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Pramipexole versus bromocriptine for levodopa-induced complications in Parkinson's disease (Review)

Clarke CE, Speller J, Clarke JA

Clarke CE, Speller J, Clarke JA.
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[Intervention Review]

Pramipexole versus bromocriptine for levodopa-induced complications in Parkinson's disease

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ABSTRACT

Background

Long-term levodopa therapy in Parkinson's disease is associated with the development of motor complications including abnormal involuntary movements 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 versus bromocriptine therapy in patients with Parkinson's disease, already established on levodopa and suffering from motor complications.

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 bromocriptine 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

One randomised controlled trial has compared pramipexole with bromocriptine using a double-blind, parallel group, multicentre design. It was not powered to examine differences between active treatment arms. There was a larger reduction in off time with pramipexole therapy compared with bromocriptine (weighted mean difference 1.4 hours; 0, 2.8, 95% CI). No differences occurred in dyskinesia rating scale, dyskinesia as an adverse event or UPDRS complication score. The UPDRS ADL and motor scores showed similar improvements compared to placebo with both agonists. Levodopa dose reduction was similar with both agonists. Subscales of the Functional Status Questionnaire showed significant improvements compared to placebo with both agonists. The finding that the EuroQol improved significantly compared

with placebo with pramipexole but not bromocriptine should be treated with caution. Dopaminergic adverse events were similar with each agonist, as was the all cause withdrawal rate.

Authors' conclusions

Although pramipexole and bromocriptine improved off time and reduced parkinsonian motor impairments and disability compared with placebo, no conclusions regarding their comparative effectiveness and safety can be drawn as this single trial did not have adequate power to assess such differences. Further larger trials are required to examine this issue in the future.

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 comparison, bromocriptine has been available since the late 1970s and is a well established agonist. In this review, we will examine the trials performed to see whether pramipexole is better than bromocriptine in terms of effectiveness and side effects.

One trial compared pramipexole with bromocriptine but this was not designed to examine differences between the two treatments as there were too few patients included. However, there was a larger reduction in the time patients spent in the immobile off state with pramipexole therapy compared with bromocriptine by an average of 1.4 hours. No differences occurred in dyskinesia rating scale, dyskinesia as a side effect or Unified Parkinson's Disease Rating Scale (UPDRS) complication score. The UPDRS activities of daily living and motor scores showed similar improvements compared to placebo with both agonists. Levodopa dose reduction was similar with both agonists. Subscales of a quality of life measure, the Functional Status Questionnaire, showed significant improvements compared to placebo with both agonists. The finding that another quality of life scale, the EuroQol, improved significantly compared with placebo with pramipexole but not bromocriptine should be treated with caution. Side effects such as nausea, vomiting, and faintness were similar with each agonist, as was the withdrawal from treatment rate.

No conclusions regarding the comparative effectiveness and safety of pramipexole versus bromocriptine can be drawn as this single trial did not have adequate numbers of patients to assess such differences. Further larger trials are required to examine this issue in the future.

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 et al 1984) and 100% of young onset patients after 6 years of treatment (Quinn et al 1986). In a more recent study with lower doses of levodopa, Block et al 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 in later disease, 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 bromocriptine in patients with idiopathic Parkinson's disease suffering from levodopa-induced motor complications. Separate reviews by the same authors compare adjuvant pramipexole versus placebo. 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 versus bromocriptine therapy in patients with Parkinson's disease, already established on levodopa and suffering from motor complications.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised trials comparing pramipexole with bromocriptine 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 bromocriptine. 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 and Sandoz Ltd.

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.

Only 1 randomised controlled trial comparing pramipexole with bromocriptine in later Parkinson's disease has been identified. This was a double-blind, parallel group, multicentre study which also had a placebo arm and was therefore included in the Cochrane pramipexole versus placebo review.

The 2 groups in the trial were well matched at baseline for age, sex, duration and severity of Parkinson's disease.

The mean pramipexole dose in the active treatment arm was 3.36 mg/d and the equivalent dose of bromocriptine was 22.64 mg/d. The maximum allowed dose of pramipexole was 4.5 mg/d and bromocriptine 30 mg/d.

Risk of bias in included studies

See also Characteristics of Included Studies.

The authors clearly state that this study was not powered to examine "statistical differences between active treatment groups". As such, they do not present any statistical comparisons between the effects of pramipexole and bromocriptine on any outcome measure. This is appropriate as this part of the trial is subject to type 2 error: the absence of any difference between active treatments may be due to there being insufficient patients in the study.

Details of randomisation method and concealment of allocation were not given but, from discussions with the manufacturer, randomisation was by computer generated random numbers.

The trial was 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.

This was a medium term study with a maintenance period of 24 weeks.

The maximum dose of pramipexole allowed was 4.5 mg/d compared to only 30 mg/d bromocriptine. This is the maximum dose of pramipexole used in trials and more recently clinical practice. However, doses of bromocriptine greater than 30 mg/d are commonly used in clinical practice. Thus, patients randomised to bromocriptine may have been undertreated compared with those on pramipexole.

Effects of interventions

A single randomised controlled trial has compared pramipexole with bromocriptine using a double-blind, parallel group, multicentre design. However, it was not powered to examine differences between active treatment arms, so no statistical comparisons were or should be given.

From the additional data supplied by the manufacturer, a difference in the reduction in off time was apparent in favour of pramipexole compared with bromocriptine (weighted mean difference 1.4 hours; 0, 2.8, 95% CI; Table 7).

No change occurred in the dyskinesia rating scale (Table 8) and dyskinesia as an adverse event was reported with a similar frequency with each agonist (Table 13). No difference in the improvement in UPDRS complication score (part IV) was noted (Table 3).

The UPDRS ADL score was reported as an average of the off and on states (Table 1). This showed statistically significant improvements compared to placebo for both pramipexole and bromocriptine. Statistically significant improvement occurred in UPDRS motor score in the on state compared to placebo with both agonists (Table 2). Both the Hoehn and Yahr stage and the Schwab and England scale
failed to improve with both agents (Tables 4 and 5).

Levodopa dose was reduced with pramipexole and bromocriptine to a similar degree (Table 6).

Quality of life scales showed superiority of both pramipexole and bromocriptine over placebo for the Functional Status Questionnaire (FSQ) Basic ADL, Intermediate ADL, and Mental Health Scales. However, whilst pramipexole was significantly better than placebo using the European Quality of Life (EuroQol) scale, bromocriptine showed no such improvement.

Dopaminergic adverse events (Tables 10 to 13) were similar with the 2 agonists, as was the all cause withdrawal rate (Table 14).

DISCUSSION

Only a single randomised controlled trial has compared pramipexole with bromocriptine (Guttman 97). Whilst this was otherwise a well designed double-blind, parallel group, multicentre study, it was not powered to examine differences between active treatment arms, so no statistical comparisons between the agonists were appropriate.

The superior reduction in off time with pramipexole compared with bromocriptine approached significance and a larger study may have proved this conclusively (weighted mean difference 1.4 hours; 0, 2.8, 95% CI; Table 7). No significant differences compared with placebo were noted with either agonist regarding dyskinesia rating scale, dyskinesia as an adverse event or the UPDRS complications score (part IV).

Significant improvements in UPDRS ADL and motor scores occurred with both agonists. These improvements were quantitatively similar with each agent. No change occurred in the Hoehn and Yahr stage and the Schwab and England scales. Levodopa dose reduction was similar with each agonist.

Certain subscales of the Functional Status Questionnaire showed significant improvements with both agonists. The finding that the EuroQol improved significantly compared with placebo with pramipexole but not bromocriptine should be treated with caution.

The lack of any differences in the frequency of adverse events reported with each agonist may be a reflection of the relatively small numbers involved.

AUTHORS' CONCLUSIONS

Implications for practice

The single trial comparing pramipexole with bromocriptine in later Parkinson's disease was relatively small and consequently did not have the power to examine differences between the agonists. Although both agents improved off time and reduced parkinsonian motor impairments and disability compared with placebo, no conclusions regarding their comparative effectiveness and safety can be drawn.

Implications for research

Incomplete Reporting
Data on the variance of continuous variables was not available in the original report. 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
Further studies are required to examine whether pramipexole has any advantages over bromocriptine in later Parkinson's disease. Any future trial(s) must include cost benefit analysis in view of the expense of the newer agonists in comparison with bromocriptine.

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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Parkinson's Disease Study Group in the United Kingdom. Comparison of the therapeutic effects of levodopa, levodopa and selegiline, and bromocriptine in patients with early, mild Parkinson's disease: three year interim report. *BMJ* 1993;**307**:469-472.

Quinn 1986

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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.

UPDRS 1987

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 placebo arm (see Cochrane pramipexole v placebo review). Study was not powered to examine differences between pramipexole and bromocriptine. 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 < or = 36 weeks.
Participants	Pramipexole - 79 patients with 16 drop outs (20%). Bromocriptine - 84 patients with 17 drop outs (20%). 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.
Interventions	Blind titration to maximum of 1.5 mg tds of pramipexole and 10 mg tds of bromocriptine. Titration phase < or = 12 weeks. Maintenance = 24 weeks. Dose reduction = 1 week. Mean dose of pramipexole in active arm 3.36 mg/d. Mean dose of bromocriptine in active arm 22.64 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.

Guttman 1997 *(Continued)*

	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

DATA AND ANALYSES

Comparison 1. Pramipexole versus bromocriptine

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 Hoehn and Yahr stage			Other data	No numeric data
5 Schwab and England scale			Other data	No numeric data
6 Levodopa dose reduction (mg)	1	163	Mean Difference (IV, Fixed, 95% CI)	29.40 [-21.91, 80.71]
7 Off time reduction (hours)	1	152	Mean Difference (IV, Fixed, 95% CI)	1.40 [0.03, 2.77]
8 Dyskinesia rating scale			Other data	No numeric data
9 Adverse events - Nausea	1	163	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.99 [0.53, 1.87]
10 Adverse events - Postural hypotension	1	163	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.87 [0.47, 1.61]
11 Adverse events - Hallucinations	1	163	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.20 [0.48, 2.98]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12 Adverse events - Confusion	1	163	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.06 [0.76, 5.60]
13 Adverse events - Dyskinesia	1	163	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.83 [0.44, 1.53]
14 All cause withdrawal rate	1	163	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.00 [0.47, 2.14]

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

UPDRS ADL scores (part II)

Study	
Guttman 1997	Average of off and on phases: Median improvement on pramipexole 2.5 v bromocriptine 1.5.

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

UPDRS motor scores (part III)

Study	
Guttman 1997	On phase: Median improvement on pramipexole 6.0 v bromocriptine 5.0.

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

UPDRS complications scores (part IV)

Study	
Guttman 1997	Details not available but no significant differences between pramipexole and placebo or bromocriptine and placebo.

Analysis 1.4. Comparison 1 Pramipexole versus bromocriptine, Outcome 4 Hoehn and Yahr stage.

Hoehn and Yahr stage

Study	
Guttman 1997	Details not available but no significant differences between pramipexole and placebo or bromocriptine and placebo.

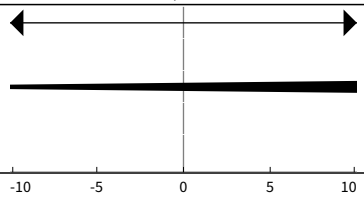
Analysis 1.5. Comparison 1 Pramipexole versus bromocriptine, Outcome 5 Schwab and England scale.

Schwab and England scale

Study	
Guttman 1997	Details not available but no significant differences between pramipexole and placebo or bromocriptine and placebo.

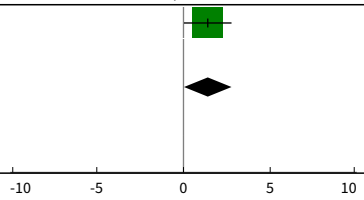
Analysis 1.6. Comparison 1 Pramipexole versus bromocriptine, Outcome 6 Levodopa dose reduction (mg).

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)	84	56 (184.3)		100%	29.4[-21.91,80.71]
Total ***	**79**		**84**			**100%**	**29.4[-21.91,80.71]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.12(P=0.26)							



Analysis 1.7. Comparison 1 Pramipexole versus bromocriptine, Outcome 7 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)	81	1.2 (4.3)		100%	1.4[0.03,2.77]
Total ***	**71**		**81**			**100%**	**1.4[0.03,2.77]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2(P=0.05)							

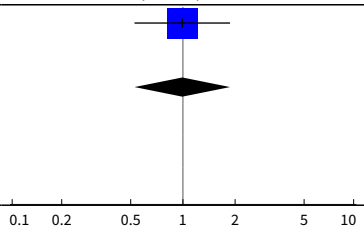


Analysis 1.8. Comparison 1 Pramipexole versus bromocriptine, Outcome 8 Dyskinesia rating scale.

Study	Dyskinesia rating scale
Guttman 1997	Details not available but no significant differences between pramipexole and placebo or bromocriptine and placebo.

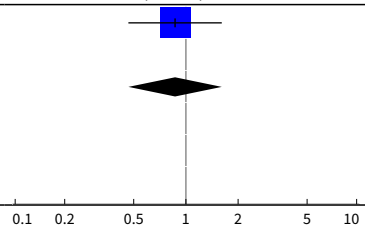
Analysis 1.9. Comparison 1 Pramipexole versus bromocriptine, Outcome 9 Adverse events - Nausea.

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	31/84		100%	0.99[0.53,1.87]
Total (95% CI)	**79**	**84**		**100%**	**0.99[0.53,1.87]**
Total events: 29 (Treatment), 31 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.03(P=0.98)					



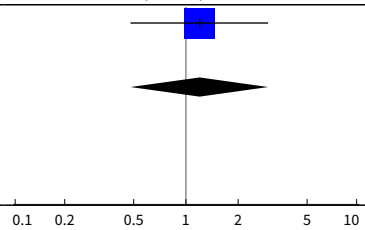
Analysis 1.10. Comparison 1 Pramipexole versus bromocriptine, Outcome 10 Adverse events - Postural hypotension.

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	37/84		100%	0.87[0.47,1.61]
Total (95% CI)	**79**	**84**		**100%**	**0.87[0.47,1.61]**
Total events: 32 (Treatment), 37 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.46(P=0.65)					



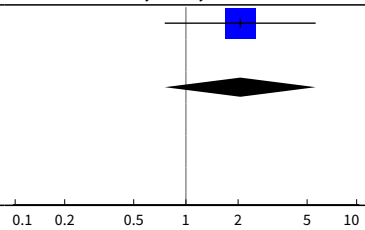
Analysis 1.11. Comparison 1 Pramipexole versus bromocriptine, Outcome 11 Adverse events - Hallucinations.

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	11/79	10/84		100%	1.2[0.48,2.98]
Total (95% CI)	**79**	**84**		**100%**	**1.2[0.48,2.98]**
Total events: 11 (Treatment), 10 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.38(P=0.7)					



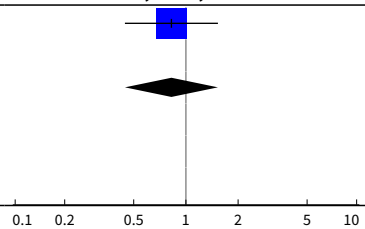
Analysis 1.12. Comparison 1 Pramipexole versus bromocriptine, Outcome 12 Adverse events - Confusion.

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	11/79	6/84		100%	2.06[0.76,5.6]
Total (95% CI)	**79**	**84**		**100%**	**2.06[0.76,5.6]**
Total events: 11 (Treatment), 6 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.41(P=0.16)					

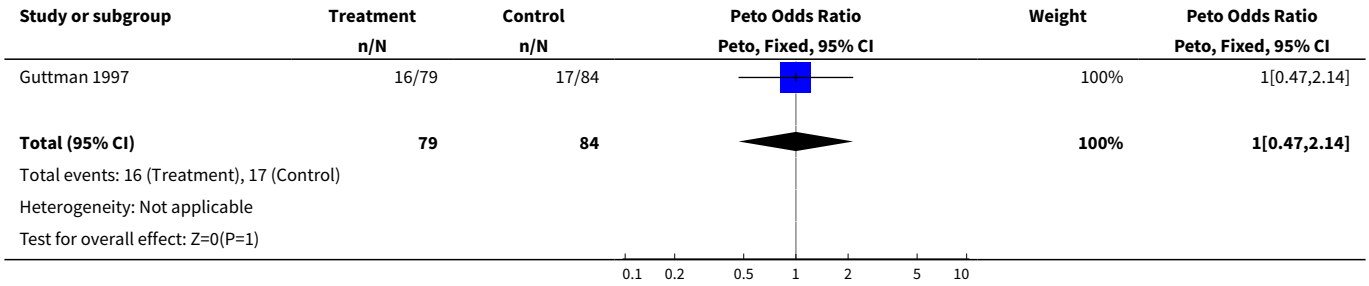


Analysis 1.13. Comparison 1 Pramipexole versus bromocriptine, Outcome 13 Adverse events - Dyskinesia.

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	38/84		100%	0.83[0.44,1.53]
Total (95% CI)	**79**	**84**		**100%**	**0.83[0.44,1.53]**
Total events: 32 (Treatment), 38 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.61(P=0.54)					



Analysis 1.14. Comparison 1 Pramipexole versus bromocriptine, Outcome 14 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; Bromocriptine [*therapeutic use]; Dopamine Agonists [*therapeutic use]; Drug Tolerance; Levodopa [*adverse effects]; Parkinson Disease [*drug therapy]; Pramipexole; Randomized Controlled Trials as Topic; Thiazoles [*therapeutic use]

MeSH check words

Humans