Comparing dopamine agonists in Parkinson's disease

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Summary

Dopamine agonists are effective in the management of both advanced and early-stage Parkinson's disease. Unfortunately, randomized head-to-head comparative studies between the many different dopamine agonists now available are sparse. Indirect comparisons of dopamine agonists show that ergot derivatives, such as pergolide and cabergoline, are as effective as non-ergot derivatives, such as ropinirole and pramipexole, in ameliorating Parkinson's disease symptoms in patients in early or advanced stages of the condition. As far as safety and tolerability are concerned, no significant differences between dopamine agonists are found. However, some specific adverse events, such as somnolence and sleep attacks, seem less frequent in monotherapy studies with pergolide than in those with the non-ergot dopamine agonists; however, because of the lack of direct-comparison studies this cannot be proved conclusively. Randomized, controlled comparative studies between dopamine agonists are necessary to verify any possible differences in their effectiveness and tolerability in the treatment of Parkinson's disease.

Keywords

dopamine agonists, comparison, Parkinson's disease

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Abbreviations

UPDRS Unified Parkinson's Disease Rating Scale

1350-7540

Introduction

Dopamine agonists are highly effective as therapy adjunctive to levodopa (L-dopa) in advanced Parkinson's disease, and are rapidly gaining popularity as monotherapy in the early stages of the illness. Since the introduction of bromocriptine in the 1970s, the number of dopamine agonists has increased substantially and the clinician is now presented with the fortunate dilemma of deciding which one of several dopamine agonists to prescribe.

Choosing a dopamine agonist is far from straightforward. There is no universally accepted first choice of dopamine agonist, and prescribing decisions are usually made on the basis of personal preference, experience with a particular agent, or a desire (by the clinician or patient) to try something new [1].

Differentiating between the dopamine agonists on the basis of their pharmacokinetics and receptor pharmacology reveals intriguing differences (see the Jenner review in this Supplement), which predict theoretical differences in anti-parkinsonian activity or safety profiles for each drug. But for the prescribing clinician, the real interest is in seeing if, and how, these differences translate into therapeutic benefits for the patient.

Unfortunately, the comparative data on which prescribing decisions might be based are relatively sparse. Very few controlled, well-designed studies directly comparing the efficacy and safety of the various dopamine agonists have been conducted [1]. Indirect comparisons of the newer dopamine agonists such as pergolide, ropinirole, cabergoline and pramipexole, based on recent randomized, controlled studies evaluating their efficacy as monotherapy in early Parkinson's disease, are hampered by differences in study design, patient characteristics, and concomitant anti-parkinsonian medications.

This review compares the efficacy and safety of the newer dopamine agonists, both as adjunctive therapy and as monotherapy in Parkinson's disease.

Dopamine agonists as adjunctive therapy

The majority of direct-comparator studies use the earliest dopamine agonist, bromocriptine, as the standard reference agent. This provides a useful way of comparing the effects of the dopamine agonists against each other as adjunctive therapy.

Comparisons with bromocriptine

Almost all dopamine agonists have been evaluated versus bromocriptine.

Table 1. Pergolide versus bromocriptine as adjunctive therapy [2–7]

Reference	Design of study	No. of patients	Duration of study	Disease stage	Mean pergolide dose (mg/day)	Results
LeWitt *et al.*, 1983 [2]	Double-blind, crossover	24	10 weeks	Advanced, 15; *de novo*, 11	3.3	Similar efficacy
Goetz *et al.*, 1985 [3]	Open	10	5 years	Advanced	3.8	Pergolide superior
Goetz *et al.*, 1989 [4]	Open	11	6 months	Advanced	Not given	Similar efficacy
Pezzoli *et al.*, 1994 [5][a]	Single-blind, crossover	68	26 weeks	Advanced	2.3 ± 0.8	Pergolide superior
Mizuno *et al.*, 1995 [6][a]	Double-blind, parallel group	345	8 weeks	Advanced, 192; *de novo*,153	1.24 ± 0.58 1.43 ± 0.58	Advanced: superior UPDRS with pergolide *de novo*: similar efficacy
Boas *et al.*, 1996 [7][a]	Open, crossover	33	24 weeks	Advanced	3.6 ± 1.1	Superior UPDRS with pergolide

UPDRS, Unified Parkinson's Disease Rating Scale. [a]Study included in the Cochrane Database Systematic Review [8].

Pergolide versus bromocriptine

There are six published studies that compare pergolide with bromocriptine: four were performed in patients with advanced Parkinson's disease and motor fluctuations, and two included both newly diagnosed and advanced patients (Table 1) [2–7]. In each of these studies, pergolide showed equivalent or superior efficacy relative to bromocriptine in terms of improvement in parkinsonian disability, particularly in activities of daily living and motor-examination scores [2–7].

A Cochrane database review of three short-term, randomized, controlled studies in which pergolide or bromocriptine was used as adjunctive therapy in patients with advanced Parkinson's disease confirmed the greater efficacy of pergolide [8]. Pergolide was superior to bromocriptine in improving parkinsonian motor impairment and disability – as rated by the Unified Parkinson's Disease Rating Scale (UPDRS) and the New York University Parkinson's Disease Scale – and scores for the activities of daily living. However, owing to a lack of data, no firm conclusions could be drawn regarding any reduction in L-dopa-induced motor complications in this analysis [8].

In a separate study in 12 patients with advanced Parkinson's disease and fluctuating motor disability and L-dopa-induced dyskinesias, pergolide significantly lengthened the 'on' mobilization period and also appeared to reduce the severity of onset and peak-dose dyskinesias [9]. Using a variant of the standard L-dopa test, patients receiving L-dopa were titrated to bromocriptine (15 mg/day) or pergolide (1.5 mg/day) plus the anti-emetic domperidone (30 mg/day) for 8 days, after which they were given a fasting challenge of 150 or 200 mg L-dopa together with either 1 mg pergolide or 10 mg bromocriptine. Pergolide and bromocriptine both produced similar improvements in motor disability, but pergolide sustained the 'on' duration for significantly longer than L-dopa alone or with bromocriptine [9].

Pramipexole versus bromocriptine

Pramipexole is a relatively 'new' non-ergot derivative with affinity for D_2 and D_3 receptors; the significance of the D_3 receptor in Parkinson's disease remains unknown. Only one randomized, double-blind, controlled trial has compared pramipexole with bromocriptine, and involved 247 patients with advanced disease and motor fluctuations [10]. In this study, both pramipexole and bromocriptine improved 'off' time and reduced parkinsonian motor impairments and disability compared with a placebo. Unfortunately, this study was not designed to examine the differences between active treatment arms, so no conclusions could be drawn about the comparative effectiveness and safety of the two drugs [10,11].

Ropinirole versus bromocriptine

Three randomized studies – two double-blind studies and one open-label switch study – compared the non-ergot derivative ropinirole and bromocriptine in patients with advanced or newly diagnosed Parkinson's disease (Table 2) [12–14]. In contrast to the findings with pergolide, the double-blind studies concluded that ropinirole was only similarly effective to bromocriptine; only patients in the open-label study showed an improvement after switching to ropinirole [12–14]. A Cochrane review of these studies showed that there were, in fact, no significant differences between ropinirole and bromocriptine in terms of reducing 'off' time, the L-dopa dose, or the incidence of dyskinesias and other adverse events (except for nausea, which was less frequent with ropinirole) [15].

Cabergoline versus bromocriptine

Cabergoline is an ergot derivative like pergolide, but is distinguished from the others in its class mainly by a long half-life of around 65 h. One randomized, double-blind, parallel group study of cabergoline versus bromocriptine in patients with advanced disease and fluctuating responses to L-dopa found that both drugs were equally effective [16]. These findings were confirmed in a Cochrane review, which concluded that cabergoline appeared to produce no significant reduction in 'off' time in comparison with bromocriptine [17]. This review found that there may even be a trend towards a higher frequency of dopaminergic adverse events

Table 2. Ropinirole versus bromocriptine as adjunctive therapy [12–14]

Reference	Design of study	No. of patients	Duration of study	Disease stage	Results
Brunt *et al*., 2002 [12]	Double-blind	550	6 months	Advanced	Similar efficacy
Korczyn *et al*., 1999 [13]	Double-blind	335	3 years	*De novo*	Ropinirole superior only in score for activities of daily living not in motor score
Canesi *et al*., 1999 [14]	Open, switch	22	4 weeks	Advanced	Better after switch to ropinirole

Table 3. Head-to-head comparisons of pergolide with other dopamine agonists as adjunctive therapy to levodopa [14,18–20]

Reference	Design of study	No. of patients	Duration of study	Disease stage	Results
Pramipexole					
Goetz *et al*., 1999 [18]	Open, switch	16 (pergolide, 8; bromocriptine, 8)	8 weeks	Advanced	Better after switch to pramipexole
Hanna *et al*., 2001 [19]	Open, switch	25	6 months	Advanced	No significant difference in UPDRS scores after switch
Ropinirole					
Canesi *et al*., 1999 [14]	Open, switch	68 (bromocriptine, 22; pergolide, 46)	4 weeks	Advanced	Better after switch from bromocriptine but not pergolide
Cabergoline					
Ulm and Schuler, 1999 [20]	Single-blind, crossover	48	20 weeks	Advanced	Similar efficacy

UPDRS, Unified Parkinson's Disease Rating Scale.

(confusion, hallucination and dyskinesia) with cabergoline in comparison with bromocriptine.

When the results of all of these studies are summarized, it is evident that pergolide showed superior efficacy relative to bromocriptine in reducing motor disability and improving parkinsonian symptoms in a majority of studies; the other dopamine agonists achieved efficacies that were only similar to that of bromocriptine.

Head-to-head comparisons

Direct comparisons of the dopamine agonists as adjuncts to L-dopa therapy in head-to-head studies are few, but those that exist are summarized below and in Table 3 [14,18–20].

Pergolide versus pramipexole

Two small, open-label studies have compared the efficacy of pergolide with pramipexole as adjunctive therapy in patients with advanced Parkinson's disease. In the first 8-week study by Goetz and colleagues [18] in 1999, 16 patients reported significantly lower UPDRS scores after overnight switching from either pergolide or bromocriptine to pramipexole.

In the second study, 25 patients with advanced Parkinson's disease and motor fluctuations converted from pergolide to pramipexole over a longer 1-month period and continued treatment for 6 months [19]. In this open study, although subjective patient reporting showed that 62% felt they had improved after the switch to pramipexole, there were no significant differences in UPDRS scores between the two drugs [19]. These findings show that the results of open-label studies need to be interpreted with caution, especially if they rely on the subjective reports of patients who know they are taking a new drug and consequently have expectations of its efficacy.

Pergolide versus ropinirole

In the only head-to-head comparison of pergolide and ropinirole as adjunctive therapy in patients with advanced Parkinson's disease, pergolide was as effective as the newer agonist. In this open-label switch study, patients who were switched from bromocriptine to ropinirole reported significant improvements in UPDRS scores, but those who switched from pergolide to ropinirole showed no improvement. Instead, many patients, after switching from pergolide to ropinirole, had to return to pergolide treatment to regain efficacy [14].

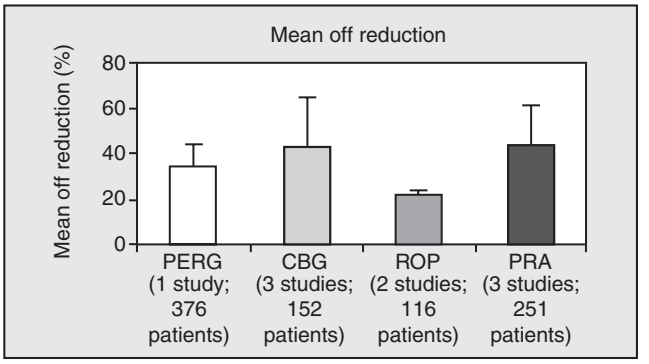
Pergolide versus cabergoline

In a single-blind, crossover study that compared pergolide with cabergoline in 48 patients with advanced Parkinson's disease, significant improvements in the duration of 'on' and 'off' time were achieved for both drugs compared to the baseline ($P < 0.05$), but, again, there was no difference between treatments [20].

These direct comparisons clearly show that pergolide is highly effective in improving motor function and parkinsonian symptoms in patients for whom L-dopa alone is no longer effective. Moreover, its efficacy is at least comparable to that of the newer dopamine agonists.

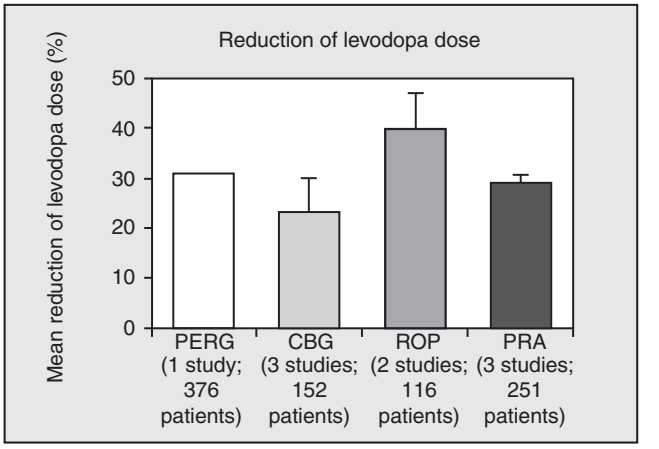
No head-to-head studies directly compare all five dopamine agonists with each other when used as adjuncts to L-dopa. Indirect comparisons reveal no clear 'leader' among the dopamine agonists that could influence a choice made on the basis of efficacy alone; all of the dopamine agonists demonstrate similar reductions in

Figure 1. Indirect comparison between dopamine agonists in advanced Parkinson's disease (controlled studies versus placebo), showing mean 'off' reduction [21–29]



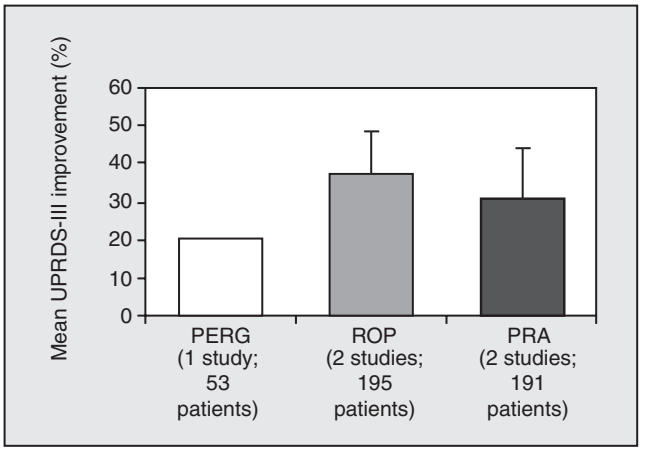
CBG, Cabergoline; PERG, pergolide; PRA, pramipexole; ROP, ropinirole.

Figure 2. Indirect comparison between dopamine agonists in advanced Parkinson's disease (controlled studies versus placebo), showing reduction of the levodopa dose [21–29]



CBG, Cabergoline; PERG, pergolide; PRA, pramipexole; ROP, ropinirole.

Figure 3. Indirect comparison of dopamine agonists in newly diagnosed Parkinson's disease, showing mean improvements in Unified Parkinson's Disease Rating Scale-III [31–35]



PERG, Pergolide; PRA, pramipexole; ROP, ropinirole; UPDRS-III, Unified Parkinson's Disease Rating Scale-III.

mean 'off' time and in mean L-dopa dose (Figs 1 and 2) [21–29].

Comparing the dopamine agonists as monotherapy

There is now significant evidence supporting the use of dopamine agonists as first-line monotherapy in newly diagnosed patients [30]. However, in terms of efficacy, again there is little to choose between the established and newer dopamine agonists. In patients newly diagnosed with Parkinson's disease, pergolide, ropinirole and pramipexole all produce comparable improvements (of around 20–30%) in UPDRS-III scores (Fig. 3) [31–35].

Four major long-term studies with ropinirole, pramipexole, cabergoline and pergolide have evaluated the effects of these dopamine agonists, in comparison with L-dopa, in the prevention of motor complications in patients with newly diagnosed Parkinson's disease (Table 4) [36–39]. The findings show that all of them significantly reduced the incidence of dyskinesias and/or motor fluctuations in comparison with L-dopa (Fig. 4) [36–39]. In the monotherapy study with pergolide, so far reported only in abstract form [39], no other anti-parkinsonian medications or open L-dopa rescue were allowed. This is a significant variation in the protocol compared to the other studies, making the results obtained with pergolide even more compelling.

Comparison of the most frequent dopaminergic adverse events in these studies shows that pramipexole and ropinirole seem to be associated with higher frequencies of somnolence and hallucination in comparison with cabergoline and pergolide (Table 5) [36–39]; pergolide was associated with a slightly higher frequency of nausea than the other dopamine agonists. This side-effect can be avoided by careful titration and, if necessary, co-administration of an anti-emetic such as domperidone.

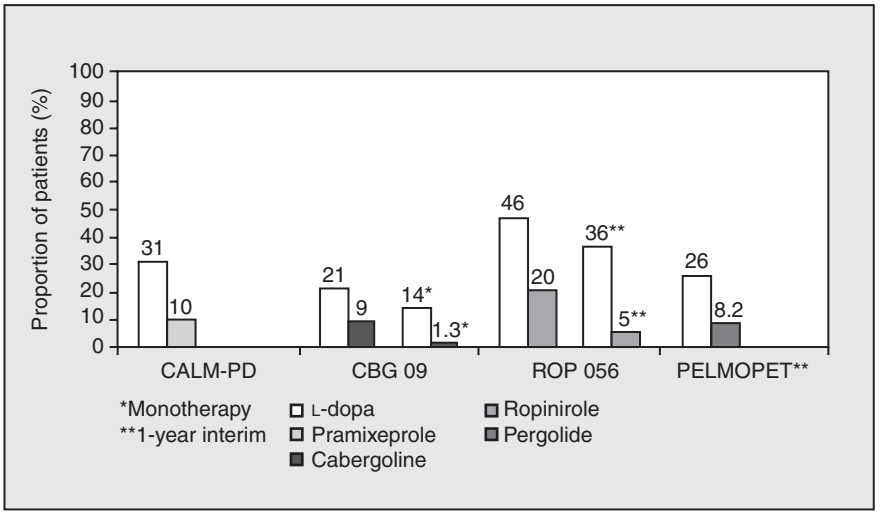
The finding of a lower incidence of somnolence with pergolide monotheraphy might be, at least partially, due to the fact that concomitant L-dopa was not administered. However, it could be particularly relevant given the recent concerns raised over sudden onset of sleep with dopamine agonists. The first report of nine cases of sudden onset of sleep in Parkinson's disease patients taking ropinirole or pramipexole, described by Frucht *et al.* in 1999 [40], was followed by an explosion of reports of somnolence or sudden onset of sleep with other dopamine agonists [41–47].

Table 4. Studies of the dopamine agonists as monotherapy, in comparison with levodopa (L-dopa), for the prevention of motor complications in early-onset Parkinson's disease [36–39]

Reference	Study	Drug	Mean daily dose (mg/day)	Duration (years)
Parkinson Study Group, 2000 [36]	CALM-PD	Pramipexole	2.87	2
Rascol *et al.*, 2000 [37]	Study 056	Ropinirole	16.5	5
Rinne *et al.*, 1998 [38]	Study 09	Cabergoline	2.7	5
Oertel *et al.*, 2001 [39]	PELMOPET	Pergolide	3.23	3

CALM-PD, Comparison of the agonist pramipexole with L-dopa on motor complications of parkinson's disease; PELMOPET, Pergolide versus L-dopa as monotherapy in early Parkinson's disease.

Figure 4. Effect of dopamine agonist monotherapy, in comparison with levodopa (L-dopa), on the development of dyskinesias [36–39]



CALM-PD, Comparison of the agonist pramipexole with L-dopa on motor complications of parkinson's disease; CBG, cabergoline; ROP, ropinirole; PELMOPET**, pergolide versus L-dopa as monotherapy in early Parkinson's disease.

Table 5. Dopamine agonist monotherapy in preventing motor complications – indirect comparison of adverse events (%) in different studies [36–39]

	CALM-PD [36]		ROP 056 [37]		CBG 09 [38]		PELMOPET [39]	
Adverse event	PRA	L-dopa	ROP	L-dopa	CBG	L-dopa	PERG	L-dopa
Nausea	36	36	39	32	37	32	41	21
Somnolence	32	17	22	12	26[a]	28[a]	10	5
Hallucination	9	3	17	6	4	5	3	0

CALM-PD, Comparison of the agonist pramipexole with levodopa on motor complications of parkinson's disease; CBG, cabergoline; PELMOPET, pergolide versus levodopa (L-dopa) as monotherapy in early Parkinson's disease; PERG, pergolide; PRA, pramipexole; ROP, ropinirole. All percentages are rounded to the nearest whole number. [a]Includes sleep disorders and insomnia.

Excessive daytime sleepiness is common among patients with Parkinson's disease [48]. However, the incidence of sudden onset of sleep, controversially defined as an 'event of overwhelming sleepiness that occurs without warning' [49], is relatively rare [48] but is a concern, as these episodes might occur whilst the subject is driving [40].

The precise relationship of the dopamine agonists to sudden onset of sleep remains to be determined. As a class, all of the dopamine agonists have a sedating, probably dose-related, effect [50], although agonists that activate the D_2/D_3 receptors (e.g. ropinirole and pramipexole) may be more likely to induce irresistible somnolence than those that stimulate the D_1/D_2 receptors [40].

Although fewer cases of sudden onset of sleep are reported with pergolide than with other dopamine agonists, in recent epidemiological surveys no significant difference between old and new dopamine agonists was evident in terms of sleep attacks and daytime sleepiness frequency [51].

Conclusion

Administered as adjuncts to L-dopa, all dopamine agonists offer patients significant improvements in motor

disability and parkinsonian symptoms when compared with L-dopa alone, particularly in subjects with advanced disease for whom L-dopa is becoming less effective. At the doses used in published studies, adjunctive therapy with pergolide produces the same improvements as the 'newer' dopamine agonists; the question of whether even greater efficacy could be achieved if all patients were titrated to higher daily pergolide doses remains an interesting one.

Similar equivalence in efficacy is seen when the dopamine agonists are used as monotherapy. As a class, the dopamine agonists appear to reduce the incidence of dyskinesias significantly in comparison with L-dopa. The L-dopa-sparing effects and the putative role as neuroprotective agents mean that the use of the dopamine agonists as monotherapy in early-onset Parkinson's disease is rapidly expanding.

Although the efficacies of the different ergot and non-ergot dopamine agonists in the treatment of Parkinson's disease seem largely similar, it is impossible, however, to form any reasonable conclusions, especially between pergolide and 'newer' compounds, such as cabergoline, pramipexole and ropinirole, in the absence of direct, head-to-head comparative studies.

As far as tolerability and safety are concerned, indirect comparison between dopamine agonists is even more difficult because of the different means of reporting and collecting drug-related adverse events in different studies. Amongst the very rare dopamine agonist-related complications, there is compelling evidence that with ergot compounds, such as bromocriptine and pergolide, serosal fibrosis (retroperitoneal, pleural and pericardial fibrosis) occurs more frequently than with the non-ergot dopamine agonists [52]. This apparently higher incidence of fibrotic reactions during long-term treatment with bromocriptine and pergolide may be biased by their more worldwide availability and use resulting from the longer period of time that has elapsed since their approval for launch.

Clinicians are now in the enviable position of having a wide range of effective dopamine agonists in their therapeutic arsenal, yet the task of choosing the most appropriate ones for their patients remains a core issue. Prescribing decisions will continue to be made on the basis of drug profiles and personal preference, and will undoubtedly continue to be influenced by the quality of the available data.

Further well-designed, controlled, head-to-head, comparative studies are needed to demonstrate whether a difference between the many old and new dopamine agonists now available for the treatment of Parkinson's disease does exist in terms of both efficacy and safety.

Conflict-of-interest statement

Professor Bonuccelli is the recipient of a research grant from TEVA, Pharmacia and GlaxoSmithKline. He is a consultant for Pharmacia, Eli Lilly and Company and BristolMeyerSquibb.

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