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[Intervention Review]**Bromocriptine versus levodopa in early Parkinson's disease**

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ABSTRACT**Background**

Drugs that mimic dopamine as bromocriptine were introduced as monotherapy or in combination with LD in the hope that this approach would prevent or delay the onset of motor complications in patients with Parkinson's disease (PD). However, hitherto, the role of bromocriptine (BR) in this issue has remained controversial.

Objectives

To assess the efficacy and safety of bromocriptine (BR) monotherapy for delaying the onset of motor complications associated with levodopa (LD) therapy in patients with PD.

Search methods

We searched the Movement Disorders Group trials register which includes MEDLINE and EMBASE; the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*); handsearched appropriate neurology journals and reference lists of reviews found by the search-strategy. We also contacted Sandoz -now Novartis- (manufacturer of BR) and contacted colleagues who had co-ordinated trials on BR.

Selection criteria

Randomised trials evaluating the efficacy of BR monotherapy for delaying the onset of motor complications compared to LD therapy alone in PD patients.

Data collection and analysis

Two review authors independently evaluated the methodological quality of identified trials and extracted the data from the trials.

Main results

Six trials with 850 participants were included. The trials were of low methodological quality and were heterogeneous so we were unable to perform a meta-analysis. The occurrence of dyskinesias in three short trials was too low to draw any conclusion. The results of the longer trials indicate a lower occurrence of dyskinesias in the BR tier. In five trials that evaluated dystonia, this motor complication occurred less frequently in the BR tier. However, for both dyskinesias and dystonia a statistically significant difference in favour of BR emerged only in the largest trial. There was a trend for wearing-off and on-off fluctuations to occur less frequently in the BR group. Although all trials evaluated participants at the impairment level, only the largest trial reported a significantly larger improvement for the LD tier during the first year of therapy. Concerning disability, which was evaluated by five trials no statistically significant differences were found. Overall, a statistically larger number of dropouts occurred in the BR group because of an inadequate therapeutic response or intolerable side effects.

Authors' conclusions

Based on a qualitative review of the available data we conclude that in the treatment of early Parkinson's disease, bromocriptine may be beneficial in delaying motor complications and dyskinesias with comparable effects on impairment and disability in those patients that tolerate the drug.

PLAIN LANGUAGE SUMMARY**Bromocriptine versus levodopa in early Parkinson's disease**

Parkinson's disease is a disabling disease characterised by slowness of movement, trembling (tremors) and stiffness. Currently, the best treatment for Parkinson's disease is levodopa. However, with the number of levodopa treatment years, new disabling fluctuations of movement occur. To overcome this problem, bromocriptine has been tried as an alternative drug. The review of six trials (850 participants) found that bromocriptine may be helpful in delaying such fluctuations of movement problems in patients with Parkinson's disease who can tolerate the drug.

BACKGROUND

Parkinson's disease (PD) is a progressive neurological disorder that produces a slowly increasing disability in movement. The main features of PD are slowness of movement (bradykinesia), trembling (tremor), increased muscle tone (rigidity), and disturbance of posture and balance. These features are caused by a depletion of the neurotransmitter dopamine due to progressive loss of the nigral neurons in the brain ([Bernheimer 1973](#); [Hornykiewicz 1966](#)). The general approach to the treatment of patients with PD is the administration of drugs to alleviate symptoms. This may be achieved by the restoration of dopamine by administering its precursor levodopa (LD). LD provides immediate and satisfactory control of most symptoms. However, after two to five years of stable response to LD treatment, approximately half of the patients develop motor complications ([Marsden 1982](#)). Some of these motor complications are believed to be highly correlated with prolonged LD exposure ([Lees 1989](#); [Marsden 1976](#); [Shaw 1980](#)). The motor complications that may appear in a predictable or unpredictable relation to the timing of LD are:

- Wearing-off (end-of-dose), a predictable motor complication in which the perception of loss of mobility or dexterity occurs gradually over minutes (up to an hour) as the effect of a dose of LD is waning.
- On-off motor fluctuations, generally sudden (seconds to minutes) shifts between on (mobility) and off (immobility or worsening of parkinsonian features) that are not apparently related and therefore unpredictable to the timing of LD. Off-periods may last minutes to hours.
- Dyskinesias, predictable abnormal involuntary movements that occur shortly after or before a single LD dose (diphasic) or in between two LD administrations (peak-dose).
- Dystonia, a movement disorder characterised by sustained or intermittent muscle activity, leading to altered voluntary movement or abnormal postures. Dystonia is one of the most complex motor complications that can occur in PD. On the one hand, dystonia may manifest itself in a predictable relation with the timing of LD, and occur both during the off- and on-periods ([Luquin 1992](#)). On the other hand, dystonia may also appear in untreated patients or as a result of the intrinsic advancement of PD ([Poewe 1988](#)).

Due to the aforementioned limitations of LD therapy new therapeutic approaches have been explored. In 1974 bromocriptine (BR), a dopamine agonist, was first introduced as an adjunct to conventional LD therapy in PD patients with motor fluctuations ([Calne 1974](#)). Dopamine agonists bypass the degenerating nigral neurons and stimulate the dopamine receptors directly ([Corrodi 1973](#); [Goldstein 1983](#)). Following this, attention focused on the possibility of using BR monotherapy or a combination of LD and BR as a first line treatment in early PD. These treatment strategies would allow either a later start (BR monotherapy) or lower dose of LD (BR/LD combination therapy), thus potentially preventing or delaying the onset of the late complications of LD therapy.

The present study is a systematic review of all randomised controlled trials of BR monotherapy compared with LD monotherapy in PD. A separate review covers the effect of BR/LD combination therapy versus LD monotherapy.

OBJECTIVES

To determine the effectiveness and safety of BR monotherapy versus LD monotherapy for delaying the onset of motor complications associated with LD therapy in patients with PD.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs) comparing bromocriptine with levodopa in early PD were considered for inclusion in the study. Crossover trials were eligible if the first phase of the study fulfilled these criteria.

Types of participants

Studies with PD patients suffering from idiopathic PD (diagnosed by the enrolling investigators) who had never used BR were included. The use of LD for only a short period (< 6 months), peripheral decarboxylase inhibition, anticholinergic co-medication, or Amantadine was permitted.

Types of interventions

Oral bromocriptine or levodopa.

Types of outcome measures

We used the following outcome measures:

1. Motor complications: the occurrence and severity of off-period related motor fluctuations (wearing-off and on-off motor fluctuations, including off-period related dystonia) and dyskinesias (chorea, including on-period related dystonia).
2. Symptomatic efficacy: scores of scales that evaluated:
  - a) Impairment
    - Webster ([Webster 1968](#))
    - Columbia University Rating Scale (CURS; [Yahr 1969](#))
  - b) Disability
    - Northwestern University Disability Scale (NUDS; [Canter 1961](#))
    - Activities of daily living scale ([Weiner 1993](#))
    - England & Schwab Disability Scale ([Schwab 1960](#))
3. The occurrence of side effects and dropouts.

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 handsearching of appropriate neurology journals. Relevant trials were included on the Group's specialised register of randomised controlled trials. Further details are available in the Group's module on the Cochrane Database of Systematic Reviews.

We also searched:

2. The Cochrane Controlled Trials Register for relevant trials.
3. The reference lists of located trials and of other bromocriptine reviews.
4. Symposia-reports and handbooks of PD.

5. Additional assistance was provided by the drug manufacturer Sandoz, now Novartis.
6. We contacted colleagues who had co-ordinated trials on BR for information on unpublished studies.

Data collection and analysis

Two review authors independently reviewed the identified trials according to a two-step review process. First, the abstracts were reviewed for eligibility. Thereafter, eligible reports of studies were reviewed and data extracted independently by two reviewers. Discrepancies were registered and resolved by consensus with a third review author.

To determine the feasibility to perform a quantitative systematic review on BR monotherapy in PD patients, we addressed the following issues for each of the eligible studies:

- Application of general principles of trial methodology.
- Participant baseline characteristics.
- Titration schedules.
- Assessment procedures and outcome measures.

If the information on the aforementioned issues was insufficiently reported, we attempted to contact the trialists to obtain additional clarifying data.

RESULTS

Description of studies

See also table 'Characteristics of included studies'.

• Number of trials identified

From 1974 to April 2007 we identified 15 RCTs that met our selection criteria. We excluded four studies that were interim analysis or preliminary reports of an included trial (Hely 1987; Hely 1989; Lees, Frankel 1989; Parkinson's 1993) and three studies (Gawel 1987; Libman 1987; Riopelle 1987) that were identical to the included trial of Riopelle (Riopelle 1988). One trial never published the final results and we could not retrieve its data (Wallis 1988). Finally, in one trial participants were randomised to either bromocriptine or lisuride versus LD and the results were not split by bromocriptine or lisuride (Caraceni 2001). Of the remaining studies four evaluated BR monotherapy versus LD monotherapy and two evaluated both BR monotherapy and BR/LD combination therapy versus LD monotherapy in PD patients. These six trials randomised more than 850 participants to a BR or a LD regimen.

• Participant characteristics

Not all of the included trials adequately described the included patient population. Reasons for inclusion were sometimes vague, suggesting that both patients with PD and other causes of parkinsonism were included. All studies, but Hely (Hely 1994), excluded patients, who had been previously treated with LD. Only two trials excluded explicitly patients with cognitive impairment (Olanow 1987; UK-PDRG 1993). The mean age of the participants of each study ranged from 60.3 to 67.5 years. The mean disease duration of the trial population ranged from 11.6 months (Weiner 1993) to 25 months (Hely 1994).

• Titration schedule

All six trials introduced BR at different daily dosages ranging from 1 mg to 5 mg. The duration of the titration phase varied between four weeks (UK-PDRG 1993) and six months (Hely 1994). At the end of this period the maximum BR dosage ranged from 30 mg (Riopelle 1988) to 120 mg daily (UK-PDRG 1993). Only the UK-PDRG study reported the diurnal distribution of the BR dosages at the end of the titration phase: three times daily. Dose increment varied between the trials from 1.25 mg BR every week (Olanow 1987) to 2.5 mg BR every third day (UK-PDRG 1993). Three studies introduced LD at a dosage of 50 mg LD (Olanow 1987; Riopelle 1988; Weiner 1993). Hely started with 20 mg LD (Hely 1994), Herskovits with 125 mg LD (Herskovits 1988) and UK-PDRG with 150 mg LD (UK-PDRG 1993). The UK-PDRG study used benserazide as the peripheral dopa decarboxylase inhibitor (DDI) in an LD/DDI-ratio of 4:1 (UK-PDRG 1993). All other studies used carbidopa in addition to LD with a similar ratio, except Herskovits (10:1) (Herskovits 1988). Between the trials, the LD dose increment varied or remained unclear.

• Assessment procedures and outcome measures

All trials evaluated the occurrence of dyskinesias. Changes in the occurrence of wearing-off were evaluated by two studies (Hely 1994; Olanow 1987) and on-off motor fluctuations by three studies (Hely 1994; Olanow 1987; UK-PDRG 1993). All studies, except Riopelle (Riopelle 1988), evaluated the occurrence of dystonia.

The severity of motor complications was evaluated by two included studies (Hely 1994; Weiner 1993). Impairment and disability were evaluated by all and four studies (Hely 1994; Riopelle 1988; UK-PDRG 1993; Weiner 1993), respectively. None of the included RCTs reported if impairment and disability scores referred to the on- or off-phase.

The principal outcome measures used in the UK-PDRG trial were mortality and assessment of disability (UK-PDRG 1993).

Herskovits, Olanow and Weiner evaluated the occurrence of side effects (Herskovits 1988; Olanow 1987; Weiner 1993), whereas Hely only reported serious side effects (Hely 1994). In the UK-PDRG study, motor complications were evaluated as side effects (UK-PDRG 1993). All studies evaluated adverse events that resulted in withdrawal of participants.

Risk of bias in included studies

All studies showed shortcomings of the reported information on relevant methodological issues of the trial. Therefore, we attempted to approach all trialists to obtain additional clarifying data. One trialist was deceased and therefore the requested information could not be retrieved (Herskovits 1988).

• Trial design

All trials used a parallel LD group. Two studies randomised participants to a BR/LD combination therapy group (Herskovits 1988; Weiner 1993). The UK-PDRG trial (UK-PDRG 1993) compared BR monotherapy with LD plus selegiline and LD monotherapy. In Hely's trial (Hely 1994) all participants started with placebo during the first month after which they were allocated to BR or levodopa/carbidopa. Subsequently, participants were followed up regardless of whether the treatment code was broken, other drugs were added or a switch to another treatment occurred. In the BR groups of Herskovits and Olanow (Herskovits 1988; Olanow 1987), 50% of the participants and five participants, respectively, required additional

LD in order to maintain their improvement (mean starting time for levodopa: 16.3 months and 17 months, respectively).

• Study duration

The studies had a highly variable duration: 23 weeks (Riopelle 1988) to five years (Hely 1994). Three trials are still in progress (Hely 1994; Riopelle 1988; UK-PDRG 1993). Herskovits follow up period varied between 18 and 45 months (Herskovits 1988) and in Weiner's study this period ranged from 36 to 48 months (Weiner 1993).

• Assessors and centres

Most trials were unclear about the number of assessors that participated in the study. In Hely's study, participants were assessed at baseline and at yearly intervals by one assessor, whereas the intermediate assessments were performed by five assessors (Hely 1994). The number of participating centres was reported in three studies (Hely 1994; Riopelle 1988; UK-PDRG 1993). Most studies concerned multi centre trials; the number of centres varied between four (Hely 1994) to 93 (UK-PDRG 1993).

• Randomisation

Only Hely partly described the allocation procedure (Hely 1994). Additionally obtained information showed that three trials adequately randomised their participants by means of randomisation tables (Hely 1994; UK-PDRG 1993) or by a computerised random allocation system (Weiner 1993). For the other three studies this remained unclear.

• Trial performance

Two studies were performed according to a double-blind design (Riopelle 1988; Weiner 1993). Hely's study was only double-blind during the titration phase (Hely 1994) and Olanow used a single-blind design (Olanow 1987). For one study the blinding remained unclear (Herskovits 1988). The UK-PDRG study was an open trial (UK-PDRG 1993).

• Sample size calculations

Only the UK-PDRG study, which included a selegiline tier, reported sample size calculations (UK-PDRG 1993). The powering in this study was based on mortality data of patients with PD.

• Attrition characteristics

All trials provided detailed information on the reasons for participants leaving the trials.

• Data analysis

Only Hely and the UK-PDRG studies provided intention-to-treat data (Hely 1994; UK-PDRG 1993).

Effects of interventions

Major differences between studies concerning the baseline characteristics, the BR titration phase, and the outcomes measured were found. Considerable variability was found with respect to the duration of the trials and the individual follow up of participants in some of the trials. The 15 participants in Weiner's study had a variable follow up between 36 to 48 months (Weiner 1993). Hence, for this study the data was evaluated for the first three years only.

Data of the participants' assessments was available for Weiner's trial (Weiner 1993) and at yearly intervals for Hely's trial (Hely 1994). For the remaining four trials, data was only available at baseline and at the end of the trial.

Due to the aforementioned methodological problems and incomparability of studies we could not pool the results from the different trials. Available data of individual studies was re-analysed with Cochrane MetaView software and trials were evaluated for potential sources of methodological heterogeneity (differences in study design) and clinical heterogeneity (differences between studies in participants characteristics, interventions or outcome measures).

• Occurrence of motor complications

Dyskinesias - (reported by six trials). In two trials (<18 months) dyskinesias did not occur (Olanow 1987; Riopelle 1988) or occurred in only one participant in both groups (Herskovits 1988). Re-analysis of three longer trials (Hely 1994; UK-PDRG 1993; Weiner 1993) indicate a lower occurrence of dyskinesia in the BR tier, only statistically significant in the largest trial after three years of treatment (UK-PDRG 1993).

Dystonia - (reported by five trials). Dystonia was reported in four studies less frequently in the BR group (Hely 1994; Olanow 1987; UK-PDRG 1993; Weiner 1993), only statistically significant in the UK-PDRG study. In the Herskovits study, dystonia occurred in two participants after an unspecified period of LD treatment (Herskovits 1988).

Wearing-off - (reported by two trials). In Hely's study, wearing-off occurred in three participants (N = 21) on BR and 1 participant (N = 60) on LD after two years follow up (Hely 1994). At four and five years wearing off was found significantly more often in the LD group. In the Olanow study, one participant developed mild wearing-off after six months of LD treatment (Olanow 1987).

On-off - (reported by 3 trials). After three years the UK-PDRG study reported a statistically significant larger number of participants with on-off fluctuations in patients using LD (UK-PDRG 1993). On-off fluctuations were reported in one participant after five years of LD treatment in Hely's trial (Hely 1994) and did not occur in Olanow's study (Olanow 1987).

• Severity of motor complications (reported by two trials)

Hely, using an item on dyskinesias from the Unified Parkinson's Disease Rating Scale (UPDRS 1987) reported that the severity of dyskinesias remained mild with no major difference between both treatment regimens (Hely 1994). Wearing-off was graded as mild in both groups (scale: mild-moderate-severe). Weiner, using a 0 to 4 scale to score the severity of all motor complications, found no significant difference between both groups (Weiner 1993).

• Impairment (reported by six trials)

In the UK-PDRG study, the sum score of the Webster rating showed only a statistically significant difference in favour of the LD monotherapy group during the first year of follow up (UK-PDRG 1993). Comparisons at three years were not reported. Hely and Weiner used a modified Columbia Rating Scale and found no significant difference in the mean change from baseline between both groups (Hely 1994; Weiner 1993). Olanow applied

a self-constructed composite score of impairment and disability scales (modified England-Schwab Disability Scale, a modified Columbia Scale and the Hoehn and Yahr stage) (Olanow 1987). This composite score showed a statistically significant improvement over baseline, but no difference between groups. Riopelle, who used the Columbia University Scale, reported similar results (Riopelle 1988). Herskovits used a Webster scale and found no significant differences between both groups at the final assessment (Herskovits 1988).

• Disability (reported by four trials)

Riopelle (North-western University Disability Scale: NUDS) (Riopelle 1988), Hely (modified NUDS) (Hely 1994), and Weiner (Activities of Daily Living scale) (Weiner 1993) reported no significant difference between both groups with respect to the change from baseline. In the UK-PDRG study no formal results (NUDS) were reported but in the published report it is mentioned that the NUDS score followed a similar trend as the Webster scale (UK-PDRG 1993).

• Side effects

Olanow reported nausea in 12 participants (N = 24) on LD and in seven participants (N = 23) on BR (Olanow 1987). In Weiner's study only one participant in each group experienced hallucinations, other side effects being reported as uncommon (Weiner 1993). Herskovits reported more nausea and hallucinations in the LD group (Herskovits 1988). Hely, UK-PDRG and Riopelle only reported side effects that resulted in withdrawal (Hely 1994; Riopelle 1988; UK-PDRG 1993).

• Number of withdrawals

In Weiner's study one participant stopped BR therapy because of loss of efficacy (at 45 months) and one participant on LD dropped out because of elevation of liver enzymes (at 15 months) (Weiner 1993). Herskovits reported three dropouts; one in each treatment group due to gastric intolerance and one on BR due to allergic nodular vasculitis (Herskovits 1988). During the dose-titration phase of the Riopelle study, BR treated participants dropped out because of nausea (n = 3) and confusion (n = 1) (Riopelle 1988). No withdrawals occurred in the LD group. In Olanow's trial, one BR participant was lost to follow up after nine months (Olanow 1987). In the LD group two participants withdrew for no apparent reason after six and nine months, one participant was lost to follow up, and one participant died from amyotrophic lateral sclerosis (ALS). In the UK-PDRG study, 181 participants (N = 263) on BR and 80 participants (N = 249) on LD were withdrawn at three years follow up (UK-PDRG 1993). The main reason for withdrawal in the BR arm was adverse events, lack of response or deterioration. In the LD group, the most common reason was protocol violation mostly due to the introduction of selegiline.

Hely's intention-to-treat design resulted in a complex flowchart of the participants during the five years of follow up (Hely 1994). At five years follow up only two participants were still using BR monotherapy with anticholinergics. Most other participants were lost in follow up (n = 11) or switched to LD or other therapies (n = 40). One participant developed retroperitoneal fibrosis after three years of BR, and two participants developed pulmonary fibrosis after 2.5 and five years of BR. In the LD group, 36 participants were able to remain on the original treatment and 11 definite dropouts

occurred. In most of the participants that were unable to remain on LD, bromocriptine or anticholinergics were added. Nine of the 62 participants from the BR group and seven of the 64 participants from the LD group had died at five years follow up from pneumonia or due to cardiovascular causes.

• Mean achieved drug dose

The mean daily doses of LD (without carbidopa or benserazide) after one year's treatment ranged from 195 mg (Hely 1994) to 336 mg (UK-PDRG 1993). At final evaluations the mean dose varied from 376 mg (Hely 1994/ five years) to 635 mg (UK-PDRG 1993/ four years). The mean daily doses of BR varied after one year from 18 mg (Hely 1994) to 36 mg (UK-PDRG 1993). However, in the UK-PDRG study the BR dose ranged from 7.5 to 120 mg per day (UK-PDRG 1993).

DISCUSSION

This systematic review included six eligible trials that compared BR monotherapy with LD monotherapy (Hely 1994; Herskovits 1988; Olanow 1987; Riopelle 1988; UK-PDRG 1993; Weiner 1993). Three excluded studies were multiple publications of the same trial (Gawel 1987; Libman 1987; Riopelle 1987). Additionally, we excluded two interim reports (Hely 1987; Lees, Frankel 1989) and one study whose final data were not published and could not be retrieved (Wallis 1988).

All trials had problems regarding general and PD-related trial methodology. Particularly worrisome is the lack of available information on the type and concealment of the randomisation procedure in the initially published reports. Information provided later on revealed that this essential element of trial methodology was carried out adequately in only three trials (Hely 1994; UK-PDRG 1993; Weiner 1993). Except for two trials (Riopelle 1988; Weiner 1993), all were performed in an open manner. Only two trials analysed their data according to an intention-to-treat principle (Hely 1994; UK-PDRG 1993).

The mean duration of trials showed a wide range between five months to five years, with some of the trials still ongoing. In view of the aim of BR monotherapy in delaying the onset of motor complications, short trials (< 1 year) are of relative value.

Relevant differences between the trials emerged concerning mean age of the participants (60.3 to 67.5 years). Some studies included the results of participants that eventually turned out to suffer from PD plus syndromes in their final data analysis so as to reflect clinical practice whereas others did not. Major differences regarding the rate by which BR was introduced in the titration phase as well as the achieved mean daily dose of LD (376 to 635 mg) and BR (18 to 36 mg) were found. Such differences are likely to influence the performance of trials, the occurrence of adverse events and consequently the dropout rate. Moreover, the included studies used a wide range of methods to assess the occurrence of the various aspects of motor complications and applied different impairment and disability scales that lacked a solid clinimetric basis. Additionally, none of the included trials reported whether scores on impairment and disability level referred to the on- or off-phase.

Due to these differences concerning methodology and content we could not pool the data from the different trials in

an attempt to perform a meta-analysis. Therefore, we re-analysed the available data and evaluated possible sources of methodological heterogeneity (differences in study design) and clinical heterogeneity (differences between studies in participants' characteristics, interventions or outcome measures) between the studies.

Three short trials reported no or a very low occurrence of dyskinesias (Herskovits 1988; Olanow 1987; Riopelle 1988). The results of the more relevant longer trials (Hely 1994; ; UK-PDRG 1993; Weiner 1993) indicate a lower occurrence of dyskinesias in the BR tier, only statistically significant in the largest UK-PDRG trial (UK-PDRG 1993). In five trials that evaluated dystonia, this motor complication occurred more frequent in the LD tier; the difference being statistically significant only in the UK-PDRG trial (UK-PDRG 1993).

During the LD treatment of patients with PD, wearing off is the first and most frequent off-related motor complication to occur. Nevertheless, surprisingly only two trials evaluated this motor complication (Hely 1994; Olanow 1987). In the short trial of Olanow only one participant developed wearing off after six months of LD treatment (Olanow 1987). Hely found a significantly larger number of participants suffering wearing off in the LD tier at four and five year's follow up (Hely 1994). On-off fluctuations, reported by three trials (Hely 1994; Olanow 1987; UK-PDRG 1993), occurred in only one participant after five years LD treatment in the Hely trial (Hely 1994), suggesting that the trial design allowing low LD dosages or additional therapy prevented the occurrence of this motor complication. However, in the UK-PDRG study 82 participants (N = 263) in the LD group and only 13 participants (N = 249) in the BR group developed on-off fluctuations, the difference being statistically significant (UK-PDRG 1993).

Although all trials evaluated participants at the impairment level, only one trial reported a significantly larger improvement for the LD tier during the first year of therapy (UK-PDRG 1993). Of the other five trials that evaluated disability, none reported a statistically significant difference between the treatment groups (Hely 1994; Herskovits 1988; Olanow 1987; Riopelle 1988; Weiner 1993).

For the three studies that reported the incidence of side effects, we found no differences between both tiers. The trial design in Hely in which participants were allowed to switch to other therapies, was probably responsible for their relatively low definite dropout rates (Hely 1994). After five years only two participants, of the originally 62 randomised in this trial, were still using BR with anticholinergics. Overall, a statistically larger number of dropouts occurred in the BR group because of an inadequate therapeutic response or because of intolerable side effects.

Taken together this review identified important sources of heterogeneity between the six eligible trials that may explain the different results.

- First, the detection of possible differences between studies, if any, is confounded because the majority of the studies were inadequately powered to detect such differences between the two treatment tiers. Only the UK-PDRG study reported sample size calculations (UK-PDRG 1993).

- Second, the limited duration of many trials resulted in a low occurrence of motor complications. For several studies a trend in favour of BR was found concerning the occurrence of motor fluctuations. Only the UK-PDRG trial detected statistically significant differences in favour of BR (UK-PDRG 1993). One may argue that the UK-PDRG trial was only powered to detect a 30% reduction of mortality. Nevertheless, the sample size of this trial is likely to be sufficient for other purposes as well.
- Third, important differences concerning the trial design were found which might explain differences in the occurrence of motor complications between the UK-PDRG and Hely trials (Hely 1994; UK-PDRG 1993).

Numerous reviews discussing the role of BR in the management of motor complications in PD have appeared, but this issue remains controversial (Ahlsog 1994; Factor 1993; Goetz 1990; Watts 1997). This systematic review identified important sources of methodological as well as clinical heterogeneity including inadequate powering of the studies, clinically relevant differences in trial duration, outcomes and trial design. These important issues may explain the different results and why many findings failed to reach a statistically significant level.

AUTHORS' CONCLUSIONS

Implications for practice

The treatment of PD, lacking a cure, aims to limit the gradually increasing amount of disability. In this regard, the most effective strategy is the treatment with LD, which improves some of the PD features. However, for every year of LD treatment the number of patients that will develop motor complications increases. These complications contribute to an additional disease burden and become a source of increased medical care.

From 1974 to January 1999, six RCTs were identified that evaluated the efficacy of BR monotherapy for delaying the onset of motor complications associated with LD therapy in patients with PD. Methodological problems and incomparability of studies precluded the pooling of data in an attempt to perform meta-analysis. Nevertheless, re-analysis of available data suggest that BR is beneficial in delaying motor complications in those patients who tolerate and respond to the drug with comparable effects on impairment and disability.

Implications for research

This review emphasises methodological shortcomings in the six BR trials. The issues arising from this review have a significant bearing on the conduct of future dopamine agonist trials in this type of patient.

There is a clear requirement to apply a uniform general and PD-related trial methodology. With respect to the former our findings underscore the application of the guidelines suggested by the Consolidated Standards of Reporting Trials (CONSORT, Begg 1996) and in our previous review on BR in late PD.

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REFERENCES

References to studies included in this review

Hely 1994 {published and unpublished data}

Hely MA, Morris JG, Rail D, O'Sullivan DJ, Williamson PM, Genge S, et al. The Sydney multicentre study of Parkinson's disease: The first 18 months. *The Medical Journal of Australia* 1987;**146**:195-8.

Hely MA, Morris JG, Rail D, Reid WG, O'Sullivan DJ, Williamson PM, et al. The Sydney Multicentre Study of Parkinson's disease: a report on the first 3 years. *Journal of Neurology, Neurosurgery, and Psychiatry* 1989;**52**:324-8.

* Hely MA, Morris JGL, Reid WGJ, O'Sullivan DJ, Williamson PM, Rail D, et al. The Sydney Multicentre Study of Parkinson's disease: a randomised, prospective five year study comparing with low dose bromocriptine with low dose levodopa-carbidopa. *Journal of Neurology, Neurosurgery, and Psychiatry* 1994;**57**:903-10.

Herskovits 1988 {published data only}

Herskovits E, Yorio A, Leston J. Long term bromocriptine treatment in de novo Parkinsonian patients. *Medicina (B Aires)* 1988;**48**(4):345-50.

Olanow 1987 {published data only}

Olanow CW, Alberts MJ, Stajich J, Burch G. A randomized blinded study of low-dose bromocriptine versus low-dose carbidopa/levodopa in untreated Parkinson's patients. In: Fahn S, Marsden D, Calne D, Goldstein M editor(s). *Recent developments in Parkinson's disease*. Vol. II, New York: Macmillan Healthcare, 1987:201-208.

Riopelle 1988 {published and unpublished data}

Riopelle RJ, Gawel MJ, Libman I, King DB, McLean DR, Paulseth R, et al. A double-blind study of bromocriptine and L-dopa in de novo Parkinson's disease. Short term results. *European Neurology* 1988;**28 Suppl 1**:11-4.

UK-PDRG 1993 {published and unpublished data}

Lees AJ, Frankel J, Eatough V, Stern GM. New approaches in the use of selegiline for the treatment of Parkinson's disease. *Acta Neurologica Scandinavica. Supplementum* 1989;**126**:139-45.

* Lees AJ. Comparison of therapeutic effects, mortality data of levodopa, levodopa combined with selegiline in patients with early, mild Parkinson's disease. Parkinson's Disease Research Group of the United Kingdom. *BMJ* 1995;**311**:1602-7.

Parkinson's Disease Research Group in the United Kingdom. Comparisons of therapeutic effects of levodopa, levodopa and selegiline, and bromocriptine in patients with early, mild Parkinson's disease: three year interim report. *BMJ* 1993;**307**:469-72.

Weiner 1993 {published and unpublished data}

Weiner WJ, Factor SA, Sanchez-Ramos JR, Singer C, Sheldon RN, Cornelius L, et al. Early combination therapy (bromocriptine and levodopa) does not prevent motor fluctuations in Parkinson's disease. *Neurology* 1993;**43**(1):21-7.

References to studies excluded from this review

Caraceni 2001 {published data only}

* Caraceni T, Musicco M. Levodopa or dopamine agonists, or deprenyl as initial treatment for Parkinson's disease. A randomized multicentre study. *Parkinsonism and Related Disorders* 2001;**107**:107-14.

Gawel 1987 {published data only}

Gawel M, Riopelle R, Libman I, Bouchard S. Bromocriptine in the treatment of Parkinson's disease: a double-blind study against L-dopa/carbidopa. *Advances in Neurology* 1987;**45**:535-8.

Libman 1987 {published data only}

Libman I, Gawel MJ, Riopelle RJ, Bouchard S. A comparison of bromocriptine (Parlodel) and levodopa-carbidopa (Sinemet) for treatment of "de novo" Parkinson's disease patients. *The Canadian Journal of Neurological Sciences* 1987;**14**:576-80.

Riopelle 1987 {published data only}

Riopelle RJ. Bromocriptine and the clinical spectrum of Parkinson's disease. *The Canadian Journal of Neurological Sciences* 1987;**14(Suppl)**:S455-S9.

Wallis 1988 {published data only}

Wallis WE. A progress report on the New Zealand Multicentre Parkinson's disease trial. A comparison of low-dose treatment with bromocriptine or L-dopa. *European Neurology* 1988;**28(Suppl 1)**:S9-S10.

Additional references

Ahlskog 1994

Ahlskog JE. Treatment of Parkinson's disease. From theory to practice. *Postgraduate Medicine* 1994;**95**:52-4.

Begg 1996

Begg C, Cho M, Eastwood S, Horton R, Moher D, Olkin I, et al. Improving the quality of reporting of randomized controlled trials. The CONSORT statement. *JAMA* 1996;**276**(8):637-9. [MEDLINE: 652]

Bernheimer 1973

Bernheimer H, Birkmayer W, Hornykiewicz O, Jellinger K, Seitelberger F. Brain dopamine and the syndromes of Parkinson and Huntington. Clinical, morphological and neurochemical correlations. *Journal of Neurological Sciences* 1973;**20**(4):415-55. [MEDLINE: 622]

Calne 1974

Calne DB, Teychenne PF, Leigh PN, Bamji AN, Greenacre JK. Treatment of parkinsonism with bromocriptine. *Lancet* 1974;**2**(7893):1355-6. [MEDLINE: 621]

Canter 1961

Canter CJ, de la Torre R, Mier M. A method of evaluating disability in patients with Parkinson's disease. *The Journal of Nervous and Mental Disease* 1961;**133**:143-7.

Corrodi 1973

Corrodi H, Fuxe K, Hokfelt T, Lidbrink P, Ungerstedt U. Effect of ergot drugs on central catecholamine neurons: evidence for a stimulation of central dopamine neurons. *The Journal of Pharmacy and Pharmacology* 1973;**25**(5):409-12. [MEDLINE: 623]

de Rijk 1995

de Rijk MC, Breteler MM, Graveland GA, Ott A, Grobbee DE, van der Meche FG, et al. Prevalence of Parkinson's disease in the elderly: the Rotterdam Study. *Neurology* 1995;**45**(12):2143-6. [MEDLINE: 639]

Dickersin 1994

Dickersin K, Scherer R, Lefebvre C. Identifying relevant studies for systematic reviews. *BMJ* 1994;**309**(6964):1286-91. [MEDLINE: 624]

Factor 1993

Factor SA, Weiner WJ. Early combination therapy with bromocriptine and levodopa in Parkinson's disease. *Movement Disorders* 1993;**8**(3):257-62. [MEDLINE: 158]

Goetz 1990

Goetz CG. Dopaminergic agonists in the treatment of Parkinson's disease. *Neurology* 1990;**40**(10:Suppl 3):50-4. [MEDLINE: 709]

Goldstein 1983

Goldstein M, Engel J, Lieberman A, Regev I, Bystritsky A, Mino S. Therapeutic potentials of centrally acting dopamine and alpha 2- adrenoceptor agonists. *Journal of Neural Transmission. Supplementum* 1983;**18**:257-63. [MEDLINE: 627]

Hely 1987

Hely MA, Morris JG, Rail D, O'Sullivan DJ, Williamson PM, Genge S, et al. The Sydney multicentre study of Parkinson's disease: The first 18 months. *The Medical Journal of Australia* 1987;**146**:195-8.

Hely 1989

Hely MA, Morris JG, Rail D, Reid WG, O'Sullivan DJ, Williamson PM, et al. The Sydney Multicentre Study of Parkinson's disease: a report on the first 3 years. *Journal of Neurology, Neurosurgery, and Psychiatry* 1989;**52**:324-8.

Hoehn 1967

Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. *Neurology* 1967;**17**(5):427-42. [MEDLINE: 632]

Hornykiewicz 1966

Hornykiewicz O. Dopamine (3-hydroxytyramine) and brain function. *Pharmacological Reviews* 1966;**18**(2):925-64. [MEDLINE: 633]

Lees 1989

Lees AJ. The on-off phenomenon. *Journal of Neurology, Neurosurgery, and Psychiatry* 1989;**Suppl**:29-37. [MEDLINE: 634]

Lees, Frankel 1989

Lees AJ, Frankel J, Eatough V, Stern GM. New approaches in the use of selegiline for the treatment of Parkinson's disease. *Acta Neurologica Scandinavica. Supplementum* 1989;**126**:139-45.

Luquin 1992

Luquin MR, Scipioni O, Vaamonde J, Gershanik O, Obeso JA. Levodopa-induced dyskinesias in Parkinson's disease: clinical and pharmacological classification. *Movement Disorders* 1992;**7**(2):117-24. [MEDLINE: 641]

Marsden 1976

Marsden CD, Parkes JD. "On-off" effects in patients with Parkinson's disease on chronic levodopa therapy. *Lancet* 1976;**1**(7954):292-6. [MEDLINE: 618]

Marsden 1982

Marsden CD, Parkes JD, Quinn N. Fluctuations of disability in Parkinson's disease: clinical aspects. In: Marsden CD, Fahn S editor(s). *Movement Disorders*. London: Butterworths Scientific, 1982. [MEDLINE: 619]

Parkinson's 1993

Parkinson's Disease Research Group in the United Kingdom. Comparisons of therapeutic effects of levodopa, levodopa and selegiline, and bromocriptine in patients with early, mild Parkinson's disease: three year interim report. *BMJ* 1993;**307**:469-72.

Poewe 1988

Poewe WH, Lees AJ, Stern GM. Dystonia in Parkinson's disease: clinical and pharmacological features. *Annals of Neurology* 1988;**23**(1):73-8. [MEDLINE: 636]

Schwab 1960

Schwab RS. Progression and prognosis in Parkinson's disease. *The Journal of Nervous and Mental Disease* 1960;**130**:556-66.

Shaw 1980

Shaw KM, Lees AJ, Stern GM. The impact of treatment with levodopa on Parkinson's disease. *The Quarterly Journal of Medicine* 1980;**49**(195):283-93. [MEDLINE: 640]

UPDRS 1987

Fahn S, Elton RL. Unified Parkinson's Disease Rating Scale. In: Fahn S, Goldstein M, Marsden D, Calne DB editor(s). *Recent Developments in Parkinson's Disease*. Vol. II, New Jersey: MacMillan, 1987. [MEDLINE: 663]

Watts 1997

Watts RL. The role of dopamine agonists in early Parkinson's disease. *Neurology* 1997;**49**(1:Suppl 1):S34-S48. [MEDLINE: 352]

Webster 1968

Webster DD. Critical analysis of the disability in Parkinson's disease. *Modern Treatment* 1968;**5**(2):257-82.

Yahr 1969

Yahr MD, Duvoisin RC, Schear MJ, Barrett RE, Hoehn MM. Treatment of parkinsonism with levodopa. *Archives of Neurology* 1969;**21**(4):343-54.

Zhang 1993

Zhang ZX, Roman GC. Worldwide occurrence of Parkinson's disease: an updated review. *Neuroepidemiology* 1993;**12**(4):195-208. [MEDLINE: 642]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Hely 1994

Methods	Randomised: randomisation tables. 'Double blind': only in titration phase. Duration: 5 years (on going), including a 6-month dose titration.
Participants	Country: Australia. Centres: 4. Inclusion criteria: idiopathic PD, receiving no or less than 3 months LD. Exclusion criteria: NA. No. Randomised: 149. Excluded patients: 13 revised diagnoses and 10 failed to complete dose titration phase. Mean age: 62 years (BR), 62 years (LD). Female:Male = 56:70. Mean disease duration: 22 months (BR), 25 months (LD).
Interventions	1) BR monotherapy (start: 1mg/day increased at weekly, then monthly intervals to a max. of 30 mg/day after 40 weeks) [62]. Mean dose: 32 mg/day, range 7.5-60 mg/day. 2) LD/carbidopa monotherapy (start: 20/5 mg/day LD increased at weekly, then monthly intervals to a max. of 600/150 mg LD after 40 weeks) [64]. Mean dose: 475 mg/day, range 300-600 mg/day.
Outcomes	Dyskinesias: significant more in LD-group at 1-2-3-4-5 year(s). Dystonia: significant more in LD-group at 1-2-3-4-5 year(s). Wearing-off: significant more in BR-group at 2 years and significant more in LD-group at 4-5 years. On-off fluctuations: 1 patient in the LD-group at 5 years. IMP: mod. CURS: NS. DIS: mod. NUDS: NS.
Notes	LD:carbidopa = 4:1. Trial design allowed switching from or addition of therapy. Dropouts: 20 (BR), 11 (LD).

Risk of bias

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

Herskovits 1988

Methods	Randomised: unclear. 'Single blind'. Duration: follow up varied between 18-45 months.
Participants	Country: Argentina. Centres: NA.

Bromocriptine versus levodopa in early Parkinson's disease (Review)

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Herskovits 1988 (Continued)

Inclusion criteria: recently diagnosed idiopathic PD, prior to trial not receiving any antiparkinsonian medication.
No. Randomised: 86. BR/LD combination treatment: 31.
Mean age: 67.5 years.
Female:Male = 52:34.
Mean disease duration: NA.

Interventions	1) BR monotherapy (start: 1.25 mg/day increased with 1.25 mg/day to a max. of 15 mg/day) [26]. Mean daily dose: 12.6 mg, range: 7.5-20 mg. 2) LD/carbidopa monotherapy (start: 125/12.5 mg/day increased with 125/12.5 mg [29]. Mean daily dose: 556.1 mg, range: 250-625 mg.
Outcomes	Dyskinesias: 1 patient on a low dose of BR and 1 patient in the LD-group. Dystonia: 2 patients in the LD-group. Wearing-off: NA. On-off fluctuations: NA. IMP: Webster: NS. DIS: no scale used.
Notes	LD:carbidopa = 10:1. Third group on BR/LD combination therapy [29]. After a mean of 16.3 months 14 patients on BR used additionally LD. Dropouts: 2 (BR), 1 (LD).

Risk of bias

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

Olanow 1987

Methods	Randomised: unclear. 'Single blind'. Duration: mean 17.2 months (all patients completed first 6 months).
Participants	Country: USA. Centres: NA. Inclusion criteria: idiopathic PD and functional disability. Exclusion criteria: previous therapy of LD or dopamine agonists, Parkinson's Plus syndromes, drug-induced parkinsonism, dementia, significant neurological or medical disease. No. Randomised: 47. Mean age: 60.6 years (BR), 63.8 years (LD). Female:Male = 8:15 (BR), 10:14 (LD). Mean disease duration: 1.3 years (BR), 1.5 years (LD).
Interventions	1) BR monotherapy (start: 1.25 mg/day, increased with 1.25 mg/week) [23]. Mean dose: 10.9 mg/day (6 months), 16.8 mg/day (15 months). 2) LD/carbidopa monotherapy (start: 50/12.5 mg/day increased with 50/12.5 mg/week) [24]. Mean dose: 322.9 mg/day (6 months), 383.3 mg/day (15 months).
Outcomes	Dyskinesias: absent. Dystonia: significant more in LD-group at 1-2 year(s). Wearing-off: 1 patient in the LD-group at 6 months. On-off fluctuations: absent. IMP & DIS: TP score: NS.

Bromocriptine versus levodopa in early Parkinson's disease (Review)

Olanow 1987 (Continued)

Notes LD:carbidopa = 4:1.
After a mean of 17 months, 5 patients on BR used additionally LD.
After 18 months, 1 patient on LD used additionally BR.
Dropouts: 1 (BR), 4 (LD).

Risk of bias

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

Riopelle 1988

Methods Randomised: unclear.
'Double blind'.
Duration: 2-week baseline, 15-week titration and a 6-week maintenance phase (= pilot study, trial on going).

Participants Country: Canada.
Centres: 7.
Inclusion criteria: idiopathic PD.
Exclusion criteria: previously antiparkinsonism therapy other than anticholinergics.
No. Randomised: 81.
Mean age: 66.5 years (BR), 66.2 years (LD).
Mean disease duration: NA.
Female:Male = 13:29 (BR), 19:20 (LD).

Interventions 1) BR monotherapy (start: 5 mg/day increased every 3rd week to a max. of 30 mg/day [42].
Mean dose: 26.1 mg/day.
2) LD monotherapy (start: 50 mg/day increased every 3rd week to a max. of 300 mg/day [39].
Mean dose: 262.8 mg/day (plain LD).

Outcomes Dyskinesias were absent.
Dystonia: NA.
Wearing-off: NA.
On-off fluctuations: NA.
IMP: CURS: NS.
DIS: NUDES: NS.

Notes LD:carbidopa = 4:1.
No change in treatment regime allowed.
Dropouts: 4 (BR), 0 (LD).

Risk of bias

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

UK-PDRG 1993

Methods Randomised: random number tables.
'Open study'.

UK-PDRG 1993 (Continued)

Duration: > 72 months (on going).

Participants	Country: UK. Centres: 93. Inclusion criteria: PD (according to the criteria of the PD Society of the UK Brain Tissue Bank), incapacity, which in the judgement of the clinician was sufficient to merit dopaminergic treatment. Exclusion criteria: previously failed to respond to dopaminergic drugs, incapacitating cognitive impairment. No. Randomised: 782. Selegine treatment: 271. Mean age: 62.1 years (BR), 62.7 years (LD). Female:Male = 114:148 (BR), 111:138 (LD). Mean disease duration: 14 months (1-144).
Interventions	1) BR monotherapy (start: 2.5 mg/day increased with 2.5 mg/ 3rd day to a max. of 120 mg/d [262]. Mean dose: NA, range: 7.5 -120 mg/day. 2) LD/benserazide monotherapy (start: 150/37.5 mg/day increased to a max. of 300/75 mg/day [249]. Mean dose: NA, range: NA.
Outcomes	Dyskinesias: statistically significant more in LD-group at 3 years. Dystonia: statistically significant more in LD-group at 3 years. Wearing-off: NA. On-off fluctuations: statistically significant more in LD-group at 3 years. IMP: mod. Webster statistically significant in favour of LD-group during first year of follow up. DIS: NUDS: no results reported; the trend was similar with Webster.
Notes	LD:benserazide = 4:1. Intention to treat. No change in treatment regime. Dropouts: 181 (BR), 80 (LD).

Risk of bias

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

Weiner 1993

Methods	Randomised: computerised random allocation. 'Double blind'. Duration: 4 years.
Participants	Country: USA. Centres: NA. Inclusion criteria: PD. Exclusion criteria: previously treated with BR or LD. No. Randomised: 25. Excluded patients: 1 lost to follow up (BR), 1 orthostatic hypotension (BR), 1 revised diagnosis (LD). Mean age: 60.3 years (BR), 65.7 years (LD). Female:Male = 11:14. Mean disease duration: 34 months (BR), 11.6 months (LD).
Interventions	1) BR monotherapy (start 1.25 mg/day increased to a max. of 30 mg/day [6]. Mean dose: 18 mg, range 6.25-30 mg. 2) LD/carbidopa monotherapy (start 50/12.5 mg/d increased to a max. of 1200/300 mg/day [9].

Weiner 1993 (Continued)

Mean dose: 417 mg, range 150-700.

Outcomes	Dyskinesias: significant more in LD-group at 1-2-3 year(s). Dystonia: significant more in LD-group at 1-2-3 year(s), only statistically significant at 3 years. Wearing-off: NA. On-off fluctuations: NA. IMP: mod. CURS: NS. DIS: ADL scale: significant difference in favour of BR at 1 moment (48 months).
Notes	LD:carbidopa = 4:1. No change in treatment regime. Dropouts: 1 (BR), 1 (LD).

Risk of bias

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

ADL: Activities-of-daily-living (scale)

BR: bromocriptine

CURS: Columbia University Rating Scale

DIS: disability

IMP: impairment

LD: levodopa

max.: maximum

(mod.) NUDS: (modified) Northwestern University Disability Scale

(mod.) CURS: (modified) Columbia University Rating Scale

NA: not available

NS: not significant

TP: Total Parkinson's score, a combination of the modified England-Schwab Disability Scale, a modified Columbia Scale and the Hoehn and Yahr stage with a maximum total score of 420

[X]: number of patients

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Caraceni 2001	Bromocriptine or lisuride could be used. Results not split.
Gawel 1987	Identical to included study of Riopelle 1988.
Libman 1987	Identical to included study of Riopelle 1988.
Riopelle 1987	Identical to included study of Riopelle 1988.
Wallis 1988	Lack of final results.

DATA AND ANALYSES

Comparison 1. Occurrence of dyskinesias

Outcome or sub-group title	No. of studies	No. of participants	Statistical method	Effect size
1 At one year	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
2 At two years	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
3 At three years	3		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
4 At four years	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
5 At five years	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only

Analysis 1.1. Comparison 1 Occurrence of dyskinesias, Outcome 1 At one year.

Study or subgroup	BR n/N	LD n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Hely 1994	0/33	3/61		0%	0.21[0.02,2.27]
Weiner 1993	0/6	1/9		0%	0.19[0,10.32]
			0.1 0.2 0.5 1 2 5 10		
			favours BR		favours LD

Analysis 1.2. Comparison 1 Occurrence of dyskinesias, Outcome 2 At two years.

Study or subgroup	BR n/N	LD n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Hely 1994	0/21	8/60		0%	0.23[0.04,1.19]
Weiner 1993	0/6	2/8		0%	0.15[0.01,2.77]
			0.1 0.2 0.5 1 2 5 10		
			favours BR		favours LD

Analysis 1.3. Comparison 1 Occurrence of dyskinesias, Outcome 3 At three years.

Study or subgroup	BR n/N	LD n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Hely 1994	0/7	14/57		0%	0.24[0.04,1.6]
UK-PDRG 1993	5/262	67/249		0%	0.13[0.08,0.21]
Weiner 1993	1/6	4/8		0%	0.26[0.03,2.18]
			0.1 0.2 0.5 1 2 5 10		
			favours BR		favours LD

Analysis 1.4. Comparison 1 Occurrence of dyskinesias, Outcome 4 At four years.

Study or subgroup	BR n/N	LD n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Hely 1994	0/3	24/52		0%	0.16[0.02,1.62]
			0.1 0.2 0.5 1 2 5 10		
			favours BR		favours LD

Analysis 1.5. Comparison 1 Occurrence of dyskinesias, Outcome 5 At five years.

Comparison 2. Occurrence of dystonia

Outcome or sub-group title	No. of studies	No. of participants	Statistical method	Effect size
1 At one year	3		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
2 At two years	3		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
3 At three years	3		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
4 At four years	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
5 At five years	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only

Analysis 2.1. Comparison 2 Occurrence of dystonia, Outcome 1 At one year.

Analysis 2.2. Comparison 2 Occurrence of dystonia, Outcome 2 At two years.

Analysis 2.3. Comparison 2 Occurrence of dystonia, Outcome 3 At three years.

Analysis 2.4. Comparison 2 Occurrence of dystonia, Outcome 4 At four years.

Analysis 2.5. Comparison 2 Occurrence of dystonia, Outcome 5 At five years.

Comparison 3. Occurrence of on/off-fluctuations

Outcome or sub-group title	No. of studies	No. of participants	Statistical method	Effect size
1 At one year	0		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
2 At two years	0		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
3 At three years	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
4 At four years	0		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
5 At five years	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only

Analysis 3.3. Comparison 3 Occurrence of on/off-fluctuations, Outcome 3 At three years.

Analysis 3.5. Comparison 3 Occurrence of on/off-fluctuations, Outcome 5 At five years.

Comparison 4. Occurrence of wearing-off

Outcome or sub-group title	No. of studies	No. of participants	Statistical method	Effect size
1 At one year	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
2 At two years	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
3 At three years	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
4 At four years	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
5 At five years	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only

Analysis 4.1. Comparison 4 Occurrence of wearing-off, Outcome 1 At one year.

Analysis 4.2. Comparison 4 Occurrence of wearing-off, Outcome 2 At two years.

Analysis 4.3. Comparison 4 Occurrence of wearing-off, Outcome 3 At three years.

Analysis 4.4. Comparison 4 Occurrence of wearing-off, Outcome 4 At four years.

Analysis 4.5. Comparison 4 Occurrence of wearing-off, Outcome 5 At five years.

Comparison 5. Withdrawal rate

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All causes	5		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
2 Lost to follow up	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
3 Poor compliance	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
4 Protocol violation	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
5 Lack of response	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
6 Deterioration	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
7 Adverse reaction	4		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
7.1 Hallucinations/confusion	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 Nausea	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.3 Orthostase	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.4 Other/unclear	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Revised diagnosis	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only

Analysis 5.1. Comparison 5 Withdrawal rate, Outcome 1 All causes.

Analysis 5.2. Comparison 5 Withdrawal rate, Outcome 2 Lost to follow up.

Analysis 5.3. Comparison 5 Withdrawal rate, Outcome 3 Poor compliance.

Analysis 5.4. Comparison 5 Withdrawal rate, Outcome 4 Protocol violation.

Analysis 5.5. Comparison 5 Withdrawal rate, Outcome 5 Lack of response.

Analysis 5.6. Comparison 5 Withdrawal rate, Outcome 6 Deterioration.

Study or subgroup	BR n/N	LD n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
UK-PDRG 1993	30/263	11/249		0%	2.58[1.36,4.88]
Favours BR 0.1 0.2 0.5 1 2 5 10 Favours LD					

Analysis 5.7. Comparison 5 Withdrawal rate, Outcome 7 Adverse reaction.

Study or subgroup	BR n/N	LD n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Peto Odds Ratio Peto, Fixed, 95% CI
5.7.1 Hallucinations/confusion				
Hely 1994	10/62	6/64		1.83[0.64,5.2]
Riopelle 1988	1/42	0/39		6.88[0.14,347.65]
5.7.2 Nausea				
Hely 1994	4/62	4/64		1.03[0.25,4.31]
Riopelle 1988	3/42	0/39		7.23[0.73,71.64]
5.7.3 Orthostase				
Hely 1994	4/62	0/64		8.02[1.1,58.35]
5.7.4 Other/unclear				
Herskovits 1988	2/28	1/29		2.07[0.21,20.76]
UK-PDRG 1993	69/263	6/249		6.7[4.11,10.93]
Favours BR 0.1 0.2 0.5 1 2 5 10 Favours LD				

Analysis 5.8. Comparison 5 Withdrawal rate, Outcome 8 Revised diagnosis.

Study or subgroup	BR n/N	LD n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
UK-PDRG 1993	22/263	16/249		0%	1.33[0.68,2.57]
Favours BR 0.1 0.2 0.5 1 2 5 10 Favours LD					

WHAT'S NEW

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

HISTORY

Review first published: Issue 2, 2000

Date	Event	Description
20 August 2007	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

JJ Van Hilten contributed to the design of the protocol and was involved in data extraction, analysis and interpretation for the review
 Claudia Ramaker contributed to the design of the protocol and was involved in data extraction, analysis and interpretation for the review
 Rebecca Stowe was involved in data extraction, analysis and interpretation for the review
 Natalie Ives was involved in data extraction, analysis and interpretation for the review

DECLARATIONS OF INTEREST

<None>

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Prinses Beatrix Fonds, Netherlands.

INDEX TERMS

Medical Subject Headings (MeSH)

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

MeSH check words

Humans