, upper limbs, lower limbs and trunk. Levodopa dose. Adverse events.
Notes	

Risk of bias

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

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

Study	Reason for exclusion
Molho 1995	Results included in Lieberman 1997

DATA AND ANALYSES

Comparison 1. Pramipexole versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 UPDRS ADL scores (part II)			Other data	No numeric data
2 UPDRS motor scores (part III)			Other data	No numeric data
3 UPDRS complications scores (part IV)			Other data	No numeric data
4 UPDRS total score			Other data	No numeric data
5 Hoehn and Yahr stage			Other data	No numeric data
6 Schwab and England scale			Other data	No numeric data
7 Clinician's global impression scale (number with satisfactory or good improvement)	1	78	Peto Odds Ratio (Peto, Fixed, 95% CI)	5.84 [2.40, 14.21]
8 Levodopa dose reduction (mg)	3	579	Mean Difference (IV, Fixed, 95% CI)	114.82 [86.64, 143.01]
9 Off time reduction (hours)	4	611	Mean Difference (IV, Fixed, 95% CI)	1.77 [1.21, 2.34]
10 Dyskinesia rating scale			Other data	No numeric data
11 Adverse events - Nausea	4	668	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.31 [0.89, 1.93]
12 Adverse events - Postural hypotension	4	668	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.44 [0.96, 2.17]
13 Adverse events - Hallucinations	3	599	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.63 [1.61, 4.32]
14 Adverse events - Confusion	1	162	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.03 [0.75, 5.53]
15 Adverse events - Dyskinesia	4	668	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.10 [1.50, 2.94]
16 All cause withdrawal rate	4	669	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.64 [0.44, 0.93]

Analysis 1.1. Comparison 1 Pramipexole versus placebo, Outcome 1 UPDRS ADL scores (part II).

UPDRS ADL scores (part II)

Study	
Guttman 1997	Average of off and on phase: Median improvement on pramipexole 2.5 v placebo 0.5 (p<0.0002)
Lieberman 1997	Off phase: Mean improvement on pramipexole 24% v placebo 5% (p<0.0001) On phase: Mean improvement on pramipexole 18% v placebo 1% (p<0.004) Average of off and on phase: Mean improvement on pramipexole 22% v placebo 4% (p<0.0001)
Pinter 1999	Average of off and on phase: Mean improvement on pramipexole 4.4 v placebo 1.2 (p=0.005)
Wermuth 1998	Details not available but a significant improvement on pramipexole compared with placebo (p=0.0015)

Analysis 1.2. Comparison 1 Pramipexole versus placebo, Outcome 2 UPDRS motor scores (part III).

UPDRS motor scores (part III)

Study	
Guttman 1997	On phase: Median improvement on pramipexole 6.0 v placebo 2.0 (p=0.0006)
Lieberman 1997	On phase: Mean improvement on pramipexole 25% v placebo 12% (p=0.01)
Pinter 1999	On phase: Mean improvement on pramipexole 13.2 v placebo 4.8 (p=0.001)
Wermuth 1998	Details not available but no significant difference between pramipexole and placebo arms

Analysis 1.3. Comparison 1 Pramipexole versus placebo, Outcome 3 UPDRS complications scores (part IV).

UPDRS complications scores (part IV)

Study	
Guttman 1997	Details not available but no significant difference between pramipexole and placebo arms
Lieberman 1997	Mean improvement on pramipexole 24% v placebo 3% (p<0.0001)
Pinter 1999	Mean improvement on pramipexole 1.8 v placebo 0.3 (p=0.008)
Wermuth 1998	Details not available but no significant difference between pramipexole and placebo arms

Analysis 1.4. Comparison 1 Pramipexole versus placebo, Outcome 4 UPDRS total score.

UPDRS total score

Study	
Guttman 1997	Not available
Lieberman 1997	Not available
Pinter 1999	Mean improvement on pramipexole 20.1 v placebo 6.1 (p<0.0003)
Wermuth 1998	Mean improvement on pramipexole 16.9 v placebo 9.0 (p=0.016)

Analysis 1.5. Comparison 1 Pramipexole versus placebo, Outcome 5 Hoehn and Yahr stage.

Hoehn and Yahr stage

Study	
Guttman 1997	Details not available but no significant difference between pramipexole and placebo arms for off or on state
Lieberman 1997	Off phase: Mean improvement on pramipexole 11% v placebo 2% (p<=0.0009) On phase: Mean improvement on pramipexole 10% v placebo 1% (p=0.002)
Pinter 1999	Not available

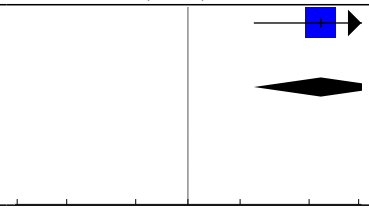
Study	Hoehn and Yahr stage
Wermuth 1998	Not available

Analysis 1.6. Comparison 1 Pramipexole versus placebo, Outcome 6 Schwab and England scale.

Study	Schwab and England scale
Guttman 1997	Details not available but no significant difference between pramipexole and placebo arms
Lieberman 1997	Off phase: Mean improvement on pramipexole 9% v placebo -1% (p=0.0009) On phase: Mean improvement on pramipexole 2% v placebo -1% (p=0.01)
Pinter 1999	Not available
Wermuth 1998	Not available

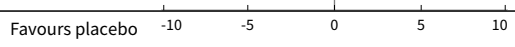
Analysis 1.7. Comparison 1 Pramipexole versus placebo, Outcome 7 Clinician's global impression scale (number with satisfactory or good improvement).

Study or subgroup	Pramipexole n/N	Placebo n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Pinter 1999	26/34	14/44		100%	5.84[2.4,14.21]
Total (95% CI)	**34**	**44**		**100%**	**5.84[2.4,14.21]**
Total events: 26 (Pramipexole), 14 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.89(P=0)					



Analysis 1.8. Comparison 1 Pramipexole versus placebo, Outcome 8 Levodopa dose reduction (mg).

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Guttman 1997	79	85.4 (149)	83	23.5 (120.7)		45.29%	61.9[20.02,103.78]
Lieberman 1997	179	209.5 (272.6)	172	45.2 (115.9)		41.94%	164.28[120.76,207.8]
Wermuth 1998	33	150.7 (196.9)	33	10.6 (121)		12.77%	140.1[61.25,218.95]
Total ***	**291**		**288**			**100%**	**114.82[86.64,143.01]**
Heterogeneity: Tau^2=0; Chi^2=11.49, df=2(P=0); I^2=82.59%							
Test for overall effect: Z=7.99(P<0.0001)							



Analysis 1.9. Comparison 1 Pramipexole versus placebo, Outcome 9 Off time reduction (hours).

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Guttman 1997	71	2.6 (4.3)	76	0.3 (4.4)		16.18%	2.3[0.89,3.71]
Lieberman 1997	174	2.4 (3.4)	172	0.7 (3.7)		57.08%	1.7[0.95,2.45]
Pinter 1999	23	2.3 (2.7)	37	-0.4 (3.5)		12.86%	2.7[1.12,4.28]
Wermuth 1998	29	1.2 (2.9)	29	0.6 (3)		13.88%	0.6[-0.92,2.12]
Total * **	**297**		**314**			**100%**	**1.77[1.21,2.34]**
Heterogeneity: Tau^2=0; Chi^2=4.19, df=3(P=0.24); I^2=28.46%							
Test for overall effect: Z=6.14(P<0.0001)							

Favours placebo — Favours pramipexole

Analysis 1.10. Comparison 1 Pramipexole versus placebo, Outcome 10 Dyskinesia rating scale.

Study	Dyskinesia rating scale
Guttman 1997	Details not available but no significant differences between pramipexole and placebo arms
Lieberman 1997	Mean deterioration on pramipexole 8% v placebo 16% (NS)
Pinter 1999	Details not available but no significant differences between pramipexole and placebo arms
Wermuth 1998	Details not available but no significant differences between pramipexole and placebo arms

Analysis 1.11. Comparison 1 Pramipexole versus placebo, Outcome 11 Adverse events - Nausea.

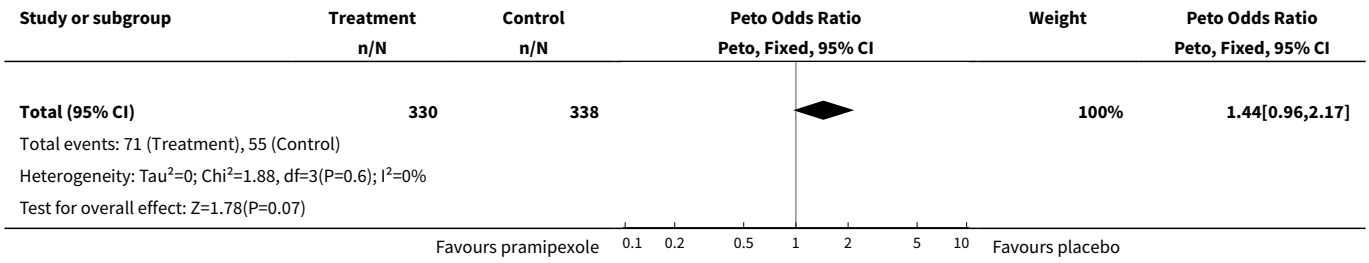
Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Guttman 1997	29/79	21/83		33.94%	1.7[0.87,3.31]
Lieberman 1997	33/181	30/178		50.86%	1.1[0.64,1.89]
Pinter 1999	3/34	3/44		5.39%	1.32[0.25,7.01]
Wermuth 1998	7/36	5/33		9.8%	1.34[0.39,4.63]
Total (95% CI)	**330**	**338**		**100%**	**1.31[0.89,1.93]**
Total events: 72 (Treatment), 59 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.99, df=3(P=0.8); I^2=0%					
Test for overall effect: Z=1.38(P=0.17)					

Favours pramipexole — Favours placebo

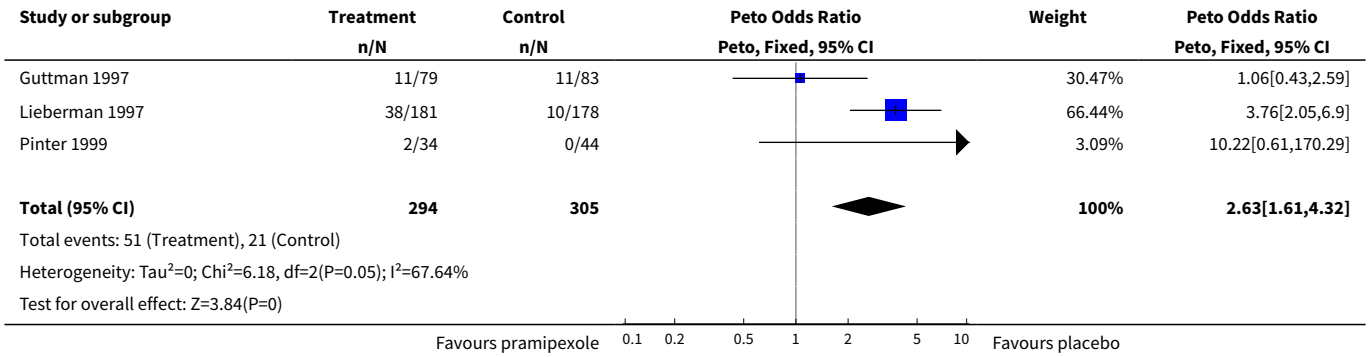
Analysis 1.12. Comparison 1 Pramipexole versus placebo, Outcome 12 Adverse events - Postural hypotension.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Guttman 1997	32/79	31/83		41.37%	1.14[0.61,2.14]
Lieberman 1997	29/181	20/178		45.34%	1.5[0.82,2.74]
Pinter 1999	3/34	1/44		4.04%	3.78[0.5,28.36]
Wermuth 1998	7/36	3/33		9.25%	2.28[0.6,8.63]

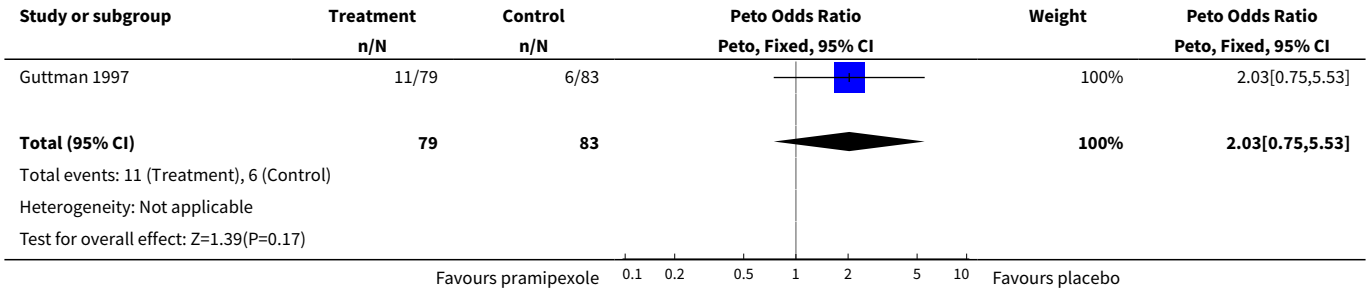
Favours pramipexole — Favours placebo



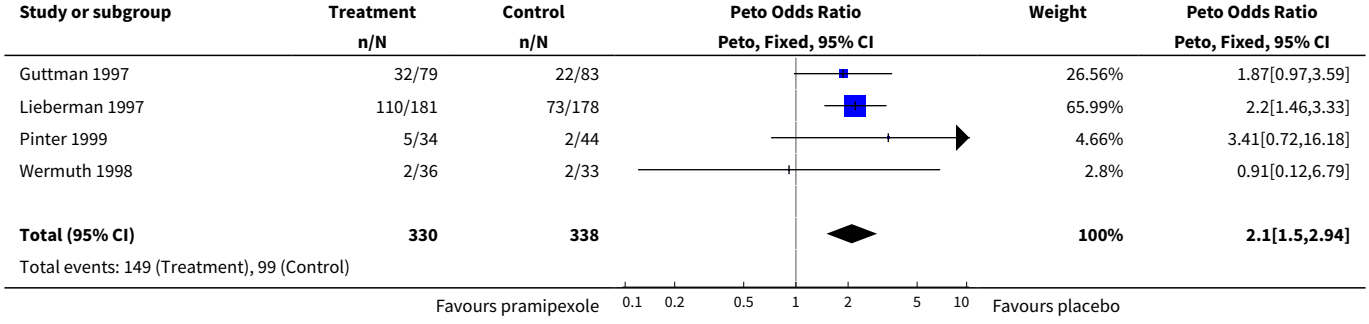
Analysis 1.13. Comparison 1 Pramipexole versus placebo, Outcome 13 Adverse events - Hallucinations.

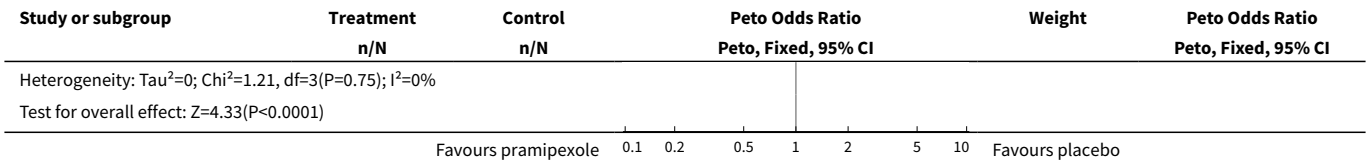


Analysis 1.14. Comparison 1 Pramipexole versus placebo, Outcome 14 Adverse events - Confusion.

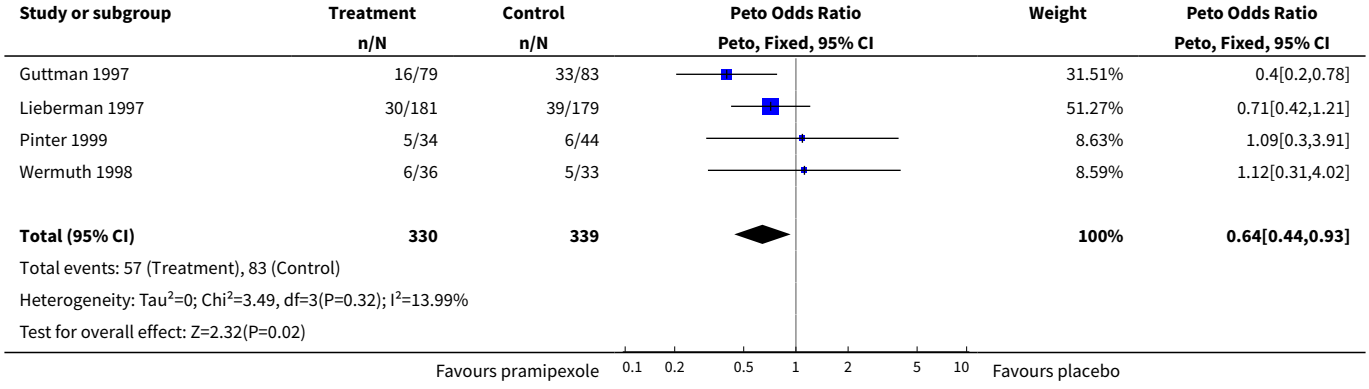


Analysis 1.15. Comparison 1 Pramipexole versus placebo, Outcome 15 Adverse events - Dyskinesia.





Analysis 1.16. Comparison 1 Pramipexole versus placebo, Outcome 16 All cause withdrawal rate.



WHAT'S NEW

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

HISTORY

Review first published: Issue 3, 2000

Date	Event	Description
24 January 2000	New citation required and conclusions have changed	Substantive amendment

DECLARATIONS OF INTEREST

CEC was an investigator in the Guttman 97 trial.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- <None >, Not specified.

INDEX TERMS

Medical Subject Headings (MeSH)

Antiparkinson Agents [adverse effects] [*therapeutic use]; Benzothiazoles; Clinical Trials, Phase II as Topic; Clinical Trials, Phase III as Topic; Dopamine Agonists [*therapeutic use]; Levodopa [*adverse effects]; Pramipexole; Randomized Controlled Trials as Topic; Thiazoles [*therapeutic use]

MeSH check words

Humans