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The Efficacy and Safety of Adjunct Bromocriptine Therapy for Levodopa-Induced Motor Complications: A Systematic Review

Claudia Ramaker, MD, Willem Johan T. van de Beek, MSc, Martijn J. J. Finken, MSc, and Bob J. J. van Hilten, MD, PhD

Department of Neurology, Leiden University Medical Center, Leiden, The Netherlands

Summary

OBJECTIVES: To assess the efficacy and safety of adjunct bromocriptine (BR) compared with placebo in the treatment of patients with Parkinson's disease (PD) who have motor complications.

DESIGN: A systematic review of the literature from 1966–1999 on randomized, controlled trials. Outcome measures were occurrence and severity of motor complications, scores on impairment and disability, and the occurrence of side effects.

RESULTS: We included eight trials of which the methodologic quality of seven showed important shortcomings. All studies failed to adequately describe randomization procedures and seven studies failed to report sample size calculations. Only one trial was analyzed according to the intention-to-treat principle. It frequently remained unclear if patients with PD actually had motor complications. Differences between studies concerning the baseline characteristics, the BR titration phase, and the applied outcomes were found. The various methods used to evaluate the occurrence and/or severity of motor complications lacked a sound clinimetric basis. A great diversity of impairment and disability scales were applied. For those studies that reported the incidence of side effects, no clear pattern of BR-related side effects emerged. A trend was found for orthostatic hypotension, which more frequently resulted in withdrawal of patients in the BR group.

CONCLUSIONS: Major methodologic problems and sources of heterogeneity not only hamper the comparability of trials, but also preclude a conclusion on the efficacy and safety of BR in the adjunct treatment of patients with PD who have motor complications.

Key Words: Bromocriptine—Parkinson's disease—Motor complications—Systematic review.

Parkinson's disease (PD) is a progressive neurologic disorder that results in a slowly increasing disability in movement. The motor impairments of PD are caused by a dopamine depletion resulting from progressive neuronal loss of the substantia nigra.[1,2] The treatment of patients with PD is symptomatic by administration of levodopa (LD), the precursor of dopamine. LD provides satisfactory control of most symptoms. However, after 2–5 years of stable response to LD treatment, approximately half of the patients develop motor complications.[3] Some of these motor complications are thought to be highly correlated with prolonged LD exposure.[4–6] Because of these long-term complications of LD therapy, new therapeutic approaches were explored. In the 1970s bromocriptine (BR), a dopamine agonist, was introduced as an adjunct therapy to LD in patients with PD who have motor complications.[7] This treatment strategy would allow a lower dose of LD, thus potentially alleviating the severity of LD-related motor complications. Although several reviews on BR in the management of patients with PD who have motor complications have appeared, this issue has remained controversial.[8–11] Therefore, we conducted a systematic review of the literature to examine the evidence of efficacy and safety of adjunct BR treatment of patients with PD who have LD-induced motor complications.

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Address correspondence and reprint requests to Bob J. J. van Hilten, MD, PhD, Department of Neurology, K5 Q 91, Leiden University Medical Center, P.O. Box 9600, 2300 RC, Leiden, The Netherlands; e-mail: jvhilten@neurology.azl.nl

METHODS

All published BR studies reporting randomized, controlled trials (RCTs) in patients with PD who have motor complications were included. These were identified from a computerized search of Medline (1966 to January 1999), the Cochrane Library, reference lists of the reviews found by the MEDLINE search strategy, Sandoz (now Novartis, producer of BR), symposia reports, PD handbooks, contacts with colleagues who had coordi-

nated trials on BR, and reference lists of all included studies. Randomized, controlled, double-blind trials were eligible for inclusion if they evaluated the efficacy of BR as adjunct to LD therapy compared with placebo. Cross-over trials were eligible if the first phase of the study fulfilled these criteria.

Three reviewers independently reviewed the identified trials according to a two-step review process: (1) the abstracts were reviewed, and (2) eligible studies were reviewed. Discrepancies were registered and resolved by consensus with a fourth reviewer.

Studies with patients with PD who had motor complications associated with LD therapy were included. All trials included a group of patients using LD and placebo and a group using LD and BR. Anticholinergic comedication, peripheral decarboxylase inhibitors, and/or the use of amantadine was permitted.

The following outcome measures were evaluated: (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 on impairment and disability level; and (3) the occurrence of side effects.

To determine the feasibility of performing a quantitative systematic review, the following issues for each of the studies were first addressed: (1) application of general principles of trial methodology; (2) patient baseline characteristics; (3) BR titration schedules; and (4) assessment procedures and outcome measures. If the information on the aforementioned issues was insufficiently reported, we attempted to contact the trial coordinators to obtain additional data.

RESULTS

During the period from 1974 to January 1999, nine eligible RCTs were identified. One trial, reported as being carried out according to a randomized, double-blind design, finally turned out to be a nonrandomized, open trial after additional information was obtained from the trialist and it was excluded.[12] The remaining eight studies randomized 563 patients to either a BR or a placebo regimen (Table 1).

Description of Studies

Inclusion Criteria

Not all of the included trials adequately described the included patient population. Reasons for inclusion sometimes suggested a possible role of motor complications. Some listed the number of patients who had motor complications per type of fluctuation.[13–16] Bateman included a patient with Shy-Drager syndrome and Toyokura included 10 patients with symptomatic parkinsonism.

Baseline Characteristics

The mean age of the participants of each study varied between 58.1[17] and 65.3 years[14] (range, 30–81 yrs). Only one trial reported age at onset.[13] The mean disease duration ranged from 8.5[18,19] to more than 13 years.[14] There were substantial differences between the studies with regard to the mean pretrial daily dosages of LD and the reported ratios of LD/decarboxylase inhibitor. The mean duration of the pretrial LD treatment ranged from at least 1 year[13] to 7 years.[15]

Titration Schedules

Five trials introduced BR at a dosage of 2.5 mg per day; the remaining three studies started with 1.25 mg BR per day.[13,15,20] Dose increment of BR varied between the trials, ranging from 1.25 mg every 2 weeks[15] to 2.5 mg every second day[17,18] (Fig. 1). Maximum BR dosages at the end of the titration phase were reported by all trials and ranged from 20[14,15] to 100 mg per day.[19] Only four trials reported the diurnal distribution of the BR dosages at the end of the titration phase: three[16–18,20] or four times per day.[16,17]

Methodologic Quality

Several trials showed shortcomings of the reported information on relevant methodologic issues. Therefore, we attempted to approach all trial coordinators for additional data. Six of eight coordinators responded.[13,14,16,17,19,20] One trialist was deceased and therefore the requested information could not be retrieved.[18]

Trial Design

Six trials used a parallel placebo group. Bateman's and Gron's study had a cross-over design. The trial performed by Guttman compared pramipexole versus placebo and included a treatment group with bromocriptine to validate the study design. In Hoehn's trial, all patients started with placebo during the first 4 weeks. Subsequently, the patients were allocated to BR or placebo for 32 weeks. Thereafter, both groups continued on placebo for 4 weeks. Temlett broke the randomization code after a 5-week duration and patients allocated to placebo were transferred to BR. Therefore, only these first 5 weeks were evaluated in this review.

Trial Duration

The periods of evaluation varied between trials from 4[16] to 32 weeks.[15]

TABLE 1. *Characteristics of included studies*

Study	Objective and design	Sample and characteristics	Interventions	Notes
Bateman (1978, UK)	Randomized: random number tables; double-blind design: two period cross-over (no wash-out); duration: 6 weeks in each period (preceded by 4 weeks dose-titration)	11 parkinsonism patients with the "on-off" syndrome; mean age: 58.1 (36–72) yrs; mean disease duration: not available; mean LD treatment duration: over 2 yrs; mean daily LD dosage: 357.5 mg Sinemet~1(4), 1191.7 mg Sinemet~2(3), drop-outs (4): NA	1. BR 2. placebo	LD:DDI ratio = 10:1 (Sinemet) and 4:1 (Sinemet) Scales: visual analog scales
Gron (1977, Denmark)	Randomized: method not described; double-blind; design: two period cross-over; duration: 12 weeks in each period (wash-out varied between 1 day and 2 weeks)	20 idiopathic parkinsonism patients with a decreasing LD effect or increasing side effect; mean age: 64 (50–81) yrs; mean disease duration: 8.5 yrs; mean LD treatment duration: 4 yrs; mean daily LD dosage: 2663 mg LD (4) 554 mg Madopar (7), 653 mg Sinemet (9)	1. BR (10) 2. placebo (10)	LD:DDI ratio = 4:1 (Madopar) and 4:1 (Sinemet) Scales: Webster and NUDS
Guttman (1997, international)	Randomized: a computer-generated randomization schedule; double-blind; design: parallel group; duration: 24 weeks (preceded by 12 weeks dose-titration and followed by 2 weeks wash-out)	167 PD patients with motor fluctuations resulting from LD therapy; mean age: 61.5 yrs (BR), 63.7 yrs (placebo); mean disease duration: 8.1 yrs (BR), 8.4 years (placebo); mean LD treatment duration: 6.5 yrs (BR), 6.6 yrs (placebo); mean daily LD dosage: 609.8 mg LD (BR), 668.4 mg LD (placebo)	1. BR (84) 2. placebo (83) LD reduction was permitted	LD:DDI ratio = Fixed ratio was not required (Sinemet) Scales: UPDRS, mod. Schwab + Eng, PDS timed walking test, GCAE, Quality of life assessment scales
Hoehn (1985, USA)	Randomized: method not described (placebo: BR-ratio = 1:3); double-blind; duration: 32 weeks (preceded and followed by 4 weeks placebo for both groups)	36 Parkinson patients with peak-dose dyskinesias, wearing-off effects and/or off-dose movements; mean age: 62.9 (41–78) yrs; mean disease duration: 9.9 (1–25) yrs; mean LD treatment duration: 7 (1–13) yrs; mean daily LD dosage: 3188 mg LD (2), 677.6 mg Sinemet (34)	1. BR (27) 2. placebo (9)	LD:DDI ratio = not available (Sinemet) Scales: modified CURS
Jansen (1978, Netherlands)	Randomized: by means of a computer; double-blind; duration: 10 weeks dose titration, followed by 10 weeks at maximally effective dose	23 advanced PD patients with deteriorating response, insufficient LD response and/or initial LD failure; mean age: 58.5 yrs (BR), 59 yrs (placebo); mean disease duration: 8.8 yrs (BR), 8.5 yrs (placebo); mean LD treatment duration: 4.6 yrs (BR), 4.3 yrs (placebo); mean daily LD dosage: 2930 mg LD (BR), 2237 mg LD (placebo)	1. BR (12) 2. placebo (11)	Only plain LD Scales: Webster and NUDS
Schneider (1982, Germany)	Randomized: randomization schedule; double-blind; duration: 4 wks	40 PD patients with decreasing LD effect, dyskinesias and/or on-off syndrome; mean age: 64.8 yrs (BR), 64.5 yrs (placebo); mean disease duration: 8.6 yrs (BR), 9.6 yrs (placebo); mean LD treatment duration: 68.5 mos (BR), 77.0 mos (placebo); mean daily LD dosage: 700 mg LD+DDI (BR), 710 mg LD+DDI (placebo)	1. BR (20 2. placebo (20) LD reduction was permitted	LD:DDI ratio = not available Scales: modified Webster

(continues)

TABLE 1. (*Continued*)

Study	Objective and design	Sample and characteristics	Interventions	Notes
Temlett (1990, South Africa)	Randomized: computer-generated random numbers; double-blind; duration: 5 wks followed by 6 wks open phase	44 PD patients with dyskinesias, freezing, on-off phenomena and/or dystonia; mean age: 64.3 yrs (BR), 65.3 yrs (placebo); mean disease duration: 13.4 yrs (BR), 13.3 yrs (placebo); mean LD treatment duration: not available; mean daily LD dosage: 669.3 mg LD (BR), 622.2 mg LD (placebo)	1. BR (23) 2. placebo (21)	LD:DDI ratio - not available Scales: Webster, CURS, NUDS, and self-made scale
Toyokura (1985, Japan)	Randomized: by means of a computer; double-blind; duration: 8 wks	222 PD patients with declining efficacy of LD, wearing-off phenomena, frozen gait and/or on-off phenomena; mean age: 62.5 yrs (BR), 63.2 yrs (placebo); mean disease duration: see text; mean LD treatment duration: over 1 yr; mean daily LD dosage: 418.3 mg LD+DDI (BR), 465 mg LD+DDI (placebo) see text	1. BR (114) 2. placebo (108)	LD:DDI ratio = 4:1 Scales: self-made scales

NUDS, Northwestern University Disability Scale; CURS, Columbia University Rating Scale; mod. Schwab + Eng, modified Schwab and England Disability Scale; PDS, Parkinson's Dyskinesia Scale; GCAE, Global Clinical Assessment of Efficacy; LD:DDI, ratio of levodopa/decarboxylase inhibitor.

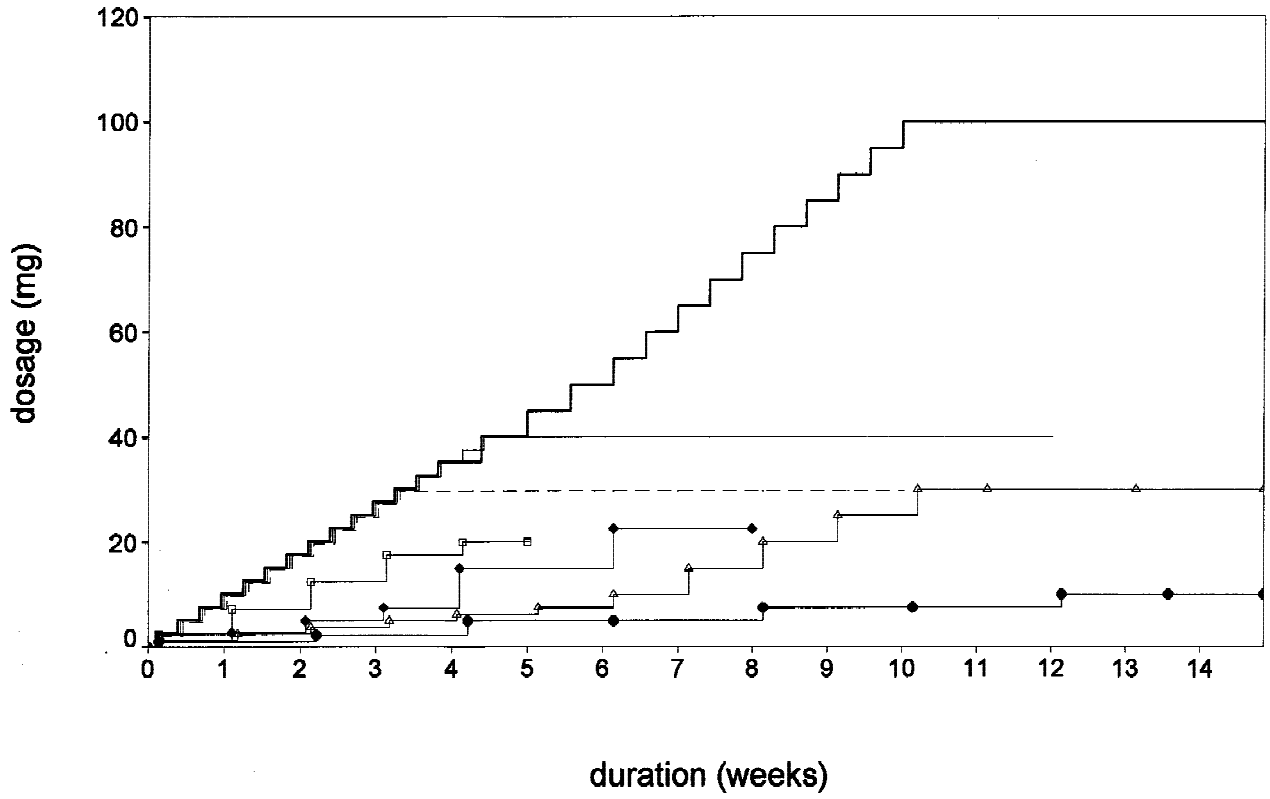

FIG. 1. The variability of the applied bromocriptine titration schedules in seven randomized, controlled trials. —— Bateman, –– Gron, —△— Guttman, —●— Hoehn, –– Jansen, —□— Temlett, —♦— Toyokura. Schneider did not provide exact data on BR-titration schedules.

Centers and Assessors

The patients were evaluated by one assessor in the trials performed by Bateman and Jansen, by at least two assessors in Temlett's study, and by 41 investigators in Guttman's study. For all other studies this remained unclear. In the studies of Toyokura and Guttman, 59 and 29 centers participated, respectively.

Randomization

Only Bateman partly described the allocation procedure. Additionally obtained information showed that six trials[13,14,16,17,19,20] adequately randomized their patients by means of a computer randomization procedure or a randomization schedule. Hoehn apparently randomized 27 patients to the BR branch, whereas nine patients were allocated to the placebo group. None of the studies reported if treatment assignment was concealed until the evaluation of the outcomes. Additionally obtained information showed that this was adequately done by five trial coordinators.[13,14,16,19,20]

Trial Performance

All studies were performed according to a double-blind design. One study, however, was unblinded before the end of the follow-up period[17]; only the data of the double-blind period was evaluated for this review.

Sample Size Calculations

Guttman reported that the trial was designed to show that pramipexole and bromocriptine were "equally effective" under the condition that either drug was superior to placebo. None of the other trials reported sample size calculations.

Attrition Characteristics

All trials provided detailed information on the reasons for patients leaving the trials. Toyokura and Guttman did not specify all side effects that caused the withdrawal of patients from the study.

Data Analyses

Only Guttman's trial provided intention-to-treat data.

Motor Complications

All trials reported outcomes in motor complications but focused on different aspects. Unfortunately, two trialists did not provide data on motor complications at the end of the first phase of their trial and therefore the results could not be evaluated.[17,18] Changes in wearing-off were reported by two studies.[13,15] They found no (or marginal) difference between the two tiers. On–off fluctuations were assessed by five studies.[13,14,16,17,19] Schneider and Toyokura reported improvement of patients in the BR tier. This difference was statistically significant in the former and nonsignificant in the latter. Three trials reported no change in "on" and "off" time.[14,19,20] All trials assessed the occurrence of dyskinesias. Three trials[13,14,19] reported an increase of dyskinesias in the group using BR. Only Toyokura reported this difference to be statistically significant. The reanalyzed data of Guttman's study and the trial performed by Schneider indicated no difference with respect to the occurrence of dyskinesias, but these studies allowed an LD reduction during the trial. Hoehn reported no difference in occurrence between the two groups. Additionally, three studies reported the occurrence of dystonia (Hoehn, Temlett, and Guttman). Compared with placebo, the patients on BR improved with respect to duration and severity of dystonia in the trial performed by Hoehn. Temlett (original paper) and Guttman (additional provided data) reported no differences in dystonia between the two groups.

Six included trials recorded the severity of motor complications but used different and nonstandardized methods for this purpose. Toyokura and Temlett used four categories ("none," "mild," "moderate," or "severe"). Bateman reported global severity of on–off fluctuations with a visual analog scale. In the trial performed by Schneider, the duration of "on"- and "off"-hours during the day was reported, whereas it remained unclear how the severity of dyskinesias was assessed. Hoehn only reported severity of motor complications without specifying any categories. Guttman used the Parkinson Dyskinesia Scale and the Unified Parkinson's Disease Rating Scale (UPDRS, part IV) to evaluate the complications of therapy. The provided data showed no significant difference in the scores at baseline and at final evaluations between the two groups.

Impairment and Disability

All trials used impairment and seven implemented disability scales. Temlett did not provide data on disability when patients using placebo switched to BR. Likewise, both Gron and Bateman did not provide data at the time of cross-over. Hence, the results of these studies could not be evaluated.

Only one of the included RCTs reported if impairment and disability scores referred to the "on"- or "off"-phase.[20] Bateman used a visual analog scale to assess items such as writing, tremor, walking, speech, and global severity of motor complications. Toyokura evaluated parkinsonian features, that is, akinesia, tremor, rigidity, and gait disturbance, and activities of daily life using a semiquantitative scale ranging from 0–4 assessing, respectively, impairment and disability. Compared with

placebo, BR reduced impairment scores, which were statistically significant in two studies.[16,19] Hoehn reported the results on impairment for different subgroups of the BR tier, which were based on the disease severity at baseline. Statistically significant improvement was reported only for the patients with baseline scores less than 50 (modified Columbia scale, the maximal score being 96).[15] Toyokura found a statistically nonsignificant improvement at the impairment level. Jansen and Schneider found a statistically significant improvement for disability in the BR tier, whereas Toyokura reported a trend toward improvement. In Guttman's study, BR treatment was better than placebo in alleviating PD symptoms as measured by the UPDRS II (activities of daily living) and III (motor examination) subscales, but this was not statistically significant. Quality-of-life assessments showed nonstatistically significant improvements of BR treatment compared with placebo.

Side Effects

Occurrence of side effects was reported by three trials[13,15,20] and partly by Schneider and Jansen (Table 2). Compared with placebo, Hoehn found only transient nausea, vomiting, and episodic sweating slightly more frequent in those patients receiving BR (statistical significance not available). In Guttman's study, nausea was more common in the BR group but this was not statistically significant. Toyokura reported no statistically significant differences in the incidence of side effects between the two groups. Three trialists revealed only the side effects that resulted in the withdrawal of patients (Fig. 2).

DISCUSSION

The treatment of PD, lacking a cure, aims to limit the gradually increasing amount of disability. In this regard, the most effective strategy is treatment with LD, which improves some of the PD features. However, for every year of LD treatment, the number of patients who will develop motor complications increases. These motor complications contribute to an additional disease burden and become a source of increased medical care. Hence, one of the major challenges of long-term management of PD is the prevention or control of motor complications. In the 1970s, BR was introduced as an adjunct to conventional LD therapy in patients with PD who have motor complications.[7] This treatment strategy aimed to alleviate the severity of LD-related motor complications.

TABLE 2. *Side effects that resulted in withdrawal of patients*

Study	No. randomized	No. of withdrawals	
		BR group	Placebo group
Bateman*	11	n = 2: headache n = 2: orthostatic hypotension	n = 0
Gron	20	n = 1: orthostatic hypotension	n = 0
Guttman	167	n = 12: worsening of disease during study n = 5: adverse events n = 1: unsatisfactory therapeutic effect n = 1: unspecified reasons	n = 24: worsening of disease under study n = 7: adverse events n = 4: unsatisfactory therapeutic effect n = 2: worsening of other pre-existing disease n = 1: protocol violation n = 1: withdrawal of consent n = 1: unspecified reasons
Hoehn	36	n = 1: exacerbation of angina pectoris n = 1: emotional lability n = 1: poor memory leading to some confusion n = 1: severe orthostatic hypotension, syncope, and falling n = 1: increased falling resulting from peak-dose hypotonic akinesia	n = 3: hallucinations, severe mental disturbances n = 1: died because of a myocardial infarction
Jansen	23	n = 1: delirium n = 1: confusion and increased prostatism	n = 1: poor compliance
Schneider	40	n = 1: orthostatic hypotension n = 1: psychosis	n = 4: lack of effort n = 1: died because of an accident
Temlett	44	n = 1: confusion n = 1: orthostatic hypotension n = 1: poor compliance	n = 3: poor compliance
Toyokura	222	n = 18: unspecified side effects n = 4: poor compliance n = 3: unspecified reasons n = 2: worsening of PD symptoms	n = 7: unspecified side effects n = 5: worsening of PD symptoms n = 4: unspecified reasons n = 1: poor compliance

* The patient with Shy-Drager syndrome was not among the drop-outs.

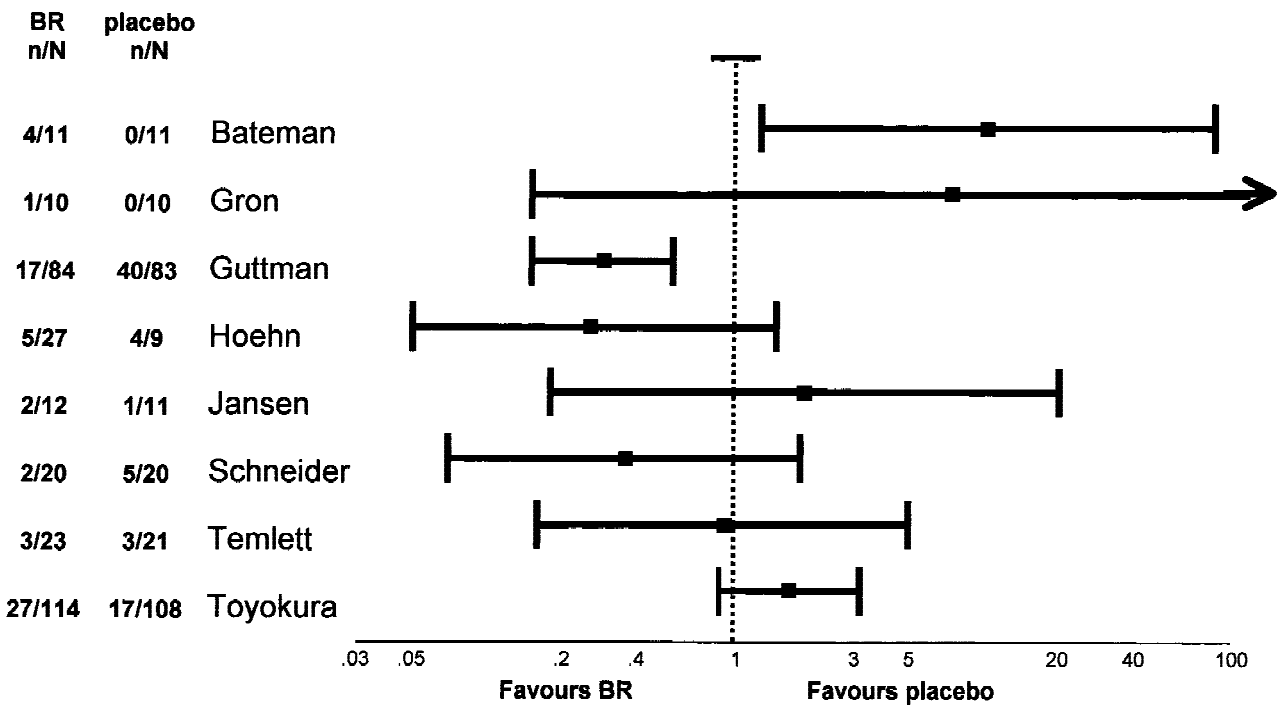

FIG. 2. Peto odds ratio (95% confidence interval) of withdrawal rates (all causes) in all trials comparing bromocriptine with placebo. n/N - number of drop-outs/total number of patients.

Several reviews on BR in the management of patients with PD who have motor complications have appeared,[8–11] but they summarized and/or evaluated the results of uncontrolled and nonrandomized trials.

From 1974 to January 1999, we identified eight RCTs evaluating adjunct BR therapy in patients with PD who have motor complications. Several trials showed important shortcomings regarding general and PD-related trial methodology. Seven trials failed to adequately describe the randomization procedure in their published report. However, additionally obtained information revealed that six trials were adequately randomized. Furthermore, seven trials failed to report sample size calculations. Inadequate powering of the studies might explain the different results or why many findings on the applied outcomes failed to reach a statistically significant level.

We found a conspicuous variability in the duration of trials: 1–9 months. There is no consensus on the minimum duration of a clinical drug trial in this phase of PD. It is not unusual for patients in this phase of Parkinson's disease to develop further worsening after a previous short-lasting good control of motor complications. Hence, the clinical validity of short-term results in this phase of PD is questionable.

With regard to the inclusion criteria, it frequently remained unclear if patients with PD actually had LD-induced motor complications. Trials included patients who initially did not respond to LD or cases of Parkinson-plus syndromes. Although randomization would equally distribute these patients over both tiers of the trial, they are likely to influence the trial outcome in small studies. Moreover, between studies, clinically relevant differences regarding the baseline characteristics, including disease duration, LD-pretrial duration, and dosage, emerged which may influence the outcomes of trials.

Prominent differences regarding the rate by which BR was introduced during the titration phase were found. Large differences between trials concerning the execution of the titration phase may influence the occurrence of adverse events and consequently the drop-out rate.

Major differences between studies emerged regarding the evaluated outcomes. Although all studies assessed the occurrence of different aspects of LD-induced motor complications, different and nonstandardized methods were applied. Additionally, many different impairment and disability scales were used that hamper the comparability of the studies. Only one of the included trials reported whether scores on impairment and disability level referred to the "on"- or "off"-phase.

The conspicuous differences in applied general principles of trial conduct and PD-related methodology between the trials hamper the comparability of trials

and preclude a final quantitative synthesis. Nevertheless, some limited qualitative conclusions can be drawn.

Three trials, which did not allow an LD dose reduction, reported an increased occurrence of dyskinesias in the BR tier. Only the largest of these trials reported this difference to be statistically significant. Two trials allowed an LD dosage reduction and found no difference with respect to the occurrence of dyskinesias. This underscores the influence of trial design on the occurrence of dyskinesias. Two studies that evaluated wearing-off reported no clinically relevant difference between both tiers. No overall consistent effect on on–off fluctuations was found in four studies that evaluated this motor complication. Five trials reported an improvement of impairment for the BR tier, which was statistically significant in two. Improvement in disability in favor of BR was statistically significant in two of four studies. The incidence of side effects was fully reported by three and incompletely by two other studies. From these studies, no clear pattern of BR-related side effects emerged. With respect to the side effects that resulted in the withdrawal of patients, a trend was found for orthostatic hypotension which occurred more frequently in the group using BR.

Only one trial analyzed the data according to the intention-to-treat principle. Although this principle first appeared in print in the 1961 edition of Bradford Hill's *Principles of Medical Statistics*,[21] its general application followed many years later. Intention-to-treat analysis reflects clinical practice and failure to analyze by this principle can give misleading interpretations.

Our review identified important shortcomings regarding general and PD-related trial methodology in eight eligible trials of adjunct BR therapy in patients with PD who have LD-induced motor complications. However, it should be noted that four RCTs included in this review have appeared before 1985, a period in which trial methodology was still in its infancy. The methodologic problems and sources of heterogeneity that were encountered not only hamper the comparability of BR trials, but also preclude a conclusion on the efficacy of BR in patients with PD who have motor complications.

The issues arising from our review bear on the conduct of future dopamine agonist trials in these patients. There is a clear requirement to apply a uniform general and PD-related trial methodology. With respect to the former, we underscore the application of the guidelines suggested by the Consolidated Standards of Reporting Trials.[22] In addition to the CONSORT statement, trials should encompass a clear description of relevant aspects of PD-related trial methodology.

- *Inclusion and exclusion criteria:* trials should aim to enroll uniform cohorts of patients with PD.
- *Titration phase:* titration schedules strongly depend on the drug that will be evaluated. Nevertheless, there is a need for standardization of titration schedules for trials that deal with the same drug.
- *Assessments:* motor complications in PD contribute to an additional disease burden. Hence, the evaluation of the efficacy of dopamine agonists in this phase of PD should not only focus on motor complications, but also encompass the assessment of disability. Trials should record similar types of motor complications. This raises the need for more information on the assessor reliability on evaluations of dyskinesias. Scales that assess motor complications should be standardized and based on a sound clinimetric methodology. Regardless of the scale used, trials should report if scores on impairment and disability refer to the "on"- or "off"-phase. A standardized scale that evaluates impairment and disability is strongly desired to generate comparable scores. However, the development of new scales is an ongoing process that will probably hinder the international application of a standardized rating scale. We suggest the use of standardized outcomes that can be used parallel with the end points that are selected by a trialist. These co-end points would facilitate the international comparability of trials that deal with the same drug and population.

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