DOI 10.1007/s00702-003-0059-x
J Neural Transm (2004) 111: 1375–1446

Journal of Neural Transmission
Printed in Austria

Dopamine receptor agonists in the therapy of Parkinson's disease

P. Foley[1,2], **M. Gerlach**[1,3], **K. L. Double**[1,2], and **P. Riederer**[1]

[1] Clinical Neurochemistry, Clinic for Psychiatry and Psychotherapy, University of Würzburg, Germany
[2] Prince of Wales Medical Research Institute, Randwick, Australia
[3] Child and Adolescent Psychiatry, Clinic for Psychiatry and Psychotherapy, University of Würzburg, Germany

Received December 3, 2002; accepted September 4, 2003
Published online December 29, 2003;

Summary. Forty years after its introduction by Birkmayer and Hornykiewicz (1961), L-DOPA-based therapy of Parkinson's disease remains the central pillar in the management of the disorder. Nevertheless, it is not unproblematic, and dopamine receptor agonists play increasingly important roles in antiparkinsonian therapy. Pharmacological and pharmacokinetic properties of these agents are briefly reviewed and followed by a detailed summary of available literature concerning controlled trials in Parkinson's disease. It is concluded that there is little unequivocal evidence to suggest that any of the major dopamine receptor agonists should be invariably preferred in the therapy of Parkinson's disease; their application must be based on the needs and responses of individual patients.

Keywords: Parkinson's disease, dopamine receptor agonists, clinical trials.

L-DOPA-based therapy remains the central pillar in the management of Parkinson's disease, forty years after its introduction by Birkmayer and Hornykiewicz (1961). It was recognized quite early, however, that L-DOPA therapy itself is accompanied by certain problems, most notably the abnormal movements (dyskinesias) which most patients develop after an extended period of treatment, and the decrease in duration of response to a given L-DOPA dose (that is, an increase in length of 'off' periods). The proportion of patients experiencing such difficulties has been estimated as being up to 50% after five years of L-DOPA therapy (Miyawaki et al., 1997); in younger onset patients, this figure approaches 100% after a similar period (Golbe, 1991).

Dopamine receptor agonists have thus enjoyed increasing popularity in antiparkinsonian therapy since the introduction of bromocriptine by Donald Calne and colleagues in 1974. Their major value was long regarded as being their

function as adjunct therapies aimed at reducing the untoward motor effects of L-DOPA therapy. More recently, dopamine receptor agonist monotherapies have gained ground in the clinic, partly as a means for postponing initiation of L-DOPA therapy. Such deferral has been partially motivated by the putative neurotoxicity of L-DOPA, which would suggest that its application early in the disease might be partially counterproductive, while the presentation and severity of dyskinesias and motor fluctuations also appear to be delayed and reduced in intensity if L-DOPA therapy commenced as late as possible. Secondly, direct receptor activation with specific agonists might be expected to elicit a more specific and controllable panel of effects than is achieved by administration of a transmitter precursor to patients with a damaged extrapyramidal system. Finally, there is evidence that dopamine receptor agonists (and MAO-B inhibitors; Foley et al., 2000) exert direct anti-oxidative and neuron-rescuing effects, at least in the laboratory; this may involve reduced dopamine turnover following stimulation of autoreceptors, leading to reduced availability of extracellular dopamine for oxidative processes, as well as direct 'scavenging' of free radicals.

The current review will not examine in detail the mechanisms by which dopamine receptor agonists achieve their effects; for discussion of such issues the reader is referred to Sit (2000) and Le and Jankovic (2001). The question to be addressed here is whether significant clinical differences between the currently available dopamine receptor agonists have been demonstrated, a question of both theoretical and practical interest. There are undoubtedly pharmacological differences between the various agonists, as briefly discussed below; if these differences have clinical consequences, insights into the neurochemical pathology of parkinsonism might be gained by carefully analyzing differences in their effects. From a practical point of view, the clinician needs to know whether the choice of agonist, which may be influenced as much by the relative price of the alternatives as by pharmacological factors, will have significant therapeutic consequences for the patient.

Similar questions have always been a part of antiparkinsonian therapy, whether the choice was between a variety of solanaceous plant extracts and purified alkaloids, as was the case before the Second World War, or between the bewildering range of synthetic anticholinergic agents which became available from 1948 onwards. Review of the literature reveals that a consensus regarding the answers to such questions was rarely reached, primarily because there existed no consensus with regard to how the effectiveness of drugs should be assessed. This situation has recently improved considerably, although not to the point where trials of antiparkinsonian drugs are conducted according to a standardized procedure. Nevertheless, it is now generally accepted that for a trial to be easily interpreted and comparable with other trials, it should be double blind, placebo-controlled (at least where a direct comparison between two alternative agents is not made), employ a parallel design with randomized allocation of patients to treatment groups, and, preferably, be conducted on a multicentre basis. The duration of the trial and the type of patients included are also crucial factors to be considered, as is the protocol for administration of the test agent. Regulatory authorities have published recommendations for the construction of

clinical trials required for registration purposes (for example: EMEA, 1998), but it is nevertheless recognized, for example, that a minimum of one hundred subjects per group are required to lend even well controlled trials the necessary statistical power for detection of significant therapeutic effects.

Another issue which must be addressed is that of the appropriate endpoints for clinical studies of antiparkinsonian medications. As will be noted from the tables in this paper, there as yet no consensus on how the efficacy of these agents should be assessed; a variety of instruments (such as the Unified Parkinson's Disease Rating Scale (UPDRS), Clinical Global Impressions Scale (CGIS), Schwab & England (S&E) and parts thereof), patient diaries and, more recently, imaging techniques have been employed to assess the effects of dopamine receptor agonists, so that drug comparisons are also made difficult by the different treatment outcomes employed. The UPDRS appears to be establishing itself as a partial standard in this area, but the use of other and novel assessment methods can be expected to continue, and should naturally be accepted under the appropriate circumstances.

Published trials of dopamine receptor agonists which satisfy the criteria discussed here have until recently been few in number, and variations within the described framework still render direct comparisons difficult. Nonetheless, cautious comparison of the results of such trials will form the bulk of this review. Medline and EMBASE were searched in order to locate published trials. Preference was given to trials published as full papers in peer-reviewed journals; it should be noted, however, that some trials were reported up to four years earlier as conference presentations/abstracts. Finally, in order to restrict attention to the employment of the discussed agents under reasonably comparable conditions, attention was focussed upon studies investigating orally administered dopamine receptor agonists; apomorphine studies have thus not been included.

The current paper is not a 'meta-analysis' of the described studies, but rather a compact summary of their major findings by the interested reader, an approach preferred by the authors as it consciously avoids obscuring the differences between various research strategies. This is especially true as clinical trials in antiparkinsonian therapy, in contrast to those for somatic disorders, such as cardiac disease and cancer, tend to be much smaller, so that the findings of individual trials are of comparatively lower predictive value. The specific deficiencies of antiparkinsonian medication trials have recently been discussed by Wheatley and colleagues (2002), and will not be pursued here.

The dopamine receptor agonists considered in this review fall into two major classes: ergolines (bromocriptine, pergolide, lisuride, cabergoline) and non-ergolines (piribedil, pramipexole, ropinirole). Ergolines, derivatives of ergot alkaloids, have a longer history in antiparkinsonian therapy than non-ergolines, which were developed in the hope that they might provide the benefits of the ergoline agents without their side effects. Further ergolines (for example, α-dihydroergocryptine, terguride) and non-ergoline dopamine receptor agonists (quinagolide, N-0423, talipexole, piroheptine) have also been trialled in Parkinson's disease, but the paucity of studies of the type described above necessarily limits their discussion in this review (Fig. 1).

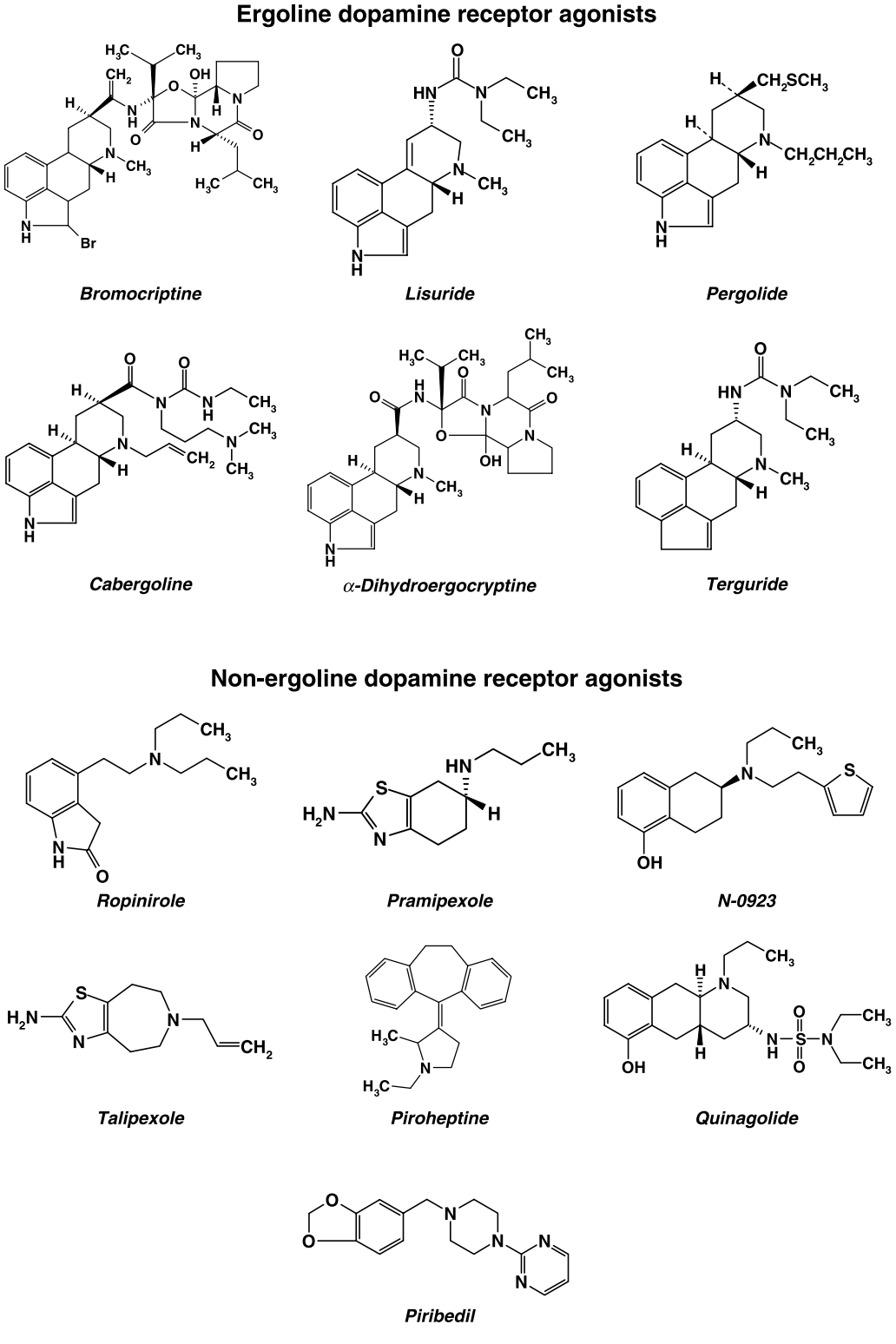

Fig. 1. The major dopamine receptor agonists employed in the therapy of Parkinson's disease

I. Pharmacological and pharmacokinetic characteristics of dopamine receptor agonists

The pharmacological properties of the dopamine receptor agonists discussed in this review are summarized in Table 1. The older agents bind with high affinity to D_2 receptors, but are clearly anything other than pure D_2 receptor or even D2 family receptor-binding agents, with affinity of varying degrees not only for D_1 receptors but also for adrenergic and serotonergic receptors. The newer agents (ropinirole, pramipexole) are more specific, in that they bind only D2 family receptors with high affinity; pramipexole is different from all the other agents in that its reported affinity for the D_3 receptor is almost an order of magnitude greater than that for the D_2 receptor. Nevertheless, caution must be advised in the interpretation of relative binding data for the various agents, as there exists considerable spread in reported estimates of binding affinity, particularly to the D_2 receptor.

Table 1. Overview of literature on pharmacological data for dopamine receptor agonists

	Dopamine receptors					Noradrenaline receptors			5HT receptors
	D_1	D_2	D_3	D_2:D_3	D_4	α_1	α_2	β	
Bromocriptine	0/±	++	+/++	0.1	+	+/++	+/++	0	++ ($5HT_{1A}$) + ($5HT_2$)
Cabergoline	+	+++	++	–	++	+	+	ND	+
α-Dihydroergocryptine	±	+++	ND	–	ND	ND	ND	ND	ND
Lisuride	−/±	+++	+++	0.2	+++	±/++	±/+++	ND	±/+++
Pergolide	+	+++	+++	1.0	+++	±/+	++	0/+	+++ ($5HT_{1A}$) ++ ($5HT_2$)
Piribedil	+	+++	+++	–		+++	+++/−	0	+ ($5HT_{1A}$)
Pramipexole	0	+++	+++	7.6	++	0	+	0	0
Ropinirole	0	+++	++	0.4	0	0	0	0	0

K_i (nM): +++ 0–10; ++ 10–100; + 100–1000; 0 > 1000; ± partial agonist; – antagonist; *ND* no data. No measurable binding to acetylcholine receptors has been reported. Based on data in Sautel et al. (1995), Piercey et al. (1996), Watts (1997), Perachon et al. (1999), Sit (2000), Millan et al. (2001, 2002), Deleu et al. (2002)

Table 2. Affinity of dopamine receptor agonists for dopamine receptors in human putamen tissue, based on dissociation constants derived from competition binding experiments (K_i; nM). All results reported by Gerlach et al. (2003)

	D_1 [^{3}H]SCH23390	D_2 [^{3}H]Spiperone	D_3 [^{3}H]PD128907	D_2:D_3
α-Dihydroergocryptine	35.4	4.7	26.3	0.2
Bromocriptine	119.6	4.9	30.5	0.2
Cabergoline	1462	1.6	1.3	1.3
Lisuride	56.7	1.2	1.1	1.1
Pergolide	447	36.6	0.9	43
Pramipexole	>100000	473.4	1.0	488
Ropinirole	>100000	3277	34.9	94

Table 3. Summary of published data on the pharmacokinetic characteristics of the dopamine receptor agonists

	Oral bio-availability (%)	Plasma protein binding (%)	t_{max} (h)	$t_{½}$ (h)	Metabolism/ elimination	Excretion	Linearity of kinetics	Distribution volume ($L \cdot kg^{-1}$)	Typical daily dose (mg/doses)
Bromocriptine	3–8 26*	90–95	1–3	3–8; 15 (biphasic)	Extensive; hepatic	Biliary: 95% Renal: 2.5–5.5%	ND	~4.0	10–40/3
Lisuride	10–20	60–70	0.2–3	2–3	Complete; hepatic/renal	Renal: 90%	ND	~2.5	0.6–5/3
Pergolide	20–60*	>90	1–3	7–27	Complete; hepatic/renal	Renal: 55%	ND	17–32	1.5–5/3
Cabergoline	<20/50–80	40	0.5–4	65–110	Extensive; hepatic	Fecal: 60% Renal: 22%	yes	ND	2–6/1
Piribedil	<10	75?	1	2–5	Extensive; hepatic/renal	ND	ND	ND	150–250/3
α-DHEC	2.4–5	50–55	1.6	15	Complete; hepatic	ND	ND	ND	60–120/2–3
Pramipexole	>90	15–20	1–3	8–12	Minimal; (~10%) renal	Renal: 90%	yes	6–7	0.375–4.5**/3
Ropinirole	~50	10–40	0.5–5	3–6	Extensive; hepatic/renal	Renal: 88%	yes	7–8	3–24/3

ND no data; * Includes (generally inactive) metabolites; ** Refers to pramipexole salt. Based on Watts (1997), Brecht (1998), Kuzel (1999), Colosimo and de Michele (2000), Contin et al. (2000), Lledó (2001), Deleu et al. (2002); USP DI (2002)

Table 4. Abbreviations used in Tables 5 to 17. In all tables, the symbol '>' is to be interpreted as 'more effective than'. Shaded boxes indicate comparison with another agent, white boxes comparison with placebo or no control

Agents	Pl	placebo	Ro	ropinirole
	Br	bromocriptine	Pe	pergolide
	Ca	cabergoline	Pr	pramipexole
	DP	deprenyl	Pi	piribedil
	L-D	L-DOPA	α-DHEC	α-dihydroergocriptine
	Li	lisuride		
Subjects	$\bar{A}$	mean age	H-Y	mean Hoehn-Yahr stage
	$\bar{D}$	mean duration of L-DOPA therapy	$\bar{O}$	mean duration of parkinsonism
	$\bar{d}$	mean L-DOPA dose	(number)	Number of subject dropouts
Study design	C/O	crossover	O/L	Open label
	D/B	double blind	P	parallel
	exper.	experimental	Prosp.	prospective
	M	matched	R	randomized
	maint.	maintenance	S/B	single blind
	MC	multicentre	titr.	titration
	mo	month(s)	wk	weeks
	n.g.	not given	y	year(s)
Subjects and Results	ADL	activities of daily living	PDQ	Parkinson's Disease Questionnaire
	CGIS	Clinicians' Global Impression Scale	S&E	Schwab & England score
(where used in 'Subjects' column: mean score for group)	CURS	Columbia University Rating Scale	SIP	Sickness Impact Profile
	GIR	Global Impressions Rating	UPDRS	Unified Parkinson's Disease Rating Scale
	NS	not significant	UPDRS-II	UPDRS Activities of Daily Living Scale
	NUDS	Northwestern University Disability Scale	UPDRS-III	UPDRS Objective Motor Examination Scale
	NYUPDS	New York University Parkinson's Disease Scale	UPDRS-IV	UPDRS Complications of Therapy Scale: IVa: dyskinesia scale IVb: clinical fluctuations scale

Further, there may also exist differences between the binding characteristics of certain agents to reconstituted dopamine receptors in model systems and to human basal ganglia dopamine receptors. The only major comparative study of binding in human striatum of the range of currently available dopamine receptor agonists found that the affinity of the newer agents (pramipexole and ropinirole) for D_2 receptors was minimal, so that these agonists might be regarded as fairly specific D_3 receptor agonists, contrasting with previous reports in model systems (Gerlach et al., 2003). Similarly, the 'classic' D_1 receptor agonist pergolide did not exhibit great affinity for the D_1 receptor in this study, a finding also reported by de Keyser et al. (1995) in their investigation of dopamine receptor agonists in human striatum. Gerlach et al. (2003) also identified that three of the older dopamine receptor agonists acted as antagonists at the D_1 receptor, while cabergoline, lisuride and pergolide exhibited affinity for the D_3 receptor similar to that of pramipexole (Table 2). As results in human basal ganglia tissue are clearly more relevant to the clinical action of dopamine receptor agonists than other models, these results will certainly provoke new thinking regarding the roles of individual dopamine receptors in the pharmacology of parkinsonism and its therapy.

Pharmacokinetic properties of dopamine receptor agonists are summarized in Table 3. Differences with respect to these features are also evident; the broadest generalizations possible on the basis of the data appear to be that the bioavailability of the newer agents tends to be greater than that of the older dopamine receptor agonists, reflecting the greater hepatic metabolism of the latter; the reduced protein binding of the newer agents also reduces pharmacokinetic interactions with other protein-bound medications.

There thus exist demonstrable physical differences between the physiological responses of the body to the various dopamine receptor agonists. It is not our intention, however, to discuss these differences further, but rather to move directly to the question of whether these differences have significant consequences for the clinic of these agents.

II. Clinical effectiveness of dopamine receptor agonists

1. Dopamine receptor agonists as adjuncts to L-DOPA therapy

(a) Bromocriptine (Table 5). Bromocriptine was the first dopamine receptor agonist to be accepted into standard antiparkinsonian therapy, and continues to serve as the yardstick against which novel agonists are measured. It is thus unsurprising that a number of controlled studies directly comparing bromocriptine and alternative agents have been conducted, although bromocriptine agonist itself was introduced and accepted before controlled, randomized studies were the norm. Nevertheless, a number of larger studies of its effectiveness as an adjunct to L-DOPA have been conducted in recent years, though rarely placebo-controlled. In general, it has been found that patients receiving bromocriptine as adjunct require lower L-DOPA doses and experienced motor complications only at a later time point.

(b) Lisuride (Table 6). The size of the few randomized, controlled studies has been quite small, making firm conclusions difficult. The results suggest,

Table 5. Bromocriptine as adjunct to L-DOPA therapy in Parkinson's disease

Study	Control	Subjects		Design	Duration	Mean end daily dose	Results
Toyokura et al. (1985)	Pl	Br: 114 (27) $\bar{A}$ = 62½ y H-Y: 3.0 $\bar{O}$ = 5.7 y $\bar{D}$ = 5.7 y $\bar{d}$ = 418 mg	Pl: 108 (17) $\bar{A}$ = 63 y H-Y: 3.2 $\bar{O}$ = 7.5 y $\bar{D}$ = 7.5 y $\bar{d}$ = 465 mg	DB MC (59 Japan)	8 wk	16.7 mg	• Semiquantitative, four-point assessment scales used • Showed improvement in global improvement rating: Br > Pl (29% patients v. 14.8%; similar for all H-Y stages) • Wearing-off, freezing: Br > Pl • Akinesia: Br > Pl (27% v. 20%) • Gait: Br > Pl (27% v. 21%) • Tremor: Br = Pl (37% v. 25%) • Rigidity: Br = Pl (25% v. 21%) • Side effects: Br = Pl
Bakheit et al. (1990)	Pl	Br: 16 (3) $\bar{A}$ = 57 y H-Y: 2.0 $\bar{O}$ = 32.8 mo $\bar{D}$ = 10.3 mo $\bar{d}$ = 376 mg NUDS: 45.0	L-D: 15 (1) $\bar{A}$ = 59 y H-Y: 2.1 $\bar{O}$ = 29.5 mo $\bar{D}$ = 11.3 mo $\bar{d}$ = 430 mg NUDS: 45.4	R DB	1 y (ongoing)	Br: 25 mg L-D: (−Br): 136 mg (+Br): 361 mg	• L-DOPA dose reduction: Br > Pl (240 mg = 64% v. 69 mg = 16%; at 6 mo, 4 Br-patients no longer using L-DOPA) • Disability: no significant change in NUDS scores of either group (Br: 46.4 at 6 mo, 46.0 at 12 mo v. 45.6 at 6 mo, 45.5 at 12 mo); but difference Br > Pl reported to be significant • Adverse events: Br = Pl (8 v. 7 cases)

(*continued*)

Table 5 (*continued*)

Study	Control	Subjects		Design	Duration	Mean end daily dose	Results
Olsson et al. (1990)	–	Br/L-D: 137 (16) $\bar{A} = 58$ y $\bar{D} = 10.2$ mo $\bar{d} = 352$ mg H-Y: 1.9	L-D: 140 (14) $\bar{A} = 59$ y $\bar{D} = 10.6$ mo $\bar{d} = 420$ mg H-Y: 2.0	R O/L M/C (9 European countries)	1 y (ongoing)	Br: 13 mg L-D: (−Br): 352 mg (+Br): 420 mg	• Webster scale: Br/L-D ≥ L-D • NUDS score: Br/L-D = L-D • L-DOPA dose: Br/L-D > L-D (−6% v. +7%)
Nakanishi et al. (1991)	Pl	Br: 286 (122) $\bar{A} = 61$ y H-Y: 2.6 de novo, no L-DOPA	L-D: 200 (50) Br/L-D: 216 (86) $\bar{A} = 61$ y H-Y: 2.3/2.6 de novo, prior L-DOPA (<5 y)	Partly R	4 y (ongoing)	Br: 11.3 ± 4.5 mg Br/L-D: Br 10.9 ± 4.5 mg L-D 386 ± 186 mg L-D: 397 ± 181 mg	• At end of 4 y: 74 patients in Br group treated with Br, 78 with Br/L-DOPA, 1 with L-DOPA 123 patients in Br/L-D group treated with Br/L-D, 6 with L-DOPA 22 patients in L-D group treated with L-DOPA/Br, 114 with L-DOPA • No significant effect of either drug on dose of the other; L-DOPA dose increased slowly with time, Br dose stable since 9 mo • All three groups experience declining effect with time, especially on akinesia and gait; improvements in daily life lost by end of 4 y • H-Y at 1 y: Br 2.1, Br/L-D 2.2, L-D 2.2; at 4 y: Br 2.4, Br/L-D 2.5, L-D 2.5 • Wearing off and dyskinesia: less in Br group; usually after start of L-DOPA therapy

patient data for patients involved at 4 y:
Br (n = 74): $\bar{A} = 62$ y; $\bar{O} = 19$ mo (on entry); H-Y: 2.1 ▶ 2.2

Br, L-DOPA added (n = 78): : $\bar{A} = 59$ y; $\bar{O} = 25$ mo (on entry); H-Y: 2.4 ▶ 2.5

Br/L-D (n = 123): $\bar{A} = 60½$ y; $\bar{O} = 49$ mo (on entry); H-Y: 2.5 ▶ 2.5
L-D (n = 114): $\bar{A} = 60$ y; $\bar{O} = 38$ mo (on entry); H-Y: 2.2 ▶ 2.4

Kuno (1993)	Pl	Br: 30 (successful Br patients from Nakanishi et al., 1991)	Br/L-D: 66	O/L follow-up	1 y	Br: 11.9 mg Br/L-D: 12.2 mg	• H-Y: improved in 30%, declined in 20% (Br alone) v. improved in 18%, declined in 42% (Br/L-D)
Kowa et al. (1997)	–	Br: 11 (monotherapy since beginning of study) Data at commencement of study: $\bar{A} = 65$ y $\bar{O} = 14.8$ mo H-Y: 1.5	Br/L-D: 35 (L-DOPA added at some point in study) $\bar{A} = 57$ y $\bar{O} = 23.5$ mo H-Y: 2.1	O/L follow-up	9th year follow-up of Nakanishi et al., 1991 study	Br: 11.1 mg Br/L-D: Br: 12.7 mg L-D: 351 mg	• H-Y: improved in 2 patients, stable in 5, declined in 4 (Br alone) v. improved in 4, stable in 11, declined in 20 (Br/L-D) • Br levels stable for past 7 y; only slight increased in L-DOPA during past 4 y (see also Tashiro et al., 1996 for 8 y follow-up)
Przuntek et al. (1992, 1996)	–	Br: (285) $\bar{A} = 65$ y H-Y: 2.2 $\bar{O} = 18$ mo $\bar{D} = 2.5$ mo prior L-DOPA: 31.8% Median Webster rating: 9.0	L-D (302) $\bar{A} = 65$ y H-Y: 2.2 $\bar{O} = 20½$ mo $\bar{D} = 2.7$ mo prior L-DOPA: 30.5% Median Webster rating: 10.0	R MC (27; Germany, Hungary)	3 mo L-DOPA monother. 4 y exper.[1]	Br/L-D: Br: 13.8 ± 7.1 mg L-D: 310 ± 140 mg L-D alone: 440 ± 170 mg	• At end of L-DOPA monotherapy phase, L-DOPA dose in Br group was 395 ± 134 mg, in monotherapy group 392 ± 147 mg; ~15.5% of each group received ≥ 625 mg. At same time, Webster rating had improved to 6.9 (Br/L-D) and 7.0 (L-D) • Webster scale: L-D = Br/L-D over 4 y; mean score lowest in both at 9 mo, followed by gradual rise • H-Y stage: Number of improvers (Br/L-D 36½% v. L-D 38%) and deteriorated (9% v. 11%): Br/L-D = L-D • Motor side effects: Br/L-D > L-D (29% v. 20%); reduced risk associated with greater Br substitution

(*continued*)

Table 5 (*continued*)

Study	Control	Subjects		Design	Duration	Mean end daily dose	Results
Montastruc et al. (1994, 2001)	–	Br: 31 (1) $\bar{A} = 62$ y H-Y: 1.7 $\bar{O} = 2.6$ y L-DOPA added after 3 y	Br/L-D: 29 (1) $\bar{A} = 59$ y H-Y: 1.6 $\bar{O} = 2.5$ y follow-up time: 10.3 y	R O/L	5y + mean 5.3 y follow-up	Br: 52 ± 5 L-D (−Br): 569 ± 47 mg L-D (+Br): 471 ± 46 mg	• Motor complications: Br/L-D > L-D (14 cases v. 26; of which dykinesia: 3 v. 14 cases); appeared later in combination group (4.9 v. 2.7 y from commencement of treatment) • Wearing off: Br/L-D = L-D (10 v. 10 cases), but appeared later in combination group (4.5 y v. 2.9 y) • UPDRS-III: Br/L-D = L-D (10.6 v. 11) • Probability of survival at 10 y: Br = Br/L-D (79% v. 73%)
Giménez-Roldán et al. (1997)	Pl	Br: 27 (6) $\bar{A} = 61$ y H-Y: 1.5 $\bar{O} = 9.0$ mo $\bar{d} = 492$ mg UPDRS: 28.8 UPDRS-III: 19.4	Pl: 23 (4) $\bar{A} = 60$ y H-Y: 1.6 $\bar{O} = 7.4$ mo $\bar{d} = 479$ mg UPDRS: 28.8 UPDRS-III: 17.0	R D/B (part) MC (5; Spain)	8 mo (fixed B dose: 15 mg) + 5y O/L follow-up	Br: 24.2 ± 5.7 mg L-D: (−Br): 726 mg (+Br): 515 mg	• UPDRS: Br > Pl (−10.0 points = 35% v. +6.8 = 24%) • UPDRS-III: Br > Pl (−6.7 = 39% v. +3.2 = 16%) • Fluctuations and dyskinesia: Br > Pl (14% v. 47%) • L-DOPA dose: significantly lower dose in Br group in follow-up period (but not at end of 8 mo L-D/Br period)
Tolcapone Study Group (1999)	Tolc	Br: 74 (8) $\bar{A} = 65$ y $\bar{O} = 9.9$ y $\bar{d} = 779$ mg UPDRS-I: 1.8 UPDRS-II: 7.8 UPDRS-III: 19.9	Tolc: 72 (8) $\bar{A} = 61$ y $\bar{O} = 9.2$ y $\bar{d} = 750$ mg UPDRS-I: 1.8 UPDRS-II: 6.8 UPDRS-III: 16.1	R O/L MC (France)	8 wk	Br: 22.4 ± 9.0 mg Tolc.: 3×200 mg (fixed)	• L-DOPA dose: significantly greater reduction of dose in Tolc. group at 8 wk (−16.5% v. −4% for Br group) • On-time increase (Br +13.4% v. Tolc +17.6%), off-time decrease (Br −14.9% v. Tolc −18.8%), UPDRS-II (Br −0.1 v. Tolc −0.9), UPDRS-III (Br −3.3 v. Tolc −3.1): Br = Tolc • Differing side effect profiles (Br: hallucinations, orthostatic hypotension, nausea; Tolc: muscle cramps, dystonia). • Tolc: absence of titration, quicker efficacy.

[1] At 6 mo, half the patients were switched from L-DOPA monotherapy by substituting bromocriptine for 40% of the previous L-DOPA dose at a predetermined exchange rate

Table 6. Lisuride as adjunct to L-DOPA therapy in Parkinson's disease

Study	Control	Subjects	Design	Duration	Mean end daily dose	Results
LeWitt et al. (1982)	Br	28 $\bar{A} = 55$ y $\bar{O} = 10$ y	R D/B C/O	7–10 wk	Li: 4.5 mg Br: 56.5 mg	• Generally: Li = Br • Akinesia: Br > Li • See also LeWitt et al. (1983): Pe = Br in a similar group
Rabey et al. (1989)	——	Li + L-D: 24 (9) $\bar{A} = 65$ y $\bar{O} = 7.5$ y $\bar{d} = 590$ mg H-Y: II–V CURS: 38.7 L-D alone: 20 (7) $\bar{A} = 66$ y $\bar{O} = 7.0$ y $\bar{d} = 531$ mg H-Y: II–IV CURS: 35.3	R O/L	4 y	Li: 1.07 mg L-D (alone): 625 mg	• DOPA dose in Li group fixed (amount not given) • Bradykinesia, rigidity (significantly improved), tremor (no change) CURS scores: Li/L-D = L-D alone • Improvement in off-time: Li/L-D (−33% = 70 min) > L-D alone (−15% = 28 min) • Dyskinesia (own scale): Li/L-D (−23%) > L-D alone (no significant change)
Vermersch et al. (1991)	Pl	74 de novo[1] $\bar{A} = 59$ y	R Prosp.	12 mo (ongoing)[2]		• Mean DOPA dose lower in Li group (274 ± 74 v. 381 ± 121 mg) • UPDRS-II, UPDRS-III: Li > Pl • Adverse effects: Li = Pl
Laihinen et al. (1992)	Br	20 two trial groups: $\bar{A} = 62$ y $\bar{O} = 11.6$ y $\bar{D} = 6.8$ y H-Y: IV[3] $\bar{A} = 61$ y $\bar{O} = 10.3$ y $\bar{D} = 6.8$ y H-Y: IV[3]	R D/B C/O M	8 wk titr. + 4 wk	Li: 1.3 mg Br: 15 mg	• Fluctuations: Br = Li (14 v 13 patients showed 'marked improvement')[4] • Motor improvement: Br = Li (CURS: 29 v. 30) • Adverse effects: Br = Li (dyskinesia: 13 v. 12 patients)

(*continued*)

Table 6 (*continued*)

Study	Control	Subjects		Design	Duration	Mean end daily dose	Results
Battistin et al. (1999)	α-DHEC	Li: 36 (18) $\bar{A}$ = 62 y $\bar{d}$ = 593 mg H-Y: 3.0 UPDRS-IV: 5.2	α-DHEC: 32 (5) $\bar{A}$ = 64½ y $\bar{d}$ = 573 mg H-Y: 3.25 UPDRS-IV: 5.1	R D/B Parallel	3 mo	Li: 1.2 mg α-DHEC: 60 mg[5]	• UPDRS-V: α-DHEC > Li (4.3 point improvement v. 2.5) • Symptom severity (CURS) and patient disability (NUDS): α-DHEC = Li • Adverse effects: α-DHEC > Li (25% v. 67%)
Allain et al. (2000)	Pl	Li: 41 (17) $\bar{A}$ = 59 y $\bar{O}$ = 21 mo $\bar{D}$ = 5.1 mo H-Y: 1.6 UPDRS-III: 18	Pl.: 41 (26) $\bar{A}$ = 59 y $\bar{O}$ = 20 mo $\bar{D}$ = 5.7 mo $\bar{d}$ = 243 mg H-Y: 1.4 UPDRS-III: 21	R D/B (1st year only) MC (8; France)	5 y	1 mg	• Mean DOPA dose lower in Li group (387.5 v. 446.7 mg) • UPDRS: Li > Pl. (no change v. deterioration of 10.6 points = 28%) • UPDRS-II: Li > Pl. • UPDRS-III: Li > Pl. (no change v. deterioration of 4 points = 17%) • Adverse effects: Br = Li (rare) • Dropout rate greater in placebo group

[1] Receiving low doses of L-DOPA < one year; [2] No further published report; [3] Patients experiencing inadequate L-DOPA response and fluctuations; [4] Assessed with clinicians' self-devised scale; [5] Fixed target dose. Number of subjects refers to total in study; unless otherwise noted, groups were of equal size

however, that lisuride and bromocriptine are generally equipotent with respect to reduction of L-DOPA dose, management of motor symptoms (except akinesia: bromocriptine was superior) and production of adverse effects; the same was generally true in a comparison of lisuride and α-DHEC. The long term study by Rinne's group suggests that increased incidence of confusional states may accompany reduced motor side effects in lisuride-supplemented L-DOPA therapy.

(c) Pergolide (Table 7). Two placebo-controlled studies indicated a real benefit for pergolide therapy. Comparison with lisuride (one trial) found no major difference between the two agents; comparison with bromocriptine (four trials) suggested, on the hand, that pergolide was more effective, while the change from bromocriptine to pergolide (one trial) produced similar results.

(d) Cabergoline (Table 8). Placebo-controlled trials (three) generally indicate a genuine benefit for cabergoline as an adjunct to L-DOPA therapy; comparison with bromocriptine (five trials) suggests that the two agents are fairly comparable with respect to both their negative and their positive effects.

(e) Ropinirole (Table 9). Five placebo-controlled trials indicated a positive benefit with respect to reduction of L-DOPA dose and of 'off-time'; dyskinesia as an adverse event was reported less often than in placebo-treated groups. A therapeutic advantage in comparison with bromocriptine (four trials) was, however, not detected, although the study by the 043 Research Group suggested that it might be slightly more effective in patients experiencing L-DOPA-related fluctuations.

(f) Pramipexole (Table 10). Six placebo-controlled studies and one baseline-controlled suggest a positive role for pramipexole adjunct therapy with respect to L-DOPA dose reduction and improvement of UPDRS scores. Pramipexole has been compared with bromocriptine in only one major controlled trial, and was found to be significantly more effective in the measured areas without eliciting more frequent or severe adverse events. The recent report by Pogarell et al. (2002) suggests that pramipexole might be especially useful in the management of refractory tremor.

(g) α-Dihydroergocryptine (Table 11). Only a few small controlled studies have been reported, and suggest that α-dihydroergocryptine as an adjunct is better tolerated and at least as effective as either bromocriptine or lisuride, an impression confirmed by the large observational study of Jörg (1998).

(h) Piribedil (Table 12). Two somewhat widely spaced controlled studies support the effectiveness of piribedil as an adjunct therapy. Piribedil is regarded in France as the agent of choice for treatment of parkinsonian tremor (see Lebrun-Feray and Borg, 2002).

Summation (Table 13). On the basis of the data summarized here, it may be concluded that the first six agents discussed (there are insufficient reports for DHEC and piribedil to draw conclusions) are effective adjuncts to L-DOPA therapy, both with respect to reduction of L-DOPA dose required and improvement of disease symptoms as assessed by a variety of instruments. On the other

Table 7. Pergolide as adjunct to L-DOPA therapy in Parkinson's disease

Study	Control	Subjects		Design	Duration	Mean end daily dose	Results
Lieberman et al. (1985)	Li	Pe: 56 (28) $\bar{A} = 63$ y $\bar{O} = 12.8$ y $\bar{D} = 8.9$ y NYUPDS: 38.1 (on; stage 3.4), 61.4 (off; 4.4)[1] On-time: 4.6 h 39 had previously received Br 25 of these patients treated with both, 7 with Pe first, 18 with Li	Li: 63 (41) $\bar{A} = 65$ y $\bar{O} = 11.3$ y $\bar{D} = 8.2$ y NYUPDS: 37.9 (on; stage 3.4), 61.3 (off; 4.3)[2] On-time: 5.5 h 31 had previously received Br	O/L	Pe: mean 13 mo (range: 1 d-30 mo) Li: mean 9 mo (range: 2 d-30 mo)	Pe: 2.5 mg Li: 2.6 mg	• Pe: NYUPDS (on): mean decrease of 44% (to stage 2.3); improvement in 73% of patients • Pe: NYUPDS (off): mean decrease of 25% (to stage 3.8); improvement in 58% of patients • Pe: Hours on increased by 148%. • Pe: No increases and some decreases in L-DOPA dose • Li: NYUPDS (on): mean decrease of 34% (to stage 2.8); improvement in 59% of patients • Li: NYUPDS (off): mean decrease of 16% (to stage 2.3); improvement in 53% of patients • Pe: Hours on increased by 96%. • Li: No increases and some decreases in L-DOPA dose • Patients treated with both drugs: no significant differences in effects of two agents, except that increase in hours on greater with P (174% to 10 h v. 115% to 8.6 h)
Narabayashi et al. (1992) Mizuno et al. (1995)	–	314 (5) $\bar{O} = 9.1$ y $\bar{d} = 429$ mg mean H-Y: 3.0		O/L MC (94; Japan)	8 wk	0.90 ± 0.53 mg	• 53.8% showed improvement, 32% mild improvement • 151 still in study at 3 y, 127 at 4 y • L-DOPA dose stable (−4.0%)
	Br	Pe: 172 (30)[3] (a) de novo n = 49 H-Y: 2.6 (b) add-on n = 93 (18)	Br: 173 (25)[3] (a) de novo n = 49 H-Y: 2.5 (b) add-on n = 99 (18)	R D/B MC Parallel (94; Japan)	8 wk	Pe (de novo): 1.43 ± 0.58 mg Pe (adjunct): 1.24 ± 0.58 mg Br (de novo): 15.1 ± 0.6 mg Br (adjunct): 14.6 ± 0.6 mg	• De novo patients: Pe = Br • L-DOPA-treated patients: Pe > Br: ○ H-Y stage (off) ○ Severity and duration of off-time ○ ADL ○ Tremor, akinesia • CGI: Pe alone = Br alone (41%

		H-Y: 2.8 $\bar{d} = 354$ mg	H-Y: 2.8 $\bar{d} = 367$ mg				of each showed at least moderate improvement; 49% v. 46% mild improvement) • CGI: as adjunct to L-DOPA, Pe = Br (49½% v. 40%; 40% v. 41%) • New dyskinesias as adverse effect: Pe = Br (4.6% v. 2.6%) • Wearing-off: Pe = Br • H-Y stage: improved by both (no comparison made)
Mizuno et al. (1995)	–	Pe alone: 62 H-Y: 2.4	Pe as adjunct: 314 (extension of study 1) H-Y: 2.9 $\bar{d} = 445$ mg	O/L MC (94; Japan)	4 y	Pe (alone): 1.3 ± 0.7 mg Pe (adjunct): 1.1 ± 0.5 mg	• improvement attributed to Pe as adjunct maintained in 151 of 314 patients for up to 3 y; in 127 for up to 4 y. Mean H-Y at 4 y: 2.4 • as monotherapy: 32 of 62 patients dropped out or required L-DOPA by end of first year; 18 of 62 patients continued monotherapy until third year. Mean H-Y at 4 y: 2.0
Olanow et al. (1994)	Pl	P: 189 (30) $\bar{A} = 62$ y $\bar{O} = 11.4$ y $\bar{d} = 891$ mg Parkinson score: 167 mean H-Y: 3.1	Pl.: 187 (33) $\bar{A} = 63$ y $\bar{O} = 10.4$ y $\bar{d} = 940$ mg Parkinson score: 176 mean H-Y: 3.3	R D/B Parallel MC (16; UK) M	24 wk	2.94 mg	• Off-time: Pe > Pl. (reduced by 1.8 h = 32% v. 0.2 h = 4%) • Development of dyskinesia: 62% (25% with placebo), but controlled by reduction of L-DOPA dose • Reduction of L-DOPA dose: Pe > Pl. (235 mg = 24.7% v. 51 mg = 4.9%) • H-Y stage: improved slightly (end values, Pe v. Pl: 2.8 v. 3.1) • Modified CURS motor score: Pe > Pl. (34.6% v. 15.7%) • Modified CURS ADL score: Pe > Pl. (30.5% v. 8.3%) • Modified CURS total score: >25% improvement in 56% Pe-treated patients (v. 25%); >50% in 24% (v. 5%)

(*continued*)

Table 7 (*continued*)

Study	Control	Subjects	Design	Duration	Mean end daily dose	Results
Pezzoli et al. (1994) = Pezzoli et al. (1995)	Br	68 (11) $\bar{A} = 61$ y $\bar{O} = 6.6$ y $\bar{d} = 658$ mg mean H-Y: 3.2	R S/B C/O MC	2×12 wk	Pe: 2.3 ± 0.1 mg Br: 24.2 ± 8.4 mg	• NUYPDS motor score: Pe > Br (30.8% v. 20.1%) • NUYPDS ADL score: Pe > Br (23.0% v. 17.4%) • Dyskinesia rating: Pe > Br (no improvement with Br) • CGI scores: Pe > Br (CGI-I/disease severity: 49% v. 39% of patients; CGI-II/global: 81% v. 63%) • L-DOPA reduction (negligible): Pe = Br (4.4% v. 4.7%) • PGI: Pe > Br (88% v. 61% patients at least markedly better) • Pe preferred by patients and physicians (fewer adverse effects)
Boas et al. (1996)	Br	Group 1: 17 $\bar{A} = 63$ y $\bar{O} = 7.6$ y $\bar{d} = 614$ mg H-Y: 2.6 Group 2: 16 $\bar{A} = 64$ y $\bar{O} = 7.0$ y $\bar{d} = 735$ mg H-Y: 2.6	R O/L C/O MC	2×12 wk	Pe: 3.6 ± 1.1 mg Br: 21.7 ± 5.6 mg	• Control of fluctuations: Pe ≥ Br (UPDRS) • Dyskinesia: Pe ≤ Br (UPDRS) • Motor signs: Pe > Br (UPDRS)
Facca and Sanchez-Ramos (1996)	–	13 $\bar{A} = 66$ y $\bar{O} = 12.9$ y $\bar{d} = 825$ mg mean H-Y (on): 2.8 mean H-Y (off): 3.9 off-time: 26.5% dyskinesia since: 5.8 y dyskinesia time: 71% bromocriptine: 16.8 mg	O/L Switch from Br to Pe	Switch: 3–4 mo	6.5 mg	• H-Y: no change • Off-time: Pe ≥ Br • Dyskinesia: Pe > Br (13% of day) • L-DOPA dose: Pe > Br (reduced to 98 mg)

Hanna et al. (2001)	Pr	21 $\bar{A} = 67$ y $\bar{O} = 12½$ y $\bar{d} = 619$ mg (20 patients) H-Y: 2.6 pergolide: 41.8 mo, 2.1 mg		O/L Switch from Pe to Pr	Transition: 1 mo Mean follow-up: 5.9 mo	3.2 mg	• Patient impressions: 13 improved. 5 stable, 3 deteriorated; 18 remained on pram. after trial • On-time (75%), S&E ADL score (80½%): no change • Dyskinesia: slight fall (16.8% afterwards, 21.2% before) • UPDRS-II: Pr ≥ Pe • L-DOPA dose: reduced by 16.5%
Kanagawa Parkinson's Disease Study Group (2001)	Br	Pe: 29 Br: 23		D/B	24 mo	n.s.	• GIR: Pe > Br • ADL: Pe > Br (slower deterioration) • Pe: more rapid improvement of cardinal symptoms
Koller et al. (2001)	Tolc	Pe: 102 $\bar{A} = 65½$ y $\bar{O} = 8$ y $\bar{d} = 563$ mg H-Y: ~2.3 (0–5) UPDRS-II: 9.7 UPDRS-III: 18.1 UPDRS-IVa: 1.4 UPDRS-IVb: 3.2	Tolc: 101 $\bar{A} = 65$ y $\bar{O} = 7$ y $\bar{d} = 586$ mg H-Y: ~2.2 (0–5) UPDRS-II: 9.8 UPDRS-III: 18.4 UPDRS-IVa: 1.6 UPDRS-IVb: 3.2	R O/L S/B Par 24 (USA, UK, Aust)	12 wk	Pe: 2.2 mg Tolc: 144 mg (100 or 200 mg)	• UPDRS-II: Pe = Tolc (16% v. 19%) • UPDRS-III: Pe = Tolc (15% v. 18%) • UPDRS-IVa: Pe = Tolc (no change in number of patients) • UPDRS-IVb: Pe = Tolc • (Off-time: Pe = Tolc (80% predictable OT at begin, 70% at end; 50% and 33% unpredictable) • L-DOPA dose reduction: Pe = Tolc (16% v. 18%) • SIP: Pe = Tolc (20% v. 23%) • PDQ-39: Tolc > Pe (16% v. 10%) • Adverse effects leading to withdrawal: Tolc > Pe (5% v. 15%)

[1] For 45 patients with on-off fluctuations; [2] For 40 patients with on-off fluctuations; [3] Excluded by investigators for practical reasons

Table 8. Cabergoline as adjunct to L-DOPA therapy in Parkinson's disease

Study	Control	Subjects		Design	Duration	Mean end daily dose	Results
Lieberman et al. (1993)	–	61 (4) $\bar{A} = 66$ y $\bar{O} = 11.9$ y $\bar{d} = 838$ mg H-Y: 2–4 (on) UPDRS-II: 16.9 UPDRS-III: 24.7 (off), 14.8 (on) offtime: 29.4%		R D/B MC (USA; 3)	5 wk	Five doses: 0.5–2.5 mg	• UPDRS-II: mean reduction of 4.0 = 22% • UPDRS-III: mean reduction of 3.4 = 14% (off), 3.3 = 22% (on) • L-DOPA dose reduction: 93 mg = 12% • Off-time: mean reduction = 9% (NS)
	–	37 (from first part of study)		O/L Dose elevated until 25% reduction in UPDRS II/III achieved	8 wk	Maximum: 5 mg	• UPDRS-II: −1.9 = 35% overall • UPDRS-III: −0.9 (17%, off) or −0.2 (25%, on) • Off-time: mean reduction = 31% overall
Miguel et al. (1993) (Phase II trial)	Pl	C: 23 (5) $\bar{A} = 60$ y	Pl.: 20 (6) $\bar{A} = 62$ y	R D/B P MC (5)	6 (a) or 10 wk (b) titr. + 4 wk[1]	2.64 mg (a) max. 2 mg (b) max 3 mg	• UPDRS-II, UPDRS-III, S&E: Ca = Pl • Reduction in off-time: Ca = Pl
Ahlskog et al. (1996) Hutton et al. (1996) (Phase III trial)	Pl	C: 123 (13) $\bar{A} = 63$ y $\bar{O} = 10.6$ Median H-Y: 2 UPDRS-II: 15.2 UPDRS-III: 16.4	Pl.: 65 (11) $\bar{A} = 63$ y $\bar{O} = 10.5$ y Median H-Y: 2 UPDRS-II: 14.9 UPDRS-III: 17.4	R D/B P MC (USA; 10)	24 wk	3.66 mg	• UPDRS-II: Ca > Pl (−2.9 = 19% v. −0.6 = 4%) • UPDRS-III: Ca > Pl (−2.7 = 16% v. −0.9 = 6%) • L-DOPA dose reduction: Ca > Pl (175 mg/d = 18% v. 26 mg/d = 3%) • Reduction in off time: Ca > Pl (39% v. 15%) • UPDRS-I, UPDRS-IV; modified H-Y; modified S&E ADL: Ca = Pl

Steiger et al. (1996) (Phase II trial)	Pl	C: 19 (1) $\bar{A} = 61$ y $\bar{O} = 13.6$ $\bar{D} = 10.5$ y $\bar{d} = 769$ mg H-Y: 3.5 (off), 2.4 (on) offtime: 5 h	Pl.: 18 (2) $\bar{A} = 63$ y $\bar{O} = 11.9$ $\bar{D} = 10.1$ y $\bar{d} = 1145$ mg H-Y: 3.5 (off), 2.6 (on) offtime: 4 h	R D/B P MC (2)	12 wk titr. + 3 mo[1]	5.4 ± 1.9 mg	• S&E, H-Y stage: Ca = Pl (no change) • CGIS: Ca > Pl (1.5 ± 1.1 v. 0.6 ± 1.2 • Reduction in off-time: C > Pl. (2 h = 45% v. 0.7 h = 18%) • L-DOPA levels: controlled at initial level.
Gershanik et al. (1994a) Destee et al. (1996) (Phase III trial)	Br	Ca: 191 (28)[2] $\bar{A} = 62$ y H-Y: 2 or 2.5[3]	Br: 193 (34) $\bar{A} = 62$ y H-Y: 2 or 2.5[3]	R D/B P MC (69; 13 countries)	mean 10 wk titr. + 3 mo[1] + mean 10 mo followup[4]	Ca: median 4 mg Br: median 25 mg	• Responders: Ca = Br (83% v. 77%) • Reduction in off-time: Ca = Br (63% v. 55%) • UPDRS-II, UPDRS-III, S&E, CGIS: Ca = Br • Reduction in L-DOPA dose: Ca = Br (8% v. 3%) • Dyskinesia as adverse effect: Ca < Br
Gershanik et al. (1994b) Schneider et al. (1996) (Phase III trial)	Br	Ca: 181 (23) $\bar{A} = 62$ y H-Y: 2.1 (on), 3.4 (off)	Br: 185 (21)[4] $\bar{A} = 62$ y H-Y: (on), 3.5 (off)	R D/B P MC (67; Europe, Latin America, Israel)	Mean 2 mo titr. + 3 mo[1] + mean 10 mo followup[4]	Ca: 4.4 mg Br: 28.7 mg	• Responders: Ca = Br (both 78%) • Reduction in off-time: Ca = Br (51% v. 45%) • UPDRS-II, UPDRS-III, S&E, CGIS: Ca = Br • Reduction in L-DOPA dose: Ca = Br (8% v. 1%) • Dyskinesia as adverse effect: Ca < Br
Korczyn et al. (1994) (Phase II trial)	Br	Ca: 22 (3)[3] $\bar{A} = 61$ y H-Y: 2.3 (on), 3.2 (off)	Br: 20 (5)[3] $\bar{A} = 60$ y H-Y: 2.5 (on), 3.4 (off)	R D/B P MC (12)	13 wk titr. + 3 mo[1]	Ca: max.4 mg Br: max 40 mg	• Reduction in off-time: Ca = Br • UPDRS-II, UPDRS-III, S&E, CGIS: Ca = Br • Reduction in L-DOPA dose: Ca = Br • Dyskinesia as adverse effect: Ca < Br

(*continued*)

Table 8 (*continued*)

Study	Control	Subjects		Design	Duration	Mean end daily dose	Results
Inzelberg et al. (1996) (Phase II trial)	Br	Ca: 22 (7) $\bar{d} = 675$ mg UPDRS-III: 35 ADL: 11 S&E: 81 Offtime: 34% $\bar{A} = 71$ y H-Y: 2 or 3 (on)	Br: 22 (12) $\bar{d} = 705$ mg UPDRS-III: 38 ADL: 11 S&E: 84 Offtime: 32%	R D/B P	Titr. + 6–12 mo mean: 9 ± 5 mo	Ca: 3.2 ± 1.6 mg Br: 22.1 ± 10.3 mg	• Reduction in off-time: Ca > Br (50% v. 19%) • UPDRS-III (20% v. 23.7%), UPDRS-II (both 18.2%), S&E (no change), CGI: Ca = Br • Reduction in L-DOPA dose: Ca = Br (9.9% v. 9.1%) • Dyskinesia as adverse effect: Ca = Br • Dropouts: Ca > Br
Yanagisawa et al. (1996) (Phase III trial)	Br	Ca: 115 (26) $\bar{A} = 66$ y H-Y: 2.7 (on)	Br: 120 (27) $\bar{A} = 64$ y H-Y: 2.8 (on)	R D/B P MC (12)	8 wk titr. + 4 wk	Ca: 2.74 mg Br: 16.44 mg	• Reduction in off-time: Ca = Br • UPDRS-II, UPDRS-III, S&E, CGIS: Ca = Br • Reduction in L-DOPA dose: Ca = Br • Dyskinesia as adverse effect: Ca = Br

[1] For patients who were classified as responders during titration period; [2] At end of titration; [3] In approximately two-thirds of each group; [4] If improvement maintained during stable dose period

Table 9. Ropinirole as adjunct to L-DOPA therapy in Parkinson's disease

Study	Control	Subjects		Design	Duration	Mean end daily dose	Results
Korczyn et al. (1990) (phase II trial)	Pl	Ro 46 (15) $\bar{A} = 62$ y H-Y: 2.9	Pl: 22 (4) $\bar{A} = 64$ y H-Y: 2.8	R D/B P MC (6 UK, 2 Israel)	12 wk	max 10 mg[1]	• Reduction in L-DOPA dose: Ro = Pl (157 mg v. 131 mg) • Off-time reduction: Ro = Pl (1.33 h v. 0.75 h) • All causes withdrawals: Pl > Ro
Perez-Aharon et al. (1994)	Pl	Ro: 46 $\bar{A} = 63$ y $\bar{O} = 5.6$ y $\bar{d} = 520$ mg	Pl: 22 $\bar{A} = 63$ y $\bar{O} = 7.0$ y $\bar{d} = 675$ mg	R	12 wk (titr.: 6 wk)	n.s.	• Responders (20% reduction in L-DOPA dose and off-time): Ro > Pl (63% v. 29%)
Kreider et al. (1996) Lieberman et al. (1998) (phase III trial)	Pl	Ro: 95 (21) $\bar{A}$ = n.g. $\bar{O} = 8.6$ y $\bar{D} = 7.3$ y $\bar{d} = 759$ mg H-Y: 2.8 offtime: 39.3%	Pl: 54 (19) $\bar{A}$ = n.g. $\bar{O} = 9.4$ y $\bar{D} = 7.5$ y $\bar{d} = 843$ mg H-Y: 2.8 offtime: 43.4%	R D/B P MC (16 USA)	26 wk	max 24 mg	• 35% achieved 20% reduction of L-DOPA dose and 20% reduction of off-time after 6 mo (13% with placebo); no selegiline effect in Ro group • Reduction in L-DOPA dose after 6 mo: Ro > Pl (242 mg = 31% v. 51 mg v. 6%) • CGI improvement: Ro > Pl (59% v. 32% of patients; but almost entirely cin those patients not receiving selegiline) • Off-time reduction: Ro > Pl (11.7% v. 5.1%)
Brunt et al. (1999) (phase III trial)	Pl	Ro: 74 (31)	Pl: 35 (14)	DB	26 wk follow-up to Lieberman et al., 1998	max 24 mg	• 24% achieved 20% reduction of L-DOPA dose and 20% reduction of off-time after 1 y (5% with placebo) • Reduction in L-DOPA dose after 1 y: Ro > Pl (23% decrease v. 24% increase) • Off-time reduction: Ro = Pl (1.53 h = 13.1% v. 1.22 h = 9.9%) • Dyskinesia as adverse effect: Pl > Ro (34% v. 13%) • All causes withdrawals: Ro > Pl

(*continued*)

Table 9 (*continued*)

Study	Control	Subjects		Design	Duration	Mean end daily dose	Results
Rascol et al. (1996) (phase II trial)	Pl	Ro: 23 (2) $\bar{A} = 62$ y $\bar{O} = 8$ y $\bar{D} = 7$ y $\bar{d} = 663$ mg off-time: 47% H-Y: 2.8	Pl: 23 (9) $\bar{A} = 63$ y $\bar{O} = 8$ y $\bar{D} = 7$ y $\bar{d} = 715$ mg off-time: 43% H-Y: 3.0	R D/B P MC (1 UK, 1 France)	12 wk	3.3 mg[1]	• Off-time reduction (overall): Ro = Pl (1.74 h v. 2.22 h) • Off-time reduction (those who completed study): Ro > Pl (50% v. 20%) • CGE: Ro > Pl (85% v. 42% of patients) • Dyskinesia as adverse effect: Pl > Ro (35% v. 22%) • All causes withdrawals: Ro > Pl
Brunt and Aitken (1996) Ropinirole 043 Study Group (1996) Brunt et al. (1999) Brunt et al. (2002)	Br	Ro: 370 (134)	Br: 189 (67)	R D/B P MC (66: Europe, Israel, Canada, South Africa)	titr. max. 13 wk total: 25 wk	Ro: 10 mg Br: 18 mg	• L-DOPA dose reduction: Ro = Br (10%) • Patients achieve 20% reduction: Ro = Br (28% v. 26%) • Mean UPDRS reduction: Ro = Br (28% v. 24%) • Improved CGI: Ro = Br (73% v. 75%) • Responders: Ro = Br (20% v. 15%)
		Group A: low dose L-DOPA group Ro: 131 $\bar{A} = 65½$ y $\bar{O} = 5½$ y H-Y: 2.4 $\bar{d} = 414$ mg UPDRS: 25.9	Br: 75 $\bar{A} = 66$ y $\bar{O} = 6$ y H-Y: 2.7 $\bar{d} = 404$ mg UPDRS: 25.7				
		Group B: high dose L-DOPA group with fluctuations					• L-DOPA dose reduction: Ro = Br (8% v. 7%) • Patients achieve 20% reduction: Ro = Br (24% v. 22%)

							• Mean UPDRS reduction: Ro = Br (21%) • Improved CGI: Ro = Br (76% v. 66%) • Responders: Ro ≥ Br (9% v. 0%) • Off-time reduction: Ro > Br (18% v. 5%)
		Ro: 88 Ā = 63½ y Ō = 8½ y H-Y: 2.8 d̄ = 786 mg UPDRS: 25.7	Br: 51 Ā = 65 y Ō = 9½ y H-Y: 2.9 d̄ = 835 mg UPDRS: 8.1				
		Group C: high dose L-DOPA group together with agonist					• L-DOPA dose reduction: Ro = Br (4% v. 3%) • Patients achieve 20% reduction: Ro = Br (21%) • Mean UPDRS reduction: Ro = Br (19% v. 17%) • Improved CGI: Ro = Br (67% v. 70%) • Responders: Ro = Br (18% v. 14½%)
		Ro: 148 Ā = 63½ y Ō = 9 y H-Y: 3.0 d̄ = 678 mg UPDRS: 25.8	Br: 62 Ā = 64 y Ō = 9.3 y H-Y: 3.0 d̄ = 731 mg UPDRS: 24.8				
Murayama (1996)	Br	Ro: 132 (27) Ā = 66 y H-Y: median stage III	Br: 135 (35) Ā = 64 y H-Y: median stage III	R D/B Parallel MC (105, Japan)	8 wk	Ro: 4 mg Br: 9.2 mg	• UPDRS-III: Ro = Br • Dyskinesia as adverse effect: Ro = Br (4.5% v. 6%) • Nausea as adverse effect: Ro > Br (16% v. 27%) • CGIS: Ro = Br (39 v. 37% at least 'much improved')
Canesi et al. (1999) Canesi et al. (2000)	Br Pe	L-D/Pe: 42 (3) mean dose: 2.8 ± 0.8 mg H-Y: I–III All receiving L-DOPA	L-D/Br: 36 (1) mean dose: 20 ± 5 mg	O/L overnight switch to R at pre-determined exchange rates	4 wk + 6 mo follow-up	10:6 Br:Ro 1:6 Pe:Ro	• UPDRS-II improved for Br ▶ Ro (7.0 ± 1.4 ▶ 3.2 ± 1.4); no change for switch from Pe • No changes in other UPDRS scores • No side effects

(*continued*)

Table 9 (*continued*)

Study	Control	Subjects		Design	Duration	Mean end daily dose	Results
Im et al. (2003)	Br	Ro: 37 (5) $\bar{A} = 63½$ y H-Y: 2.5	Br: 39 (6) $\bar{A} = 60$ y H-Y: 2.4	R O/L Parallel	16 wk	Ro: 4.5–9 mg Br: 10–17.5 mg (allowed ranges)	• Reduction in L-DOPA dose: Ro > Br (183 mg v. 81 mg) • Off-time reduction: Ro = Br (1.65 h v. 0.69 h; 20% reduction: 81% v. 52%) • UPDRS-III: Ro = Br (20% improvement: 70% v. 63%) • Dyskinesia as adverse effect: Ro < Br (22% v. 10%) • Nausea as adverse effect: Ro > Br (8% v. 18%); side effects in general: Ro = Br • CGIS: Ro = Br (84 v. 58% at least 'much improved')

[1] Administered in two daily doses

Table 10. Pramipexole as adjunct to L-DOPA therapy in Parkinson's disease

Study	Control	Subjects		Design	Duration	Mean end daily dose	Results
Molho et al. (1995)	Pl	Pr: 12	Pl: 12	R S/B P MC	L-DOPA titr.: 3 wk 11 wk Pr/Pl. (7 wk titr., 3 wk maint., 1 wk reduction)	Target: 4.5 mg	• UPDRS-II (off): Pr > Pl. (−5.0 points = 24% v. +0.3 = 1%) • UPDRS-II (on): no significant change (data not shown) • UPDRS-III: Pr = Pl. (−12% v. −26%; neither significant changes) • Off-time reduced by mean 56% in 5 Pr-treated patients; otherwise no significant change in this group • Offtime reduced by mean 26% in Pl-group (significant); >40% reduction: 4 patients • L-DOPA dose reduction: Pr > Pl. (265 mg = 30% v. 60 mg = 6%)
		$\bar{A} = 66½$ y $\bar{O} = 11.9$ y H-Y: II–IV UPDRS-II: 20.8 (off)					
		$\bar{d} = 896$ mg	$\bar{d} = 1071$ mg				
Guttman et al. (1997) (Phase III trial)	Pl	Pr: 79 (16)	Pl: 83 (33)	R D/B P MC (34; Europe, Canada)	titr. max. 12 wk maint. 24 wk dose reduction 1 wk	3.36 mg	• UPDRS-II: Pr > Pl. (−26.7% v. −4.8%) • UPDRS-III: Pr > Pl. (−34.9% v. −5.7%) • Reduction in off-time: Pr > Pl. (46% v. 6%) • GCE: Pr > Pl. • UPDRS-I, UPDRS-IV, H-Y (on, off), modified S&E, Parkinson Dyskinesia Scale, timed walking test: Pr = Pl.
		$\bar{A} = 63$ y $\bar{O} = 6$ y (median) H-Y: II–IV (on) median UPDRS-II: 11 median UPDRS-III: 25	$\bar{A} = 64$ y $\bar{O} = 7.6$ y (median) H-Y: II-IV (on) median UPDRS-II: 12 median UPDRS-III: 24				

(*continued*)

Table 10 (*continued*)

Study	Control	Subjects		Design	Duration	Mean end daily dose	Results
Guttman et al. (1997) (Phase III trial)	Br	Pr: 79 (16) $\bar{A} = 63$ y $\bar{O} = 6$ y (median) H-Y: II–IV (on) median UPDRS-II: 11 median UPDRS-III: 25	Br: 84 (17) $\bar{A} = 62$ y $\bar{O} = 7.2$ y (median) H-Y: II–IV (on) median UPDRS-II: 10.25 median UPDRS-III: 23	R D/B P MC (34; Europe, Canada)	titr. max. 12 wk maint. 24 wk dose reduction 1 wk	Pr: 3.36 mg Br: 22.64 mg	• UPDRS-II: Pr > Br (−26.7% v. −14.0%) • UPDRS-III: Pr > Br (−34.9% v. −23.8%) • Reduction in off-time: Pr ≥ Br > Pl (46% v. 30% v. 6%) • GCE: Pr ≥ Br > Pl • Onset of efficacy: Pr > Br (commenced at 4 wk, then maintained v. commenced at 8 wk, not maintained) • Quality-of-life assessments. Pr ≥ Br in several tests • Adverse events: Pr = Br • UPDRS-I, UPDRS-IV, H-Y (on, off), modified S&E, Parkinson Dyskinesia Scale, timed walking test: Pr = Br (no change)
Lieberman et al. (1997) (Phase III trial)	Pl	Pr: 181 (30) $\bar{A} = 63$ y $\bar{O} = 9$ y (H-Y: 2.3 (on), 2.9 (off) UPDRS-II: 7.7 (on), 17.4 (off) UPDRS-III: 23.3 (on)	Pl: 179 (39) $\bar{A} = 63$ y $\bar{O} = 9.4$ y H-Y: 2.3 (on) 3.0 (off) UPDRS-II: 7.3 (on), 17.4 (off) UPDRS-III: 22.8 (on)	R D/B P MC (26; N. America)	titr. max. 7 wk maint. 24 wk dose reduction 1 wk		• UPDRS-II: Pr > Pl (off: −24% v. −5%; on: 18% v. 1%; mean: −22% v. −4%) • UPDRS-III: Pr > Pl (−25% v. −12%); especially tremor and rigidity • UPDRS-IV: Pr > Pl (−24% v. −3%)

		$\bar{d} = 843$ mg +selegiline: 52%	$\bar{d} = 819$ mg +selegiline: 56%				• Reduction in off-time: Pr > Pl (31% v. 7%) • Modified H-Y: Pr > Pl (off: −11% v. −2%; on: −10% v. −1%) • Modified S&E: Pr > Pl (off: −9% v. +1%; on: −2% v. +1%) • L-DOPA dose reduction: Pr > Pl (209 mg = 27% v. 45 mg = 5%)
Wermuth et al. (1993, 1998) (Phase II trial)	Pl	Pr: 36 (6) $\bar{A} = 63$ y $\bar{O} = 10.1$ y H-Y: 2.7 UPDRS: 56.7 $\bar{d}$: ≤600 mg: 14 patients >600 mg: 22 patients Offtime: 36%	Pl: 33 (5) $\bar{A} = 62$ y $\bar{O} = 9.9$ y H-Y: 2.9 UPDRS: 51.9 $\bar{d}$: ≤600 mg: 11 patients >600 mg: 22 patients Offtime: 43%	R D/B P MC (8; Denmark)	titr. max. 7 wk maint. 4 wk dose reduction 1 wk	4.6 ± 1.0 mg	• UPDRS: Pr > Pl (−17% v. −9%); responders (≥ 30% improvement): Pr > Pl (56% v. 27%) • UPDRS-I, UPDRS-II: Pr > Pl • UPDRS-III: Pr ≥ Pl • UPDRS-IV: Pr = Pl • GCE: Pr > Pl (31% v. 10% improved) • Modified S&E: Pr = Pl • Reduction in off-time: Pr ≥ Pl (28% v. 7%) • L-DOPA dose reduction: Pr ≥ Pl (−151 mg = −26% v. +11 mg = +5%)
Pinter et al. (1999) (Phase II trial)	Pl	Pr: 34 (5) $\bar{A} = 59$ y $\bar{O} = 7.8$ y H-Y: 2.9 UPDRS: 53.6 UPDRS-II: 13.0	Pl: 44 (6) $\bar{A} = 61$ y $\bar{O} = 8.5$ y H-Y: 3.0 UPDRS: 50.2 UPDRS-II: 12.7	R D/B P MC (9; Germany, Austria, Switzerland)	titr. max. 7 wk maint. 4 wk dose reduction 1 wk	3.6 ± 1.8 mg	• UPDRS: Pr > Pl (−37.3% v. −12.2%); commenced in 1st week • UPDRS-III: Pr > Pl (−32.2% v. −7.5%) • UPDRS-II: Pr > Pl (−39.4% v. −15.3%)

(*continued*)

Table 10 (*continued*)

Study	Control	Subjects		Design	Duration	Mean end daily dose	Results
		UPDRS-III: 33.5 $\bar{d}$: 537½ mg (≤600 mg: 20 patients >600 mg: 14 patients) Offtime: 33%	UPDRS-III: 30.5 $\bar{d}$: 593 mg (≤600 mg: 23 patients >600 mg: 21 patients) Offtime: 33%				• UPDRS-IV: Pr > Pl (−23.2% v. −1.2%) • S&E: Pr > Pl (improved in on period: 52% v. 18%; in off period: 54% v. 27%) • Reduction in off-time: Pr > Pl (12% v. 2%) • CGI score: Pr > Pl (76% v. 32% of patients improved) • L-DOPA dose held constant
Goetz et al. (1999)	–	Rapid (overnight): 8 (4 Pe, 4 Br) $\bar{A} = 67$ y $\bar{O} = 6.2$ y UPDRS-III: 29.6 Pergolide-equiv.: 2.3 mg	Slow (over weeks): 8 (4 Pe, 4 Br) $\bar{A} = 65$ y $\bar{O} = 6.3$ y UPDRS-III: 28.6 Pergolide-equiv.: 2.2 mg	D/B switch to Pr	8 wk	2.2 mg	• UPDRS change: rapid = slow (−3.6 v. −3.4 points): but quicker in rapid titration group (2.1 v. 5.3 wk)
Möller and Oertel (2000) (European clinical phase III study)	Pl	Pr: 174 (31) H-Y: majority II or III	Pl: 180 (65)	R D/B MC	titr. max. 7 wk maint. 4 wk dose reduction 1 wk	target: 4.5 mg	• UPDRS-II: Pr > Pl (−35% v. −13%) • UPDRS-III: Pr > Pl (−38% v. −15%) • Responders: Pr > Pl (57% v. 28%) • Reduction in off-time: Pr ≥ Pl (16% v. 1%) • L-DOPA dose reduction: Pr > Pl (103 mg v. 18 mg)

	–	262 (55) (from previous study)		O/L MC	3y follow-up to previous study		• UPDRS-II: −28% (1st y), −16% (2nd y), −10% (3rd y) • UPDRS-III: −48% (1st y), −28% (2nd y), −21% (3rd y) • Responders: 55% (1st y), 44% (2nd y), 33% (3rd y)
Pinter et al. (2000)	Baseline-controlled	L-DOPA ≤500 mg: 59 $\bar{A}$ = 65 y $\bar{O}$ = 7.0 y H-Y (on): 2.4 H-Y (off; n = 31): 3.0 $\bar{D}$: 4.7 y[1] $\bar{d}$: 394 mg	L-DOPA ≥ 500 mg: 41 $\bar{A}$ = 61 y $\bar{O}$ = 9.1 y H-Y (on): 2.5 H-Y (off; n = 23): 3.4 $\bar{D}$: 7.9 y[1] $\bar{d}$: 854 mg	O/L MC (14; Germany, Austria, Holland Switz.)	12 wk	3.7±1.0 mg	• Mean reduction in L-DOPA dose: ∼40% in all groups (high/low L-DOPA, with/without off-period); 47% of patients: >40% reduction, 72% of patients greater than 20% • UPDRS-II: median 25% improvement • UPDRS-III: median 20% improvement • Off-time reduction (recorded by 39 patients): median 35% • On-time increase (recorded by 39 patients): median 26%
Weiner et al. (2001) (continuation of Lieberman et al., 1997)	Baseline controlled	Prior Pr: 164 (54) $\bar{A}$ = 63 y $\bar{O}$ = 10.1 H-Y (on): 2.1 H-Y (off): 2.8 UPDRS-II (on): 6.9 UPDRS-II (off): 16.6 S-E (on): 85.9 S-E (off): 65.4	De novo Pr: 142 (55) $\bar{A}$ = 63 y $\bar{O}$ = 9.3 H-Y (on): 2.3 H-Y (off): 2.8 UPDRS-II (on): 7.5 UPDRS-II (off): 16.4 S-E (on): 85.3 S-E (off): 66.8	O/L	Titr. 6 wk maint. <50 mo	Max. 4.5 mg	• UPDRS-II, UPDRS-III, S-E: improved during titration, returned to baseline by 16–34 mo and continued to deteriorate • UPDRS-IV: remained below baseline throughout observation period (data not shown) • Well tolerated, effective for 3 y

(*continued*)

Table 10 (*continued*)]

Study	Control	Subjects			Design	Duration	Mean end daily dose	Results
Pogarell et al. (2002)	Pl	Pr: 44 (0) $\bar{A} = 62$ y $\bar{O} = 6.5$ $\bar{D}$: 3.9 y $\bar{d}$: 300 mg[2] H-Y (on): 2.0 H-Y (off): 2.6[3] UPDRS-II: 13	Pl: 39 (1) $\bar{A} = 65$ y $\bar{O} = 6.0$ $\bar{D}$: 3.6 y $\bar{d}$: 300 mg[2] H-Y (on): 2.0 H-Y (off): 2.4[4] UPDRS-II: 11.5		DB R MC (4, Eur.)	<12 wk	4.1 mg	• UPDRS tremor score during on period: Pr > Pl (−5.8 v. −1.5; = 35% mean relative difference); similar for UPDRS items for resting, postural and reported tremor • Long term EMG (tremor occurrence): Pr > Pl(−19.3% v. −4.1%; = 45.7% mean relative difference) • Clinician's/patient's assessments: Pr > Pl
Mizuno et al. (2003)	Pl/Br	Pr: 102 $\bar{A} = 65$ y $\bar{O} = 4.8$ H-Y: 2.7 UPDRS-II: 10.4 UPDRS-III: 27.1 $\bar{d}$: 405 mg	Br: 104 $\bar{A} = 65$ y $\bar{O} = 5.0$ y H-Y: 2.6 UPDRS-II: 10.3 UPDRS-III: 27.2 $\bar{d}$: 378 mg	Pl: 107 $\bar{A} = 64$ y $\bar{O} = 5.8$ y H-Y: 2.6 UPDRS-II: 10.4 UPDRS-III: 27.4 $\bar{d}$: 422 mg	DB R MC (38, Japan)	12 wk (incl. 4 wk maint.) +4 wk dose reduction	Pr: 3.24 mg Br: 17.8 mg	• Study not designed to detect significant differences between two treatment groups • UPDRS-II/UPDRS-III: Pr/Br > Pl; mean reduction greater for Pr than Br • UPDRS-I: Pr/Br = Pl • UPDRS-IV: Pr/Br > Pl • H-Y: Pr μ Br > Pl • CGI: Pr > Br > Pl • Adverse events: Pr (85%) = Br (90%) = Pl (77%); one 'sleep attack' in Br group

Rektorová et al. (2003)	Pe	Pr: 22 (3) $\bar{A} = 60$ y $\bar{O}$ (depr) = 4.6 H-Y: 2.7 $\bar{D}$: 5.9 y $\bar{d}$: 558 mg UPDRS-II: 15.2	Pe: 19 (2) $\bar{A} = 63½$ y $\bar{O}$ (depr) = 2.6 H-Y: 3.0 $\bar{D}$: 5.4 y $\bar{d}$: 709 mg UPDRS-II: 15.5	O/L R M/C (8; Czech.)	8 mo	Pr: 2.7 mg Pe: 3.0 mg	• Major focus of study: effects on depression in Parkinson's disease • Zung Self-Rating Depression Scale: Pr = Pe (−18% v. −28%) • Montgomery and Asberg Depression Rating Scale: Pr > Pe (−39% v. −11%) • UPDRS-II, UPDRS-III, UPDRS-IV, S&E: Pr = Pe • L-DOPA dose: Pr = Pe (−22% v. −28%) • Side effects: Pr = Pe

[1] Unadjusted doses; results were similar for adjusted L-DOPA doses; [2] Median dose; [3] n = 22; [4] n = 22

Table 11. α-Dihydroergocriptine (α-DHEC) as adjunct to L-DOPA therapy in Parkinson's disease

Study	Control	Subjects		Design	Duration	Mean end daily dose	Results
Martucci et al. (1989)	Br	20 $\bar{A} = 60$ y H-Y: I–III		D/B	1.5 mo	73 mg	• Efficacy and tolerability: DHEC > Br
Battistin et al. (1991) (1999) (as adjunct)	Li	DHEC: 32 (5) $\bar{A} = 64½$ y $\bar{d} = 573$ mg H-Y: 3.25 UPDRS-IV: 5.1	Li: 36 (18) $\bar{A} = 62$ y $\bar{d} = 593$ mg H-Y: 3.0 UPDRS-IV: 5.2	R D/B MC	3 mo	Fixed end doses: DHEC: 60 mg Li: 1.2 mg	• UPDRS-IV: α-DHEC > Li (4.3 point improvement v. 2.5) • Symptom severity (CURS) and patient disability (NUDS): α-DHEC = Li • Adverse effects: α-DHEC > Li (25 % v. 67%)
Martignoni et al. (1991)	Pl	DHEC: 10 (0) $\bar{A} = 60$ y $\bar{O} = 3.0$ y H-Y: 2.4 $\bar{d} = 785$ mg CURS: 33.6 NUDS: 43.3	Pl: 10 (0) $\bar{A} = 64$ y $\bar{O} = 3.1$ y H-Y: 2.7 $\bar{d} = 710$ mg CURS: 38.5 NUDS: 43.5	R D/B	6 mo	most effective: 42 ± 16 mg	• NUDS/CURS scores: DHEC > Pl
Jörg (1998)	–	564 (79) $\bar{A} = 69$ y H-Y: 3.0 (median: 3)		Observ.* MC (149; Germany)	c.4 mo (per patient)	40!19 mg	• 90% with previous antiparkinsonian treatment, incl. L-DOPA (54%) • 38% dissatisfied with previous therapy, principally because of tolerance problems • Mean L-DOPA dose: decreased from 235 to 196 mg/day (for total group)

- H-Y stage: c.53% no change, 45% improved, 2.3% worsened. Mean for group at end: 2.8 (median: 2)
- Webster score: improved from mean 15.9!6.3 to 10.6 ± 6.2 points
- Side effects reported by 156 patients; almost half were gastrointestinal events
- Tolerance as rated by patients: '(very) good': 83½%; 'poor': 8%; effectiveness: '(very) good': 65%; 'poor': 6%

* Observational study; that is, uncontrolled review of clinical experience, included in this review because of sample size and paucity of available controlled studies

Table 12. Piribedil as adjunct to L-DOPA therapy in Parkinson's disease

Study	Control	Subjects		Design	Duration	Mean end daily dose	Results
Ziegler et al. (2003)	Pl	Pi: 61 (13) $\bar{A} = 63$ y $\bar{O} = 55$ mo UPDRS-III: 28.0 $\bar{d} = 423$ mg H-Y: 2.1	Pl: 54 (10) $\bar{A} = 65$ y $\bar{O} = 48$ mo UPDRS-III: 29.1 $\bar{d} = 398$ mg H-Y: 2.1	R D/B MC (31; France, Portugal)	6 mo (incl. 5 wk titr.)	150 mg (fixed max.)	• L-DOPA could be adjusted after 4 mo; at 6 mo: Pi −8.8 mg; Pl +15.1 mg (not significant) • Responders (30% decrease UPDRS III) at 4 mo: Pi > Pl. (56.4% v. 37.7%) • Responders at 6 mo: Pi > Pl. (61.8% v. 39.6%) • UPDRS change at 6 mo: Pi > Pl (−10.0 v. −6.7); at 4 mo: Pi = Pl • Most frequent adverse event: gastrointestinal symptoms (Pi: 27 patients; Pl: 13 patients)

Table 13. Summary of results in trials of dopamine receptor agonists as adjuncts to L-DOPA in antiparkinsonian therapy

	Comparison with bromocriptine (or with other agonist)			Comparison with placebo		
	Trials	L-DOPA dose reduction	Symptomatic effect	Trials	L-DOPA dose reduction	Symptomatic effect
Lisuride	2 (1)	Li = Br	Li = Br (Li < DHEC =	2	✓	✓
Pergolide	4 (2)	Pe ≥ Br (Pr > Pe)	Pe > Br (Pe = Li)	1	✓	✓
Cabergoline	5	Ca = Br	Ca = Br	3	✓	✓
Ropinirole	4	Ro > Br?	Ro = Br	5	✓	✓
Pramipexole	3	n.d.	Pr ≥ Br (Pr = Pe)	8	✓	✓
Bromocriptine				5	✓	✓
α-DHEC	1 (1)	n.d.	DHEC > Br (DHEC > Li)	1	n.d.	✓

hand, it would be difficult to conclude that any of these agents offers distinct advantage over the others with regard to clinical efficacy.

2. Dopamine receptor agonists as monotherapy in Parkinson's disease

The question of whether a dopamine receptor agonist is to be preferred to L-DOPA early in the course of Parkinson's disease has been discussed for many years. This issue cannot, however, be discussed here, where the emphasis concerns differences in the effectiveness of the various agents. In general, the dopamine receptor agonists are comparable with L-DOPA in their symptomatic effect early in treatment, but tend to fall behind the gold standard later in the course of therapy; this decline in efficacy, however, is usually matched by a comparatively reduced incidence and severity of untoward motor side effects (see also Caraceni and Musicco, 2001; these results were not included below as bromocriptine and lisuride were employed as 'dopamine agonists' without further differentiation between their effects). Nonetheless, a shift over the past ten years to a consensus that dopamine receptor agonists are to be preferred to L-DOPA at the commencement of therapy, particularly in younger (<50 years) patients, is clearly discernible.

(a) Bromocriptine (Table 14). In general, both positive and negative effects of bromocriptine monotherapy are comparable with those of L-DOPA monotherapy in those patients classified as 'responders'; there were, however, high numbers of 'non-responders' in these trials. Few patients could be maintained on bromocriptine alone for more than two years.

(b) Lisuride (Table 15). Two major studies suggest that the symptomatic effect of lisuride is not as great as L-DOPA at the initiation of therapy; on the other hand, addition of lisuride to L-DOPA therapy results in fewer motor complications, perhaps due to lower required L-DOPA dose, but may be accompanied by increased psychic side effects. It must, however, be noted that lisuride has not

Table 14. Bromocriptine monotherapy in Parkinson's disease

Study	Control	Subjects		Design	Duration	Mean end daily dose	Results
Olanow et al. (1987)	L-D	Br: 23 (1) $\bar{A} = 61$ y $\bar{O} = 1.3$ y	L-D: 24 (4) $\bar{A} = 64$ y $\bar{O} = 1.5$ y	R S/B MC (USA)	min. 6 mo mean 17.2 mo	Br: 10.9 mg (6 mo) 16.8 mg (15 mo) L-D: 322.9 mg (6 mo) 383.3 mg (15 mo)	• Dyskinesia/dystonia as adverse effects: Br > L-D (CF: 1 v. 9) • Motor impairment: Br = L-D (own composite scale) • After mean 17 months: 5 Br patients also used L-D.
Herskovits et al. (1988)	L-D	Br: 43 (2)	L-D: 43 (1) $\bar{A} = 67½$ y de novo combination Br/L-DOPA: 31 patients	R S/B MC (Argentina)	follow-up: 18–45 mo	Br: 12.6 mg L-D: 556.1 mg	• Dyskinesia/dystonia as adverse effects: Br = L-D (CF: 1 v. 2) • Motor impairment: Br = L-D (Webster scale)
Riopelle et al. (1988)	L-D	Br: 42 (4) $\bar{A} = 66½$ y H-Y: 2.7 (I–V)	L-D: 39 (0) $\bar{A} = 66$ y H-Y: 2.3 (I–V)	R D/B MC (7; Canada)	baseline 2 wk titr. 15 wk 6 wk maint.	Br: 26.1 mg L-D: 262.8 mg	• Dyskinesia/dystonia as adverse effects: Br = L-D (CF: 0 v. 0) • Motor impairment: Br = L-D (modified CRS: 61% v. 55% improvement) • Disability: Br = L-D (NUDS: 38% v. 37% improvement) • H-Y stage improved: Br = L-D (20% v. 16%)
Hely et al. (1989, 1994, 1999)	L-D	Br: 75 (20 at 5 y; n.g. at 10 y) data for patients completing titration phase:	L-D: 74 (11 at 5 y; n.g. at 10 y)	R D/B (titr. only) MC (4; Australia)	baseline 1 mo titr. 6 mo. follow-up 4½ y+	Br monotherapy: 18 mg (1 y), 31 mg (3 y) L-D	• By 1 y 32, 2 y 18, 3 y 5, 5 y 0 patients in Br-only therapy; for L-D alone therapy: 56, 51, 42 and 31 patients: Mean time foe Br-monotherapy: 12.1 mo;

		n = 62 $\bar{A}$ = 62 y $\bar{O}$ = 22 mo H-Y: 2.3 mod. CURS score: 18.3	n = 64 $\bar{A}$ = 62 y $\bar{O}$ = 25 mo H-Y: 2.2 mod. CURS score: 15.3			monotherapy: 344 mg (1 y) 427 mg (3 y) 471 mg (5 y) Br ▶ Br + L-D: 28 mg Br, 615 mg L-D (5y; n = 18) L-D ▶ L-D + Br: 19 mg Br, 559 mg L-D (5 y; n = 11) Br ▶ L-D: 554 mg (5 y; n = 12)	for L-D monotherapy: 52.3 mo • No significant differences in L-D dose • Motor impairment: all groups better than baseline for 2 y; Br above baseline at 3 y, Br ▶ L-D at 4 y, L-D at 5 y (modified CURS). Change in scores at 5 y: Br ▶ Br/L-D (−1.9) > L-D (+2.3) > Br ▶ L-D (+9.7); at 3 y, Br alone: +5.2 • Disability: similar changes (modified NUDS) • Dyskinesia/dystonia as adverse effects: Br > L-D. At 5 y, 35 patients randomized to L-D had developed dyskinesia, and 17 randomized to Br; none developed dyskinesia while receiving Br alone • Wearing off: Br > L-D. • At 10 years it was noted that neither L-DOPA alone or in combination with Br affected duration or progression of the disorder
Goetz et al. (1989)	–	11 $\bar{A}$ = 65 y $\bar{O}$ = 14.2 y $\bar{D}$ = 12.9 y Pe: since mean 34 mo H-Y: 2.3		O/L switch	6 mo (abrupt switch)	33.6 mg	• Patients had been switched due to failure of Pe after initial success. Br did not overcome this problem: • NUYPDS: 5.5 (before Pe); 4.3 (peak Pe benefit); 7.0 during failure); 6.3 (after Br) • NUDS: 8.5; 6.5; 11.0; 11.1 • H-Y: 2.9; 2.8; 3.4; 3.3

(*continued*)

Table 14 (*continued*)

Study	Control	Subjects			Design	Duration	Mean end daily dose	Results
Montastruc et al. (1990)	L-D	Br: 18 $\bar{A} = 63$ y $\bar{O} = 23$ mo H-Y: 2.1 mod. CURS: 34.3	L-D: 18 $\bar{A} = 61$ y $\bar{O} = 31$ mo H-Y: 1.8 mod. CURS: 40.1		R	3 y	Br: 55 ± 6 mg L-D: 485 ± 71 mg	• Motor impairment: Br = L-D (change in mod. CURS at 3y: $-2.5 = 7\%$ v. $-8.4 = 18\%$; in both cases, benefit occurred entirely in first 6 mo) • Dyskinesia, wearing-off, fluctuations as adverse effects: Br > L-D (0 v. 7 cases) • Loss of efficacy: L-D > Br (0 v. 5 cases)
Weiner et al. (1993)	L-D	Br: 6 (1) $\bar{A} = 60$ y H-Y: 2.0 $\bar{O} = 34$ mo	Br/L-D: 12 (2) $\bar{A} = 58$ y H-Y: 2.4 $\bar{O} = 13.9$ mo	L-D: 7 (1) $\bar{A} = 66$ y H-Y: 2.1 $\bar{O} = 11.6$ mo	R D/B P	4 y (patients treated 21–48 mo)	Br: 18 mg L-D: 417 mg Br: 14 mg/ L-D 386 mg	• Dyskinesia/dystonia as adverse effects: Br > L-D (CF: 7 v. 27) • Motor impairment: Br = L-D = Br/L-D (modified CURS); maximal improvement at 6 mo • Disability: Br = L-D = Br/L-D (ADL scale); maximal improvement at 6 mo
Olanow et al. (1995)	Pl	I. DP + L-D 25(5) (L-D total) $\bar{A} = 66$ y $\bar{O} = 3.2$ y UPDRS: 23.4 UPDRS-II: 9.7 UPDRS-III: 13.7	II. Pl + L-D 24(3)		R D/B MC (2 USA) Prosp.	12 mo +2 mo DP-free	I 382 mg L-D II 426 mg L-D III 85 mg L-D + 28 mg Br IV 117 mg L-D + 28 mg Br	• SINDEPAR study (to test neuroprotective effect of DP) • UPDRS: Br (-4.5) = L-D (-1.7) • UPDRS: DP (-0.4) > Pl (-5.8) • UPDRS-II: Br (-0.8) = L-D (-0.6) • UPDRS-III: Br (-3.6) = L-D (-1.0)

		III. DP + Br 27(5)	IV. Pl + Br 25(6)					
		(Br total) $\bar{A} = 67$ y $\bar{O} = 2.9$ y UPDRS: 22.7 UPDRS-II: 9.8 UPDRS-III: 12.9						
		(DP total) $\bar{A} = 65$ y $\bar{O} = 2.9$ y UPDRS: 24.5 UPDRS-II: 10.2 UPDRS-III: 14.4	(Pl total) $\bar{A} = 68$ y $\bar{O} = 3.2$ y UPDRS: 21.4 UPDRS-II: 9.3 UPDRS-III: 12.2					
Kowa et al. (1997)	–	46 (35 ultimately required L-DOPA)				9 y	(−L-DOPA): 11.1 mg (+L-DOPA): 12.7 mg	• H-Y: for monotherapy, 2 of 11 cases improved (II ▶ I), 5 were stable; for combined therapy, 4 of 35 cases improved, 11 were stable
Parkinson's Disease Research Group (UK) (1993), Lees et al. (1995)	L-D	Br: 262 (181) $\bar{A} = 62$ y $\bar{O} = 14$ mo H-Y: 2.1 NUDS: 42.9 Webster: 11.9	L-D: 249 (80) $\bar{A} = 63$ y $\bar{O} = 14$ mo H-Y: 2.1 NUDS: 43.9 Webster: 11.8	L-D +selegiline: 271 (76) $\bar{A} = 63$ y $\bar{O} = 14$ mo H-Y: 2.2 NUDS: 42.8 Webster: 11.0	R O/L MC (93; UK)	3 + 7 y	Br: 36 mg L-D −selegiline: 375 mg (median: 420 mg) +selegiline: 375 mg (median: 352 mg)	• Motor impairment: L-D > Br (Webster score improvement: 3.1 (L-DOPA alone) v. 3.4 (L-DOPA + selegiline) v. 2.1 (Br)) • Dyskinesia/dystonia as adverse effects: Br > L-D (CF: 9% v. 52% (−selegiline) v. 58% (+selegiline)) • On-off fluctuations: Br > L-D (CF: 5% v. 33% (−selegiline) v. 35% (+selegiline))
Lees et al. (2001)		(249; 140 deaths)	(205; 118 deaths)	Terminated 1995 (148 death)			Br: n.g. + 516 mg L-DOPA L-D: 663 mg	• Mortality at 10y: L-D = Br • Disability: L-D > Br (significant in first years) • Dyskinesia: Br > L-D • Moderate to severe dyskinesias: Br = L-D • Dystonias, on-off fluctuations: Br > L-D • Moderate to severe dystonias, on-off fluctuations: Br = L-D

Table 15. Lisuride as adjunct and monotherapy in Parkinson's disease

Study	Subjects			Design	Duration	Mean end daily dose	Results
Giovannini et al. (1988)	Li alone: 20 (11) $\bar{A} = 51$y $\bar{O} = 42.6$ mo H-Y: 2.1 CURS: 26.8 prior L-DOPA: 5 patients	Li/L-D: 36 (14) $\bar{A} = 53½$ y $\bar{O} = 99.6$ mo H-Y: 2.5 CURS: 22.0 prior L-DOPA: 28 patients included 8 patients originally in Li-only group mean treatment time: 73.4 mo		O/L	4 y	Li: ~2 mg Li: ~3 mg/ L-D: ~1000 mg	• H-Y: stable in combination group, improved to 1.5 in Li-group at 3 mo; return to baseline by 4y • CURS: Li = L/L-D (−8 points = 30% v. −8 points = 36%); improvement maintained over time • Rigidity: Li = L/L-D; akinesia, walking: L/L-D ≥ L • Dropouts due primarily to lack of efficacy in Li-only patients and to mental side effects in L-L/D patients.
Rinne (1989)	L-DOPA 30 (0) $\bar{A} = 61$ y $\bar{O} = 2.5$ y H-Y: 2.2	Li (later: + L-DOPA) 30 (2) $\bar{A} = 63$ y $\bar{O} = 2.2$ y H-Y: 2.3	Li + L-DOPA 30 (1) $\bar{A} = 61$ y $\bar{O} = 2.4$ y H-Y: 2.2	R Prosp.	4 y	L-D (n = 25): 665 mg Li (n = 5): 1.2 mg Comb. (n = 27): 484 mg/1.1 mg Late comb. (n = 20):[1] 630 mg/0.8 mg	• L-DOPA dose lower in combination group than in L-DOPA monotherapy group • End-of-dose and peak dose dyskinesias: Li > L-DOPA (L-1 v. 65; combination groups: 18 and 22) • Symptom severity (CURS): L-DOPA > Li in first year (56% v. 32% improvement) • But: combination of L-DOPA and Li equivalent to high dose L-DOPA in later years
Rinne (1999) (continuation)					10 y	L-DOPA (n = 15):	

					777 mg Comb. (n = 17): 653 mg/0.8 mg Late comb. (n = 20):[1] 577 mg/1.1 mg	• Reduced incidence of dyskinesia in combination group • Increased incidence of confusion/hallucinations in combination group
Stocchi et al. (2002)	L-DOPA: 20 (0) $\bar{A}$ = 54 y $\bar{O}$ = 8.8 y UPDRS-III (on): 21.7 UPDRS-III (off): 44.4 H-Y: 3.8 $\bar{D}$: 8.1y $\bar{d}$: 675 mg	Li[2]: 20 (2) $\bar{A}$ = 53 y $\bar{O}$ = 10.0 y UPDRS-III (on): 25.1 UPDRS-III (off): 49.7 H-Y: 4.0 $\bar{D}$: 9.1y $\bar{d}$: 688 mg	R O/L Prosp.	4 y	L-D: 1033 mg L-DOPA Li: 333 mg L-DOPA (day only) 0.9 mg Li	• Advanced disease; all with dyskinesia and motor complications • Lisuride continuously infused • UPDRS-III (on): Li = L-D (+1.7 v. +6.5) • UPDRS-III (off): Li = L-D (−2.5 v. +5.3) • Time off: Li > L-D (−2.9 h = −70% v. +0.9 h = +21%) • Dystonia: Li > L-D (−1.8 = −90% v. +0.6 = +32%) • Nocturnal akinesia: Li > L-D (−0.9 = −37% v. +1.4 = +56%) • L-DOPA dose: Li > L-D (−52% v. +53%) • 15 patients in L-DOPA group also received Li or Br

[1] Patients who were originally in lisuride monotherapy group, but who commenced L-DOPA treatment during trial; [2] L-DOPA initially withdrawn; could be added as required

been examined in a controlled trial of the size and quality to which newer dopamine receptor agonists have been subjected, with the exception of the infused lisuride trial reported by Stocchi et al. (2002), which supported a role for infused dopamine receptor agonists as the principle therapy in the management of severe motor complications in advanced Parkinson's disease.

(c) Pergolide (Table 16). Two placebo-controlled studies confirmed the effectiveness of pergolide as monotherapy; a small comparison (ten patients per group) suggested that it is equipotent with L-DOPA in early stage patients. The more recent and much larger PET-controlled Pelmopet (Pergolide versus Levodopa in Early Parkinson's Disease) study found L-DOPA to be superior with respect to UPDRS score and tolerability, but management of dyskinesia was better achieved with the agonist.

(d) Cabergoline (Table 17). The one major controlled study indicated a significant L-DOPA-sparing effect (>50%), and one-third of patients did not require L-DOPA even at five years. The symptomatic effect of L-DOPA was slightly greater at one year, but this difference reduced with time.

(e) Ropinirole (Table 18). Symptomatic and L-DOPA-sparing properties for ropinirole (comparable with those of bromocriptine) have been established; the symptomatic effect appears to be slightly less than that of L-DOPA, the presentation of motor complications is, on the other hand, reduced. The major study comparing ropinirole with bromocriptine monotherapy indicated that the two were largely equipotent.

(f) Pramipexole (Table 19). As for ropinirole, symptomatic and L-DOPA-sparing properties for pramipexole have been established; the symptomatic effect appears to be slightly less than that of L-DOPA, the presentation of motor complications is, however, reduced.

(g) α-Dihydroergocriptine (Table 20). Symptomatic effects of DHEC were evaluated positively in two studies, with efficacy comparable with that of bromocriptine, but with perhaps greater tolerability. See also recent overview by Albanese and Colosimo (2003).

(i) Piribedil (Table 21). One major uncontrolled study found piribedil to be effective for management of motor and affective symptoms in early, L-DOPA-naive Parkinson's disease patients.

Summation: Bromocriptine is associated with a higher non-responder rate than other D_2 receptor agonists in de novo parkinsonian patients, but, as with the employment of dopaminergic agents as adjuncts to L-DOPA therapy, there is little else to suggest that significant differences between their positive and negative effects of different dopamine receptor agonists can be advanced to justify the use of a particular agent. Most studies which have investigated the switch from one agonist to another have detected no specific problems; nevertheless, isolated reports – for example, of a neuroleptic malignant-like syndrome following rapid switch from bromocriptine to pergolide (Reimer et al., 2002) – suggest that caution must nonetheless be exercised while certain

Table 16. Pergolide as monotherapy in Parkinson's disease

Study	Control	Subjects		Design	Duration	Mean end daily dose	Results
Kulisevsky et al. (1998)	L-D	Pe: 10 (0) $\bar{A} = 64$ y $\bar{O} = 14.1$ mo mean H-Y: 1.5 UPDRS-II: 8.7 UPDRS-III: 22.9	L-D: 10 (0) $\bar{A} = 67$ y $\bar{O} = 14.4$ mo mean H-Y: 1.8 UPDRS-II: 11.8 UPDRS-III: 24.8	R O/L	6 mo	Pe: 2.8 mg L-DOPA: 435 mg	• Pe = L-DOPA, both with respect to positive outcomes (significant time effect detected) and adverse effects (UPDRS)
Barone et al. (1999)	Pl	Pe: 53 (10) $\bar{A} = 63$ y $\bar{O} = 14.1$ mo median H-Y: 2 UPDRS: 34.4 UPDRS-III: 24.5 CGI: 3.2	Pl.: 52 (6) $\bar{A} = 61$ y $\bar{O} = 14.1$ mo median H-Y: 2 UPDRS: 35.8 UPDRS-III: 25.3 CGI: 3.3	R D/B Parallel MC	3 mo (incl. 3 wk titr., 9 wk flexible dosing, 2 wk de-titr.)	2.06 ± 0.76 mg	• Responders ($\geq 30\%$ reduction in UPDRS score): Pe > Pl (57% v. 17%) • UPDRS: Pe > placebo (−9.8 v. −1.8) • UPDRS-II score: Pe > Pl (−2.3 = 27% v. +0.1) • UPDRS-III score: Pe > Pl (−7.5 = 31% v. −1.7) • S&E score: Pe > Pl (−0.4 v. +0.2) • CGIS: Pe > Pl (48.2% of patients at least much improved v. 4.8) • Adverse effects: Pe = Pl (34 v. 31 events)
Lledo et al. (1999)	Pl	Pe: 102 (11) H-Y: I–III	Pl.: 104 (4)	R D/B Parallel MC	See note 1 below	2.08 mg	• Responders: Pe > Pl 48% v. 21%); all ages, H-Y ratings • UPDRS, UPDRS-II, UPDRS-III, S&E, CGI-severity, CGI-improvement, H-Y: Pe > Pl (no data given)
Oertel et al. (2001)	L-D	Pe: 148 (71) de novo UPDRS-III = 15.1	L-D: 146 (56) de novo UPDRS-III = 15.9	R D/B	3 y	Pe: 3.2 mg L-D: 504 mg	• PET-controlled study in 88 patients ('Pelmopet'): no significant differences • UPDRS-III: L-D > Pe (−2.5 v. +3.0) • Discontinuation due to adverse effects: L-D > Pe (18% v. 9%) • Time to first dyskinesia: Pe > L-D • Dyskinesia incidence: Pe > L-D (16% v. 33%) • Motor complications (UPDRS-IV): Pe > L-D • Monotherapy Pe delayed onset of motor complications, was slightly less effective for symptomatic treatment

[1] Protocol: prestudy followed by I. fixed titration to max. 0.75 mg (3 wk); II. flexible titration to max 3 mg (9 wk); III. detitration (1–2 wk)

Table 17. Cabergoline as monotherapy in Parkinson's disease

Study	Control	Subjects		Design	Duration	Mean end daily dose	Results
Rinne et al. (1997) Rinne et al. (1998)	L-D	Ca: 208 (37)[1] $\bar{A}$ = 60½ y $\bar{O}$ = 1.9 y H-Y: 1.9 UPDRS-III: 27.5	L-D: 205 (29)[1] $\bar{A}$ = 63 y $\bar{O}$ = 2 y H-Y: 2.0 UPDRS-III: 29.1	R D/B MC (32; Europe, S. America) O/L addition of L-D[2]	24 wk + 3 y follow-up (to be continued until 5 y)	Ca: 2.8 mg[1] L-D: 468 mg[1]	• Requirement for (additional) L-DOPA: L-D > Ca (18% v. 38% at 1 y; 48% v. 65% at 3 y) • Total L-DOPA required: Ca > L-D (305 mg v. 785 mg at 1 y); total mean exposure: 303 g v. 637 g • 62% of Ca group still Ca-only at 1 y; 35% at 5 y • UPDRS-III: L-D ≥ Ca (−16.5 v. −13.7 at 1 y; most of difference attributable to those in Ca group requiring L-DOPA). >80% of all groups achieve >30% improvement by 1 y • UPDRS-I/II: L-D = Ca at 1 y • CGI: L-D = Ca at 1 y (61½% v. 66½% much improved by 1 y) • Adverse effects: Ca ≈ L-D (76% v. 66% at 1 y) • UPDRS-II, UPDRS-III: Ca = L-D (−12.9 v. −12.2); both declined since peak improvement at 1 y: UPDRS-III score 30% below baseline for L-D at 3 y, 22% for Ca • Development of motor complications: Ca > L-D (22% (of which only 4 patients were on monotherapy) v. 34%) • Adverse effects: Ca ≈ L-D (31% v. 25%) • Withdrawal rate: Ca ≈ L-D (16% v. 13%) • Mean cumulative L-DOPA dose: Ca > L-D alone (303 g v. 637 g)
Musch (2001)	L-D	C: 211 De novo	L-D: 208 De novo	R D/B O/L addition of L-DOPA	5 y	C: max. 4 mg L-D: max. 600 mg	• Motor complications: Ca > L-D (50% lower risk) • 76 patients never received L-DOPA • UPDRS: L-D > Ca • Adverse effects: Ca = L-D (except edema: L-D > Ca)

[1] At end of first year; [2] Where decrease in UPDRS motor score did not reach 30%; this was 18% of patients at 6 mo, 38% at 12 mo

Table 18. Ropinirole as monotherapy in Parkinson's disease

Study	Control	Subjects		Design	Duration	Mean end daily dose	Results
Wheadon et al. (1996) Adler et al. (1997)	Pl	Ro: 116 (37) +selegiline: n = 58 $\bar{A}$ = 59 y $\bar{O}$ = 30.4 mo H-Y: I–II.5: 53; III: 5 patients UPDRS-III: 16.7 −selegiline: n = 58 $\bar{A}$ = 65 y $\bar{O}$ = 18.8 mo H-Y: I–II.5: 49; III: 9 patients UPDRS-III: 19.1	Pl.: 125 (20) +selegiline: n = 61 $\bar{A}$ = 62 y $\bar{O}$ = 27.5 mo H-Y: I–II.5: 56; III: 5 patients UPDRS-III: 17.7 −selegiline: n = 64 $\bar{A}$ = 66 y $\bar{O}$ = 18.2 mo H-Y: I–II.5: 54; III: 10 patients UPDRS-III: 18	R D/B P MC (25; USA) only allowed co-medication: selegiline	6 mo	15.7 ± 8.3 mg (no selegiline effect)	• UPDRS-III: Ro > Pl (4.5 = 24% v. decline by 0.2 = −3%; no selegiline effect • Responders (>30% UPDRS-III reduction): overall Ro > Pl (47% v. 20%); but difference principally attributable to selegiline arm (56 v. 14%; non-selegiline: 38% v. 20%, NS) • CGI: Ro > Pl (33% v. 12% of patients improved; no selegiline effect) • Required L-DOPA: Ro > Pl (13 patients = 11% v. 36 patients = 29%; no selegiline effect)
Sethi et al. (1998) (extension of Adler et al., 1997)	Pl	Ro: 70 (5) $\bar{A}$ = 62 y $\bar{O}$ = 23.5 mo H-Y: 2.0 UPDRS-III: 9.4 +selegiline: 36 patients (drawn from those patients who had completed Adler et al., 1997)	Pl.: 77 (8) $\bar{A}$ = 62 y $\bar{O}$ = 22.6 mo H-Y: 2.1 UPDRS-III: 12.9 +selegiline: 40 patients	R D/B P MC (22; USA)	6 mo	17.9 ± 7.0 mg	• Completion of twelve month trial without L-DOPA: Ro > Pl (51 patients = 44% v. 28 patients = 22%; based on original n = 116/125) • Required L-DOPA over 12 months: Ro > Pl (22 patients = 19% v. 57% = 46%) • Insufficient therapeutic response: Ro > Pl (23 patients = 20% v. 57 patients = 48%; based on original n = 116/125) • Total withdrawals over 12 mo: Ro = Pl (37% v. 32%) • UPDRS-III over 12 mo: Ro > Pl (−33% to 10.9 v. +10% to 15.0) • CGI score: R > Pl (61% v. 18% of patients improved)

(*continued*)

Table 18 (*continued*)

Study	Control	Subjects		Design	Duration	Mean end daily dose	Results
Rascol et al. (1998, 2000) Reichmann and Lachenmayer (2000) Lang et al. (2002) (056 Study Group)	L-D	Ro: 179 (94) $\bar{A} = 63$ y $\bar{O} = 30$ mo H-Y: 2.0 UPDRS-III: 21.5 UPDRS-II: 8.0 +selegiline: 81 patients (45%) L-DOPA in previous 6 wks: 24 patients ($14\frac{1}{2}$%)	L-D: 89 (44) $\bar{A} = 63$ y $\bar{O} = 29$ mo H-Y: 1.9 UPDRS-III: 21.7 UPDRS-II: 8.0 +selegiline: 39 patients (44%) L-DOPA in previous 6 wks: 7 patients (8%)	R D/B MC (30; Europe, Israel, Canada) only allowed co-medication at start: selegiline; O/L L-DOPA	5 y	Ro: 16.5 ± 6.6 mg L-D: 753 ± 398 mg	• Dyskinesia presented (cumulative): Ro > L-D (20% v. 45%); dyskinesia as adverse event: Ro > L-D (9% v. 26%); as disabling event: Ro > L-D (8% v. 23%) • Incidence of dyskinesia in patients without supplementary L-DOPA: Ro > L-D (5% v. 36%) • Time to dyskinesia in 25 percent of patients remaining in study: Ro > L-D (214 wk v. 104 wk) • Hazard ratio for freedom from dyskinesia (Ro v. L-D) = 2.82 • UPDRS-III: L-D > Ro (−4.8 v. −0.8 points); responders: L-D = Ro (58% v. 48%) • UPDRS-II: Ro = L-D (+1.6 points v. ±0.0) • Time to wearing-off in 25% of patients: Ro (199 wk) v. L-D (145 wk); no statistical analysis • Patients experiencing wearing-off: Ro > L-D (23% v. 34% of patients; no statistical analysis) • Adverse events withdrawals: Ro = L-D (27% v. 33%) • 56 (66%) of the ropinirole patients who completed the study received L-DOPA: $\bar{d}$: 427 ± 221 mg • Ro generally equal to L-DOPA except in more advanced patients; post hoc analysis suggests that risk for development of dyskinesia did not significantly increase in Ro group following addition of L-DOPA

Korczyn et al. (1998, 1999) (053 Study Group)	Br	Ro: 168 (66) $\bar{A} = 63$ y $\bar{O} = 22.8$ mo H-Y: 2.1 UPDRS-III: 23.3 UPDRS-II: 8.5 +selegiline: 53 patients	B: 167 (55) $\bar{A} = 63$ y $\bar{O} = 26.8$ mo H-Y: 2.0 UPDRS-III: 23.1 UPDRS-II: 8.1 +selegiline: 57 patients	R D/B P MC (37; Israel, S. Africa, Europe)[1]	3 y	Ro: 12.0 ± 5.6 mg Br: 24 ± 8 mg (Patients not receiving L-DOPA: Ro: 10.1 ± 4.8 mg Br: 22.5 ± 8.4 mg	• L-DOPA required: Ro = Br (34% v. 42% of total patient group; 60% v. 53% of those who completed study) • Completed study without L-DOPA: Ro = Br (36% v. 35%) • Completed study without L-DOPA: selegiline users ≥ selegiline non-users (Ro: 47% v. 31%; Br: 42% v. 30%) • Change in UPDRS-II: Ro > Br (−2.7 v. −0.9); change occurred during first 6 mo of study • Change in UPDRS-III: Ro ≥ Br (−7.7 = 31% v. −6.3 = 22%); responders (≥30% improvement): R > B (53% v. 42%) • Change in UPDRS-II (no L-DOPA): Ro > Br (−3.4 v. −1.5) • Change in UPDRS-III (no L-DOPA): Ro = Br (−8.2 = 28% v. −6.2 = 23%); responders: Ro = Br (42% v. 39%) • Change in UPDRS-III, selegiline non-users > users (Ro: 36% v. 11%; Br: 27% v. 16%) • Classified as responders: Ro, selegiline users = non-users (43% v. 42%); L-D, selegiline users > non-users (50% v. 31%) • CGI, selegiline users: Ro = Br (53% v. 58% of patients) • CGI, selegiline non-users: Ro > Br (46% v. 30% of patients) • Dyskinesia incidence: Ro = Br (7.7% v. 7.2%; half after L-DOPA introduction) • Adverse events: Ro = Br; except nausea: Ro > Br (40½% v. 25%)

(*continued*)

Table 18 (*continued*)

Study	Control	Subjects		Design	Duration	Mean end daily dose	Results
Brooks et al. (1998)	Placebo	R: 41 (3) $\bar{A} = 59$ y $\bar{O} = 28$ mo H-Y: ≤ 2: 34 patients >2: 7 patients UPDRS-III: 18.6	Pl.: 22 (1) $\bar{A} = 57$ y $\bar{O} = 26$ mo H-Y: ≤ 2: 14 patients >2: 8 patients UPDRS-III: 19.9	R D/B MC; UK, Europe, S. Africa	12 wk	~3.9 mg	• UPDRS-III: Ro > Pl (−43.4% v. −21%) • Responders: Ro > Pl (71% v. 41%) • UPDRS-I, UPDRS-II, H-Y: Ro = Pl • CGE: Ro > Pl (71% v. 41%) • All adverse effects: Ro = Pl
De Lucia (2001)	L-D	Ro: 70 $\bar{A} = 65½$ y	L-D: 40	R	18 mo	–	• 58% (41 patients) complete Ro trial without L-DOPA; 7% with dyskinesia • 33% (14 patients) complete L-DOPA trial as monotherapy; 30% with dyskinesia; odds ratio = 15:1 compared with Ro alone, 4:1 with all patients using Ro
Rakshi et al. (2002)	L-D	Ro: 31(3) $\bar{A} = 61$ y $\bar{O} = 26$ mo H-Y: 1.8 UPDRS-III: 14.0 v. 11.0	L-D: 14(5)	D/B R MC (11; UK, France)	2 y		• ^{18}F-dopa PET study (pilot study with subgroup of patients from Rascol et al., 2000): change in putamen DOPA uptake between scans at 6 and 24 mo similar in both groups (Ro −13% v. L-D −18%); same true for best and worst putamen uptake figures • UPDRS-III: L-D > Ro (+8.2 v. +11.4)
Whone et al. (2003) (REAL-PET)	L-D	Ro: 93 (25) $\bar{A} = 61$ y $\bar{O} = 15.6$ mo H-Y: 1.8	L-D: 93 (24) $\bar{A} = 60$ y $\bar{O} = 16.3$ mo H-Y: 1.7	D/B R MC (34; Austria, Canada,	2 y	Ro: 12.2 mg L-D: 559 mg	• Rakshi et al. (2002) data interpreted as suggestive of slower progression with ropinirole; REAL-PET study designed to confirm this potential. • Primary endpoint was the change in

UPDRS-III: 19.2	UPDRS-III: 17.7	France, Germany, UK, USA)	putamen ^{18}F-dopa uptake measured with 3D PET. • 14% of Ro and 8% of L-D patients required supplementary open L-DOPA. • Central ROI analysis of putamen ^{18}F-dopa uptake showed significantly slower progression with Ro (−13% v. −20% L-D; p = 0.022). • SPM detected significantly slower progression in both putamen and nigra in the Ro (putamen: −14% v. −20% L-D, p = 0.034; nigra: Ro +3% v. −8% L-D, p = 0.035). • Local ROI analysis of spatially non-normalised putamen ^{18}F-dopa uptake showed a trend in favour of Ro (−15% v. −18% L-D; p = 0.354). • Incidence of dyskinesia: Ro > L-D (3% v. 27%). • UPDRS-III: favoured the L-DOPA group by six points

[1] Patients stratified according to concomitant selegiline therapy

Table 19. Pramipexole monotherapy in Parkinson's disease

Study	Control	Subjects	Design	Duration	Mean end daily dose	Results
Hubble et al. (1995)	Pl	Pr: 28 (0) $\bar{A} = 63½$ y $\bar{O} = 2.1$ y H-Y: I–III UPDRS-II: 10.9 UPDRS-III: 26.5	Pl: 27 (3) $\bar{A} = 63$ y $\bar{O} = 2.1$ y H-Y: I–III UPDRS-II: 10.5 UPDRS-III: 27.4	R P MC (4; USA)	9 wk	max. 4.5 mg	• UPDRS-II: Pr > Pl (−4.8 = 44% v. −2.3 = 22%) • UPDRS-III: Pr ≥ Pl (−12.0 = 45% v. −8.2 = 30%)
Shannon et al. (1997) (Pramipexole Study Group)	Pl	Pr: 164 (28) UPDRS-II: 8.2 UPDRS-III: 18.8 $\bar{A} = 63$ y $\bar{O} = 1.8$ y H-Y: 1–3	Pl: 171 (34) UPDRS-II: 8.3 UPDRS-III: 18.8	R D/B MC (18; USA)	titr. 7 wk maint. 24 wk	3.8 mg	• UPDRS-II: Pr > Pl (−1.8 = −22% v. +0.4 = +5%) • UPDRS-III: Pr > Pl (−4.7 = −25% v. +1.3 = +7%)
Parkinson Study Group (1997)	Pl	Pl: n = 51 (0), $\bar{A} = 60$ y, $\bar{O} = 1.7$ y; H-Y: 1.8; UPDRS: 28.7; prior L-DOPA: 27%; selegiline users: 59% 1.5 mg Pr: n = 54 (10), $\bar{A} = 60$ y, $\bar{O} = 1.8$ y; H-Y: 1.8; UPDRS: 29.0; prior L-DOPA: 24%; selegiline users: 56% 3 mg Pr: n = 50 (2), $\bar{A} = 62$ y, $\bar{O} = 2.0$ y; H-Y: 1.9; UPDRS: 28.3; prior L-DOPA: 22%; selegiline users: 68% 4.5 mg Pr: n = 54 (4), $\bar{A} = 63$ y, $\bar{O} = 1.9$ y; H-Y: 1.9; UPDRS: 32.9; prior L-DOPA: 20%; selegiline users: 67% 6 mg Pr: n = 55 (9), $\bar{A} = 63$ y, $\bar{O} = 2.2$ y; H-Y: 1.9; UPDRS: 32.9; prior L-DOPA: 31%; selegiline users: 58%	R Multidose (4 + Pl.) P MC (20; USA)	Escalation 6 wk maint. 4 wk withdrawal 1 wk	Doses: 1.5 mg, 3.0 mg, 4.5 mg, 6.0 mg	• Dose-related completion rates on original dosage: Pl, 98%; Pr 6 mg/day, 67% • UPDRS: mean improvement for Pr-treatment groups, 20% (−0.9 points for Pl, −6.3 for 1.5 mg, −5.9 for 3.0 mg, −6.5 for 4.5 mg, −7.0 for 6.0 mg Pr)

Parkinson Study Group (2000a, b) (CALM-PD study)	L-D	Pr: 151 (23) Ā = 61½ y Ō = 1.5 y H-Y: 1.8 UPDRS: 32.5 UPDRS-II: 9.1 UPDRS-III: 22.3 prior L-DOPA: 26.5% +selegiline: 33%	Pl: 150 (19)[1] Ā = 61 y Ō = 1.8 y H-Y: 1.8 UPDRS: 31.1 UPDRS-II: 8.3 UPDRS-III: 22.0 prior L-DOPA: 20.0% +selegiline: 37%	R D/B P MC (22; USA, Canada) O/L L-DOPA after wk 10	Escalation 10 wk maint. 22 mo	Pr: 2.78 mg L-D: 406 mg (exper.); 509 mg (incl. suppl.)	• Required supplemental L-DOPA: L-D > Pr (53% v. 39%); amount required: L-D = Pr (264 mg v. 252 mg) • Wearing-off: Pr > L-D (24% v. 38%) • Dyskinesia: Pr > L-D (10% v. 31%) • Motor fluctuations: Pr > L-D (1% v. 5%) • All dopaminergic complications: Pr > L-D (28% v. 51%) • Proportion of dopaminergic complications after supplementary L-DOPA: Pr = L-D (69% v. 68%) • UPDRS: L-D > Pr (−9.2 = 30% v. −4.5 = 14%) • UPDRS-III: L-D > Pr (−7.3 = 33% v. −3.4 = 15%) • UPDRS-II: L-DOPA > P (−2.2 = 27% v. −1.1 = 13%) • Somnolence as adverse effect: L-D > P (17.3% v. 32.4%) • rate of decline in striatal β-CIT uptake was not significantly different between the two groups at 23½ mo (Pr: 20% v. L-D: 25%; dual scans in 82 patients).
Parkinson Study Group (2002)	L-D	82 (CIT subgroup of previous study): Pr: 42 Ā = 62 y Ō = 1.3 y H-Y: 1.8 UPDRS: 34.6 UPDRS-III: 23.2 Striatal β-CIT uptake: 3.0	L-D: 40 Ā = 60 y Ō = 1.6 y H-Y: 1.8 UPDRS: 30.6 UPDRS-III: 21.5 Striatal β-CIT uptake: 2.9	R D/B P MC (17; USA, Canada)	46 mo		• Continuation of CALM study, using improved analytic techniques • Reduced loss of striatal [^{123}I]β-CIT uptake (dopamine transporter; assessed by SPECT): 16% (Pr) v. 25½% at 46 mo; figures for 22 mo given as 7½% and 13% • Transporter loss correlated with deterioration of UPDRS score

(*continued*)

Table 19 (*continued*)

Study	Control	Subjects	Design	Duration	Mean end daily dose	Results
Barone et al. (2001) = Barone and Bressman (2001)	–	717 (247 at 3 y) had participated in three earlier D/B studies: entered O/L studies on max. 4.5 mg P	3 separate studies (USA, Europe) O/L	4½ y	max. 4.5 mg	• 221 completers not receiving L-DOPA (47%); two studies indicate probability ~40% that patient will not require L-DOPA at 4 y • UPDRS: improvement until 2 y, then gradual rise • Probability that L-DOPA not required: ~60% at 3 y, ~40% at 4 y

[1] Patients received placebo in place of alternative drug; that is, all received one active agent and placebo

Table 20. α-Dihydroergocriptine (α-DHEC) monotherapy in Parkinson's disease

Study	Control	Subjects		Design	Duration	Mean end daily dose	Results
Piolti et al. (1989)	Br	28 A: 61–74 H-Y: I–III		D/B	6 mo	max. 100 mg	Efficacy: DHEC = Br Tolerability: DHEC > Br
Bergamasco et al. (2000)	Pl	DHEC: 62 (6)[1]	Pl: 61 (2)[1]	R D/B P MC (6; Italy)	18 mo (stopped at 6 mo interim analysis)		At 3 mo interim analysis: • UPDRS: DHEC > Pl (−14% v. +2.7%) • UPDRS-II: DHEC > Pl (−14% v. +5%) • UPDRS-III: DHEC = Pl (−14% v. −1%) • Tremor, bradykinesia: DHEC > Pl; rigidity: DHEC ≥ Pl
		$\bar{A}$ = 64 y $\bar{O}$ = 14.8 mo H-Y: 1.6 UPDRS: 30.5 UPDRS-II: 8.0 UPDRS-III: 20.7 S&E: 85%	$\bar{A}$ = 64 y $\bar{O}$ = 16.9 mo H-Y: 1.6 UPDRS: 29.3 UPDRS-II: 8.1 UPDRS-III: 19.7 S&E: 86%				At 6 mo interim analysis: • UPDRS: DHEC > Pl (−16.8% v. +10.5%) • UPDRS-II, UPDRS-III: DHEC > Pl (exact figures not given; diagram indicates further improvement in DHEC group, deterioration in Pl group since 3 mo) • Tremor, bradykinesia: DHEC > Pl; rigidity: DHEC ≥ Pl • Adverse reactions: DHEC = Pl (8 v. 6 patients)

[1] At 30 d after trial begin; at termination of trial (6 mo), 37 DHEC-treated and 36 placebo-treated patients had achieved the 6 mo visit

Table 21. Piribedil monotherapy in Parkinson's disease

Study	Control	Subjects	Design	Duration	Mean end daily dose	Results
Ziegler and Rondot (1999)	–	113 (23) $\bar{A} = 63$ y $\bar{O} = 2.1$ y H-Y: 1.8 L-DOPA-naive	O/L MC (23; France)	3 mo	200 mg	Overall: • Total Webster score: −39% (to 6 ± 0.5) • Improved Webster scores for tremor (41% = 0.7 points), bradykinesia (47% = 0.7 points), rigidity (31% = 0.4 points) • Gait, facial expression, arm swinging also improved Tremor-dominant: • Total Webster score: −19% • Webster rest tremor score: −29% Cardinal features group: • Total Webster score: −42% • Webster rest tremor score: −41% • Depression scores improved by 30%

aspects of the central pharmacological actions of dopamine receptor agonists remain to be elucidated.

3. Tolerability and untoward side effects of dopamine receptor agonists (Table 22)

Although the adverse side effects of the various agonists have not been discussed in detail here, dopamine receptor agonists are generally associated with a similar profile of side effects related to their action at D_2 receptors – such as nausea, vertigo, emesis, hypotension –, and there is little evidence to distinguish the agents on this basis, although pramipexole was associated with a particularly frequent presentation of hypotension in one large study (Lieberman et al., 1997). The tendency for dopamine receptor agonists to exacerbate dyskinesias in patients receiving L-DOPA and already suffering such phenomena has been reported; pergolide and pramipexole are particularly prone to elicit such responses, although Reichmann et al. (2002) found virtually nil incidence in a large but non-controlled observation study of pramipexole (4 of 657 patients). Two commonly reported adverse effects, however, have been more frequently associated with the newer agonists than with the older drugs: hallucinations (pramipexole-treated patients: 9% compared with 3% in L-DOPA-treated patients; ropinirole: 7% v. 6%) and 'sleep attacks' (pramipexole: 32% v. 17%; ropinirole: 27% v. 19%, both compared with L-DOPA-treated patients; Goetz et al., 1995; Frucht et al., 1999; Hauser et al., 2000). Edema, particularly in the lower leg, is also associated with pramipexole (see Tan and Ondo, 2000), although one study also reported a higher incidence with pergolide (Rinne et al., 1998). It remains, however, to be determined whether these phenomena are actually related to pramipexole therapy itself, or may have another explanation derived from the course of the disease (Homann et al., 2002). Paus et al. (2003) found, conversely, that sleep attacks reported by 177 of 2952 parkinsonian patients (in structured telephone interviews) were not significantly

Table 22. Reported untoward side effects of dopamine receptor agonists employed in the therapy of Parkinson's disease (based on reports reviewed in this paper, supplemented by data collated by Reichmann et al., 2003)

	Bromocriptine	Lisuride	Pergolide	Cabergoline	Pramipexole	Ropinirole	α-DHEC	Piribedil
Gastrointestinal	+	+	+	+++	±	n.r.	+++	++++
Nausea	+++	++	++	+	+++	++++	++	*
Emesis	+	+	+	±	±	++	±	*
Hypotension	++	+	++	+	+++	++	+	+
Dyskinesia	++	+	+++	+	+++	+++	n.r.	±
Psychiatric	±	+	+	++	n.r.	±	++	++
Hallucinations	+	+	+++	+	+++	++	±	±
Confusion	+++	++	±	+	+++	+	n.r.	n.r.
Sleepiness	++	+	±	0	++	+	n.r.	+
Sleep attacks	n.r.	±	n.r.	0	±	±	n.r.	±
Edema	±	+	±	++	+	+	±	n.r.

Reported incidence: 0%; ±: 0–1%; +: 1–5%; ++: 5–10%; +++: 10–25%; ++++: >25%; *n.r.* no specific reports of effect; * Included under 'gastrointestinal'

associated with either ergoline or non-ergoline dopamine receptor agonists. The risk of such attacks was significantly greater in patients receiving agonist in combination with L-DOPA (7.3%) than in those receiving L-DOPA alone (2.9%); the rate for dopamine agonist monotherapy was 5.3% (Paus et al., 2003; see also Reichmann et al., 2002). Hutton et al. (1996) found a relatively high incidence of psychiatric side effects with pergolide, but the currently available agents are generally reported to be remarkably safe in this respect, although low rates of confusion (up to 5%) are also generally noted. There is some suggestion in the reviewed literature that the older agonists are generally better tolerated by patients, but this has not been systematically examined. There is certainly no extant evidence that any of the commonly employed agonists are less safe than their competitors.

4. Dopamine receptor agonists and neuroprotection

It has long been suspected by some workers that dopamine receptor agonists may be neuroprotective, in that they retard neurodegeneration of the nigrostriatal pathway and thus progression of parkinsonian symptoms. As we have previously discussed (Foley and Riederer, 1999; see also Riederer et al., 2002), however, direct proof of such a neuroprotective role is both practically and theoretically difficult to obtain in the clinic. It is thus of interest that two recent studies have provided the first direct evidence for such activity by undertaking neuroimaging investigations of subjects both before and at the end of the therapeutic trial. Not unexpectedly, two of these trials involved the newer agonists, pramipexole and ropinirole:

– In the CALM-PD (Comparison of the Agonist Pramipexole Versus Levodopa on Motor Complications in Parkinson's Disease) Study, reduced loss of striatal [^{123}I]β-CIT uptake (dopamine transporter; assessed by SPECT) was associated with pramipexole use in early parkinsonian patients (16% compared with 25½% in L-DOPA patients at 46 mo); further, the degree of transporter loss correlated with deterioration of UPDRS score (Parkinson Study Group, 2000, 2002).
– In the REAL-PET study, ropinirole was found to reduce loss of ^{18}F-DOPA uptake in the putamen (13% v. 20% with L-DOPA therapy) and substantia nigra (ropinirole +3% v. −8% L-DOPA; Whone et al., 2003).
– In the Pelmopet study, on the other hand, no statistically significant difference between the effects of pergolide monotherapy and L-DOPA treatment was detected by PET, although the tendency was in the same direction (Oertel et al., 2001).

There are thus promising signs that the newer agents are, in fact, neuroprotective to a degree, but further investigations both with the dopamine receptor agonists and other antiparkinsonian agents are still required to clarify the significance of these findings.

Concerns, have, however been expressed about aspects of these results, including the relatively small patient numbers employed in imaging studies and thus the significance (statistical and clinical) of the results reported. On

the one hand, it cannot be overlooked that the possibility of neuroprotection in degenerative diseases is itself categorically excluded by some workers. On the other hand, Morrish (2002), for example, has raised a number of valid questions about the place of neuroimaging in assessing both the progression of parkinsonism and its response to therapy:

1. PET and SPECT techniques, by definition, assess biochemical parameters in the examined brain regions, and are thus not necessarily directly assessing the underlying disease process in Parkinson's disease. The precise relationship between the measured parameters and disease progression thus requires clarification. Nevertheless, the stated targets of neuroprotective strategies (and of dopamine-based antiparkinsonian therapy in general) are, in fact, the biochemical processes assessed by these techniques, so that the criticism is technically correct but does not entirely invalidate the imaging approach.
2. It is questioned whether imaging data represent appropriate endpoints for clinical trials, with the fear that over-reliance on individual assessment parameters can lead to erroneous conclusions. Once again, the criticism is formally correct, but imaging data represent additional information to be placed at the disposal of clinicians and research scientists and are not meant to supplant other forms of assessment, any more than the neurochemical characterization of the disorder replaces physical examination of the patient.
3. It has been questioned whether, for example, the apparent increase in neuronal survival achieved by pramipexole in the Parkinson Study Group (2002) study is artefactual, reflecting nothing more than increased dopamine transporter expression; this point remains to be clarified, as critics and defenders of these results advance conflicting evidence supporting their respective points of view. Winogrodzka et al. (2003) reported, however, that short term treatment with dopamine receptor agonists does not appear to affect β-CIT binding to the dopamine transporter.
4. Albin et al. (2002) note that even the apparent positive effect of pramipexole in the same study appears to be limited to the early period of agonist treatment, an observation not inconsistent with other reports on the employment of this agent as antiparkinsonian monotherapy. In the absence of placebo-treated patients as controls, the inclusion of which in a study of antiparkinsonian therapy would be ethically problematic, it is also difficult to separate a neuroprotective agonist effect from the absence of a toxic L-DOPA effect in agonist-treated probands (Riederer et al., 2002).
5. Finally, the design and statistical evaluation of trials involving neuroimaging is called into question, prompting Morrish (2002) to call for a moratorium on the employment of functional imaging in therapeutic trials. With the caveat that the expense of such studies should not be allowed to significantly compromise alternative approaches, it would seem rash to reject new techniques lending insights into the function of the basal ganglia on the basis that their employment is not entirely unproblematic. One is reminded of the crudity of the techniques (from today's point of view) which allowed Ehringer and Hornykiewicz to discover the dopamine deficiency in the parkinsonian brain more than forty years ago.

Nevertheless, the difficulties associated with proving a neuroprotective effect in the clinic (see Riederer and Foley, 2000) will not be alleviated simply by the employment of neuroimaging techniques; as recently calculated by Winogrodzka et al. (2003) on the basis of their own β-CIT-SPECT studies, more than 200 patients per treatment group would be required to detect a statistically significant ($p < 0.05$) effect within two years of drug treatment.

5. Dopamine receptor agonists and money

No small role is played in therapeutic decisions by the cost of the various alternatives. A summary of the estimated cost of treatment with different dopamine receptor agonists is presented in Table 23, from which it may be concluded that, until more substantial confirmation of the medium term benefits of the newer agonists is presented, the older agonists will be preferred in situations where economy plays the decisive role. On the other hand, it must also be taken into consideration that increased benefit may render a more expensive agent more cost-effective in the longer term; for example, an analysis by Davey and colleagues (2001) of all costs incurred in the care of parkinsonian patients concluded that the more expensive pergolide was more cost-efficient than bromocriptine. Further analyses of this type, combined with clinical studies of more extended duration, are, however, required before on a rational medico-economic basis will be possible. For further discussion of economics of anti-parkinsonian therapy, see Lepen et al. (1999), Dodel et al. (2001) and Smala et al. (2003).

Table 23. Reports on the daily costs of antiparkinsonian therapy with various dopamine receptor agonists, deprenyl and L-DOPA. Based on data from [1] MIMSonline (mims.hcn.net.au; accessed July 2003; *PBS* 'Pharmaceutical Benefits Scheme price'); [2] Gelbe Liste-Pharmindex (www.gelbe-liste.de; *AVP* 'average pharmacy price'; accessed July 2003) and; [3] Drug Topics Red Book, 2002 ('average wholesale price'). Mean daily doses based on Brecht, 1998. Piribedil: not licensed for treatment of Parkinson's disease in these countries. All figures given as Euros (€ = $US1.10 = $AUS1.70)

	Mean total daily dose[1]	Australia, 2003[1]	Germany, 2003[2]	United States, 2002[3]
L-DOPA (with decarboxylase inhibitor)	400–800 mg	0.65–0.88	1.01–2.79	2.27–2.95
Bromocriptine	15 mg	1.80–1.89	2.99–4.69	10.22
Lisuride	1.25 mg	–	4.95	–
Pergolide	2.5 mg	3.70	9.81	7.94
Cabergoline	3 mg	3.20	10.12	89.74
α-Dihydroergocriptine	60 mg	–	7.28	–
Pramipexole	1.05 mg	–	6.13	2.05
Ropinirole	6 mg	–	9.28	3.77
Deprenyl (selegiline)	10 mg	0.67	1.15–1.75	0.38–1.39

III. Concluding remarks regarding receptor agonists in antiparkinsonian therapy: What is required?

The decision as to which (if any) dopamine receptor agonist will be employed by a particular treating physician in a particular parkinsonian patient will depend on a number of factors, including experience with particular agents (determined to a not insignificant extent by country and current opinion of the colleagues; the agonist talipexole, for example, finds little use outside Japan, and piribedil finds greatest favor in France and α-dihydroergocriptine has been investigated mostly in Italy), the specific problems of the individual patient and the cost of the alternatives. While the controlled studies described here are invaluable in the assessment of these alternatives, both the differences between the studies of a single drug – characteristics of patient group, mode of administration, endpoints examined, concurrent L-DOPA or other therapy – and the specific choices made with respect to these variables render both their comparison with each other and their application to a specific situation difficult. As has always been the case, trial and error and personal preference, both of the physician and the patient, will continue to play an important role, despite 'evidence-based medicine' (see Movement Disorder Society, 2002).

Such choices are determined by the aim with which dopamine agonist therapy is initiated. The major advantages in comparison with L-DOPA monotherapy described by their proponents include:

- L-DOPA-sparing effect: whether L-DOPA is neurotoxic in the human central nervous system remains a moot point, and cannot be discussed here.
- Replacement, even partial, of L-DOPA with an agonist is associated with reduced intensity and frequency of dyskinesia. But, as illustrated by the letters to JAMA published on 21 September 2000 (pp. 884f.) in response to the Rascol et al. (2000) study, many patients and their physicians do not regard dyskinesia and motor fluctuations – the origin of which, in any case, remains unknown – as being as great a problem as agonist proponents suggest; specifically, prescription of an agonist on this basis is perhaps not so reasonable in older parkinsonian patients, especially where multimorbidity and mental alertness are also issues. On the other hand, the commencement of therapy with agonists might be more prudent in younger patients, particularly those affected by genetic parkinsonism, in light of the greater life expectancy of these persons.
- Neuroprotection, related to or distinct from reduced L-DOPA toxicity: evidence for this has thus far been limited, and restricted to relatively early stage patients. Is the reduced risk of dyskinesia associated with agonists worth the price paid in reduced symptomatic benefit? This question, too, must be qualified if the suggestions of neuroprotection can be substantiated.

Before the L-DOPA era, attention was concentrated on containment of parkinsonian tremor, in the belief that this constituted the major symptomatic problem, despite the fact that it had long been recognized by patients and some workers that akinesia, the symptom addressed by L-DOPA, was the major

reason for incapacity. On the other hand, cognitive and sleep disturbances linked with some agonists, if not themselves undisputed, impose a greater stress on the patient, particular where these effects manifest themselves unexpectedly or in dangerous situations.

The aims of agonist therapy must also be clear if candidates are to be rationally compared. The respective pros and cons of agonist therapy in early and advanced Parkinson's disease have been discussed in detail elsewhere; it only remains here to comment that clarity in the physician's mind as to what is to be achieved in a particular case is required for justification of the added expense of dopamine receptor agonists. In such a situation, it is particularly difficult to justify the employment of more expensive options when their superiority over older stalwarts, such as bromocriptine, lisuride and even L-DOPA, is not beyond dispute. Further, models of basal ganglia function have not yet achieved a degree of sophistication which would allow reliable predictions as to the 'ideal' characteristics of an antiparkinsonian dopamine receptor agonist with respect to receptor subtype selectivity; instead, it is more likely that further clinical experience with these agents will enhance our understanding of the neural systems upon which they exert their functions.

References

General

Birkmayer W, Hornykiewicz O (1961) Der L-3,4-Dioxyphenylalanin (=DOPA)-Effekt bei der Parkinson-Akinese. Wien Klin Wochenschr 73: 787–788

Brecht HM (1998) Dopaminagonisten im Vergleich. In: Riederer P, Laux G, Pöldinger W (eds) Neuro-Psychopharmaka, Bd 5. Springer, Wien New York, pp 226–240

Caraceni T, Musicco M (2001) Levodopa or dopamine agonists, or deprenyl as initial treatment for Parkinson's disease. A randomized multicenter study. Parkinson Rel Disord 7: 107–114

Colosimo C, De Michele M (1999) Motor fluctuations in Parkinson's disease: pathophysiology and treatment. Eur J Neurol 6: 1–21

Contin M, Riva R, Albani F, Baruzzi A (2000) Pharmacokinetic optimisation of dopamine receptor agonist therapy for Parkinson's disease. CNS Drugs 14: 439–455

Deleu D, Northway MG, Hanssens Y (2002) Clinical pharmacokinetic and pharmacodynamic properties of drugs used in the treatment of Parkinson's disease. Clin Pharmacokinet 41: 261–309

Dodel RC, Berger K, Oertel WH (2001) Health-related quality of life and healthcare utilisation in patients with Parkinson's disease: impact of motor fluctuations and dyskinesias. Pharmacoeconomics 19: 1013–1038

Drug Topics Red Book (2002) Medical Economics Co, Montvale (NJ)

European Agency for the Evaluation of Medicinal Products (EMEA) (1998) Committee for Proprietary Medicinal Products (CPMP), Note for guidance on clinical investigation of medicinal products in the treatment of Parkinson's disease. CPMP/EWP/563/95

Foley P, Riederer P (1999) Pathogenesis and preclinical course of Parkinson's disease. J Neural Transm [Suppl] 56: 29–72

Foley P, Gerlach M, Youdim MBH, Riederer P (2000) MAO-B inhibitors: multiple roles in the therapy of neurodegenerative diseases? Parkinsonism Rel Disord 6: 25–47

Frucht S, Rogers J, Greene PE, Gordon MF, Fahn S (1999) Falling asleep at the wheel: motor vehicle mishaps in persons taking pramipexole and ropinirole. Neurology 52: 1908–1910

Gerlach M, Double KL, Arzberger T, Leblhuber F, Taschner T, Riederer P (2003) Dopamine receptor agonists in current clinical use: comparative dopamine receptor binding profiles defined in the human striatum. J Neural Transm 110: 1119–1127

Goetz C, Stebbins G (1995) Mortality and hallucinations in nursing home patients with advanced Parkinson's disease. Neurology 45: 669–671

Golbe LI (1991) Young-onset Parkinson's disease: a clinical review. Neurology 41: 168–173

Hauser R, Gauger L, Anderson WM, Zesiewicz TA (2000) Pramipexole-induced somnolence and episodes of daytime sleep. Mov Disord 15: 658–663

Homann CN, Wenzel K, Suppan K, Ivanic G, Kriechbaum N, Crevenna R, Ott E (2002) Sleep attacks in patients taking dopamine agonists: review. Br Med J 324: 1483–1487

Keyser J, Backer De J-P, Wilczak N, Herroelen L (1995) Dopamine agonists used in the treatment of Parkinson's disease and their selectivity for the D_1, D_2 and D_3 dopamine receptors in human striatum. Prog Neuropsychopharmacol Biol Psychiatry 19: 1147–1154

Kuzel MD (1999) Ropinirole: a dopamine agonist for the treatment of Parkinson's disease. Am J Health-Syst Pharm 56: 217–224

Le WD, Jankovic J (2001) Are dopamine receptor agonists neuroprotective in Parkinson's disease? Drugs Aging 18: 389–396

Lebrun-Frenay C, Borg M (2002) Choosing the right dopamine agonist for patients with Parkinson's disease. Curr Med Res Opin 18: 209–214

LePen C, Wait C, Moutard-Martin F, Dujardin M, Ziegler M (1999) Cost of illness and disease severity in a cohort of French patients with Parkinson's disease. Pharmacoeconomics 16: 59–69

Lledó A (2001) Dopamine agonists: the treatment for Parkinson's disease in the XXI century? Parkinson Rel Disord 7: 51–58

Millan MJ, Maiofiss L, Cussac D, Audinot V, Boutin J-A, Newman-Tancredi A (2002) Differential actions of antiparkinson agents at multiple classes of monoaminergic receptor. I. A multivariate analysis of the binding profiles of 14 drugs at 21 native and cloned human receptor subtypes. J Pharmacol Exp Ther 303: 791–804

Miyawaki E, Lyons K, Pahwa R, Troster AI, Hubble J, Smith D, Busenbark K, McGuire D, Michalek D, Koller WC (1997) Motor complications of chronic levodopa therapy in Parkinson's disease. Clin Neuropharmacol 20: 523–530

Movement Disorders Society (2002) Management of Parkinson's disease: an evidence-based review. Mov Disord 17 [Suppl 4]

Paus S, Brecht HM, Köster J, Seeger G, Klockgether T, Wüllner U (2003) Sleep attacks, daytime sleepiness, and dopamine agonists in Parkinson's disease. Mov Disord 18: 659–667

Perachon S, Schwartz JC, Sokoloff P (1999) Functional potencies of new antiparkinsonian drugs at recombinant human dopamine D1, D2 and D3 receptors. Eur J Pharmacol 366: 293–300

Piercey MF, Hoffmann WE, Smith MW, Hyslop DK (1996) Inhibition of dopamine neuron firing by pramipexole, a dopamine D3 receptor-preferring agonist: comparison to other dopamine receptor agonists. Eur J Pharmacol 312: 35–44

Poewe W (1998) Should treatment of Parkinson's disease be started with a dopamine agonist? Neurology 51 [Suppl 2]: S21–S24

Reichmann H, Sommer U, Engfer A (2003) Morbus Parkinson Nebenwirkungs- und Interaktionsdatenbank. Schering/Thieme (online: http://www.parkinson-datenbank.de/pa_start.htm; accessed July 2003)

Reimer J, Kuhlmann A, Müller T (2002) Neuroleptic malignant syndrome after rapid switch from bromocriptine to pergolide. Parkinson Rel Disord 9: 115–116

Riederer P, Foley P (2000) The motor circuit of the human basal ganglia reconsidered. J Neural Transm [Suppl 58]: 97–110

Riederer P, Riess O, Przuntek H, Schwarz J, Müller T, Schwartz A, Vogt T, Gille G, Reichmann H (2002) Practical importance of neuroprotection in Parkinson's disease. J Neurol 249 [Suppl 3]: III/53–56

Sautel F, Griffon N, Lévesque D, Pilon C, Schwartz JC, Sokoloff P (1995) A functional test identifies dopamine agonists selective for D3 versus D2 receptors. Neuroreport 6: 329–332

Sit SY (2000) Dopamine agonists in the treatment of Parkinson's disease: past, present and future. Curr Pharm Design 6: 1211–1248

Smala AM, Spottke EA, Machat O, Siebert U, Meyer D, Kohne-Volland R, Reuther M, DuChane J, Oertel WH, Berger KB, Dodel RC (2003) Cabergoline versus levodopa monotherapy: a decision analysis. Mov Disord 18: 898–905

South Thames Regional Drug Information Service (1999) New drugs in Parkinson's disease: cabergoline, pramipexole, ropinirole, entacapone. Therapeutic Rev, Jan 1999

United States Pharmacopeia Dispensing Information (USP DI), 2002. USP DI Vol 1. Drug information for the health care provider. United States Pharmacopeial Convention, Rockville (Md)

Watts RL (1997) The role of dopamine agonists in early Parkinson's disease. Neurology 49[Suppl 1]: 34–48

Wheatley K, Stowe RL, Clarke CE, Hills RK, Williams AC, Gray R (2002) Evaluating drug treatments for Parkinson's disease: how good are the trials? Br Med J 324: 1508–1511

Winogrodzka A, Bergmans P, Booij J, van Royen EA, Stoof JC, Wolters EC (2003) [^{123}I]β-CIT SPECT is a useful method for monitoring dopaminergic degeneration in early stage Parkinson's disease. J Neurol Neurosurg Psychiatry 74: 294–298

Bromocriptine

Bakheit AM, Henderson LM, Moore AP, Simpson JA, Thomas M (1990) Long-term double masked trial of early treatment with L-dopa plus bromocriptine versus L-dopa alone in Parkinson's disease. Interim results. Eur Neurol 30: 108–111

Calne DB, Teychenne PF, Claveria LE, Eastman R, Greenacre JK, Petrie A (1974) Bromocriptine in Parkinsonism. Br Med J 4: 442–444

Giménez-Roldán S, Tolosa E, Burguera JA, Chacón J, Liaño H, Forcadell F (1997) Early combination of bromocriptine and levodopa in Parkinson's disease: a prospective randomized study of two parallel groups over a total follow-up period of 44 months including an initial 8-month double-blind stage. Clin Neuropharmacol 20: 67–76

Goetz CG, Shannon KM, Tanner CM, Carroll VS, Klawans HL (1989) Agonist substitution in advanced Parkinson's disease. Neurology 39: 1121–1122

Hely MA, Morris JG, Rail D, Reid WG, O'Sullivan DJ, Williamson PM, Genge S, Broe GA (1989) The Sydney Multicentre Study of Parkinson's disease: a report on the first 3 years. J Neurol Neurosurg Psychiatry 52: 324–328

Hely MA, Morris JGL, Reid WGJ, O'Sullivan DJ, Williamson PM, Rail D, Broe GA, Margrie S (1994) The Sydney Multicentre Study of Parkinson's disease: a randomised, prospective five year study comparing with low dose levodopa-carbidopa. J Neurol Neurosurg Psychiatry 57: 903–910

Hely MA, Morris JG, Traficante R, Reid WG, O'Sullivan DJ, Williamson PM (1999) The Sydney multicentre study of Parkinson's disease: progression and mortality at 10 years. J Neurol Neurosurg Psychiatry 67: 300–307

Herskovits E, Yorio A, Leston J (1988) Long term bromocriptine treatment in de novo parkinsonian patients. Medicina (Buenos Aires) 48: 345–350

Kowa H, Kanazawa I, Goto I, Kuno S, Mizuno Y, Ogawa N, Tashiro K, Yanagisawa N (1997) Nine-year follow-up study of bromocriptine monotherapy for Parkinson's disease. Eur Neurol 38[Suppl 1]: 23–28

Kuno S (1993) Progress note on Japanese multicenter bromocriptine monotherapy. Eur Neurol 33[Suppl 1]: 3–5

Lees AJ (1995) On behalf of the Parkinson's Disease Research Group of the United Kingdom. Comparison of therapeutic effects and mortality data of levodopa and levodopa combined with selegiline in patients with early, mild Parkinson's disease. Br Med J 311: 1602–1607

Lees AJ, Katzenschlager R, Head J, Ben-Shlomo Y (2001) On behalf of the Parkinson's Disease Research Group of the United Kingdom. Ten-year follow-up of three different initial treatments in de-novo PD. A randomized trial. Neurology 57: 1687–1694

Montastruc JL, Rascol O, Rascol A (1990) Comparaison de la bromocriptine et de la levodopa dans le traitement de première intention de la maladie de Parkinson: résultats of à 3 ans d'une étude prospective randomisée. Rev Neurol (Paris) 146: 144–147

Montastruc JL, Rascol O, Senard JM, Rascol A (1994) A randomised controlled study comparing bromocriptine to which levodopa was later added, with levodopa alone in previously untreated patients with Parkinson's disease: a five year follow up. J Neurol Neurosurg Psychiatry 57: 1034–1038

Montastruc JL, Desboeuf K, Lapeyre-Mestre M, Senard JM, Rascol O, Brefel-Courbon C (2001) Long-term mortality results of the randomized controlled study comparing bromocriptine to which levodopa was later added with levodopa alone in previously untreated patients with Parkinson's disease. Mov Disord 16: 511–514

Nakanishi T, Mizuno Y, Goto I, Iwata M, Kanazawa I, Kowa H, Mannen T, Nishitani H, Ogawa N, Takahashi A, Tashiro K, Tohgi H, Yanagisawa N (1991) A nationwide collaborative study on the long-term effects of bromocriptine in patients with Parkinson's disease. The fourth interim report. Eur Neurol 31[Suppl 1]: 3–16

Ogawa N, Kanazawa I, Kowa H, Kuno S, Mizuno Y, Tashiro K, Yanagisawa N (1997) Nationwide multicenter prospective study on the long-term effects of bromocriptine for Parkinson's disease. Final report of a ten-year followup. Eur Neurol 38[Suppl 2]: 37–49

Olanow CW, Alberts MJ, Stajich J, Burch G (1987) Recent developments in Parkinson's disease vol II. Macmillan Healthcare, New York

Olanow CW, Hauser RA, Gauger L, Malapira T, Koller W, Hubble J, Bushenbark K, Lilienfeld D, Esterlitz J (1995) The effect of deprenyl and levodopa on the progression of Parkinson's disease. Ann Neurol 38: 771–777

Olsson JE and the European Multicentric Trial Group (1990) Bromocriptine and levodopa in early combination in Parkinson's disease: first results of the Collaborative European Trial. Adv Neurol 53: 421–423

Parkinson's Disease Research Group in the United Kingdom (1993) Comparisons of therapeutic effects of levodopa, levodopa and selegiline, and bromocriptine in patients with early, mild Parkinson's disease: three year interim report. Br Med J 307: 469–472

Przuntek H, Welzel D, Schwarzmann D, Letzel H, Kraus PH (1992) Primary combination therapy of early Parkinson's disease. A long-term comparison between the combined regimen bromocriptine/levodopa and levodopa monotherapy – first interim report. Eur Neurol 32[Suppl 1]: 36–45

Przuntek H, Welzel D, Gerlach M, Blumner E, Danielczyk W, Kaiser HJ, Kraus PH, Letzel H, Riederer P, Uberla K (1996) Early institution of bromocriptine in Parkinson's disease inhibits the emergence of levodopa-associated motor side effects. Long-term results of the PRADO study. J Neural Transm 103: 699–715

Riopelle RJ, Gawel MJ, Libman I, King DB, McLean DR, Paulseth R, Raphy B, Bouchard S (1988) A double-blind study of bromocriptine and L-dopa in de novo Parkinson's disease. Short term results. Eur Neurol 28[Suppl 1]: 11–14

Parkinson's Disease Research Group in the United Kingdom (1993) Comparisons of therapeutic effects of levodopa, levodopa and selegiline, and bromocriptine in patients with early, mild Parkinson's disease: three year interim report. Br Med J 307: 469–472

Tashiro K, Goto I, Kanazawa I, Kowa H, Kuno S, Mizuno Y, Ogawa N, Yanagisawa N (1996) Eight-year follow-up study of bromocriptine monotherapy for Parkinson's disease. Eur Neurol 36[Suppl 1]: 32–37

Tolcapone Study Group (1999) Efficacy and tolerability of tolcapone compared with bromocriptine in levodopa-treated parkinsonian patients. Mov Disord 14: 38–44

Toyokura Y, Mizuno Y, Kase M, Sobue I, Kuroiwa Y, Narabayashi H, Uono M, Nakanishi T, Kameyama M, Ito H, Shimada Y, Iwata M (1985) Effects of bromocriptine on Parkinsonism. A nation-wide collaborative double-blind study. Acta Neurol Scand 72: 157–170

Weiner WJ, Factor SA, Sanchez-Ramos JR, Singer C, Sheldon RN, Cornelius L, Ingenito A (1993) Early combination therapy (bromocriptine and levodopa) does not prevent motor fluctuations in Parkinson's disease. Neurology 43: 21–27

Lisuride

Allain H, Destee A, Petit H, Patay M, Schuck S, Bentue-Ferrer D, Le Cavorzin P (2000) Five-year follow-up of early lisuride and levodopa combination therapy versus levodopa monotherapy in de novo Parkinson's disease. The French Lisuride Study Group. Eur Neurol 44: 22–30

Battistin L, Bardin PG, Ferro-Milone F, Ravenna C, Toso V, Reboldi G (1999) Alpha-dihydroergocryptine in Parkinson's disease: a multicentre randomized double blind parallel group study. Acta Neurol Scand 99: 36–42

Giovannini P, Scigliano G, Piccolo I, Soliveri P, Scuhy I, Caraceni T (1988) Lisuride in Parkinson's disease. 4-year follow-up. Clin Neuropharmacol 11: 201–211

Laihinen A, Rinne UK, Suchy I (1992) Comparison of lisuride and bromocriptine in the treatment of advanced Parkinson's disease. Acta Neurol Scand 86: 593–595

LeWitt PA, Gopinathan G, Ward CD, Sanes JN, Dambrosia JM, Durso R, Calne DB (1982) Lisuride versus bromocriptine treatment in Parkinson disease: a double-blind study. Neurology 32: 69–72

Rabey JM, Streifler M, Treves T, Korczyn AD (1989) A long-term comparative study of lisuride and levodopa in Parkinson's disease. In: Calne DB (ed) Parkinsonism and aging. Raven Press, New York, pp 261–267

Rinne UK (1989) Lisuride, a dopamine agonist in the treatment of early Parkinson's disease. Neurology 39: 336–339

Rinne UK (1999) Kombinationstherapie mit Lisurid und L-Dopa in den Frühstadien der Parkinson-Krankheit verringert und verzögert die Entwicklung motorischer Fluktuationen Langzeitstudie über 10 Jahre im Vergleich mit einer L-Dopa-Monotherapie. Nervenarzt 70: S19–S25

Stocchi F, Ruggieri S, Vacca L, Olanow CW (2002) Prospective randomized trial of lisuride infusion versus oral levodopa in patients with Parkinson's disease. Brain 125: 2058–2066

Vermersch P, Fondarai J, Petit H (1991) Étude randomisée sur une année de l'association précoce L-dopa/lisuride dans la maladie de Parkinson. Thérapie 46: 481–486

Pergolide

Barone P, Bravi D, Bermejo-Pareja F, Marconi R, Kulisevsky J, Malagu S, Weiser R, Rost N (1999) Pergolide monotherapy in the treatment of early PD: a randomized, controlled study. Pergolide Monotherapy Study Group. Neurology 53: 573–579

Boas J, Worm-Petersen J, Dupont E, Mikkelsen B, Wermuth L (1996) The levodopa dose-sparing capacity of pergolide compared with that of bromocriptine in an open-label, crossover study. Eur J Neurol 3: 44–49

Clarke CE, Speller JM (2001) Pergolide versus bromocriptine for levodopa-induced motor complications in Parkinson's disease (Cochrane Review). Cochrane Library Issue 2, 2001. Update Software, Oxford

Davey P, Rajan N, Lees M, Aristides M (2001) Cost-effectiveness of pergolide compared to bromocriptine in the treatment of Parkinson's disease: a decision-analytic model. Value in Health 4: 308–315

Facca A, Sanchez-Ramos J (1996) High-dose pergolide monotherapy in the treatment of severe levodopa-induced dyskinesias (letter). Mov Disord 11: 327–341

Goetz CG, Blasucci L, Stebbins GT (1999) Switching dopamine agonists in advanced Parkinson's disease: is fast titration preferable to slow? Neurology 52: 1227–1229

Hanna PA, Ratkos L, Ondo WG, Jankovic J (2001) A comparison of the therapeutic efficacy of pergolide and pramipexole in Parkinson's disease. J Neural Transm 108: 63–70

Inzelberg R, Carasso RL, Schechtman E, Nisipeanu P (2000) A comparison of dopamine agonists and catechol-O-methyltransferase inhibitors in Parkinson's disease. Clin Neuropharmacol 23: 262–266

Kanagawa Parkinson's Disease Study Group (KPSG): Kowa H, Kuroiwa Y, Sakai F, Shinohara Y, Shimojo S, Wakayamav Y (2001) Clinical efficacy of pergolide. Comparison with bromocriptine for Parkinson's disease under 2-year-treatment with l-Dopa (abstract). Parkinson Rel Disord 7: S60

Koller W, Lees A, Doder D, Hely M and the Tolcapone/Pergolide Study Group (2001) Randomized trial of tolcapone versus pergolide as add-on to levodopa therapy in Parkinson's disease patients with motor fluctuations. Mov Disord 16: 858–866

Kulisevsky J, Lopez-Villegas D, Garcia-Sanchez C, Barbanoj M, Gironell A, Pascual-Sedano B (1998) A six-month study of pergolide and levodopa in de novo Parkinson's disease patients. Clin Neuropharmacol 21: 358–362

LeWitt PA, Ward CD, Larsen TA, Raphaelson MI, Newman RP, Foster N, Dambrosia JM, Calne DB (1983) Comparison of pergolide and bromocriptine therapy in parkinsonism. Neurology 33: 1009–1014

Lledo A, Quail D, van Laar T, Vreeling F, Barone P (1999) An analysis of the efficacy and safety of pergolide monotherapy in the treatment of Parkinson's disease. Neurology 52[Suppl 2]: A408

Lieberman AN, Leibowitz M, Gopinathan G, Walker R, Hiesiger E, Nelson J, Goldstein M (1985) The use of pergolide and lisuride, two experimental dopamine agonists, in patients with advanced Parkinson. Am J Med Sci 290: 102–106

Mizuno Y, Kondo T, Narabayashi H (1995) Pergolide in the treatment of Parkinson's disease. Neurology 45[Suppl 3]: S13–S21

Narabayashi H, Ando K, Kowa H et al. (1992) Clinical utility of pergolide mesylate (LY 127809) in Parkinson's disease. Double-blind study in comparison with bromocriptine mesylate. Igaku Yakugaku (J Med Pharmaceut Sci) 27: 147–211; cited in Mizuno et al. (1995)

Oertel WH, Schwarz J, Leenders KL, Hundemer HP, Lledó A, Wolters EC (2001) Results of a 3 year randomized, double-blind, PET-controlled study of pergolide vs. L-dopa as monotherapy in early Parkinson's disease (Pelmopet-trial) (abstract). J Neurol Sci 187[Suppl 1]: S244

Olanow CW, Fahn S, Muenter M, Klawans H, Hurtig H, Stern M, Shoulson I, Kurlan R, Grimes JD, Jankovic J, Hoehn M, Markham CH, Duvoisin R, Reinmuth O, Leonard HA, Ahlskog E, Feldman R, Hershey L, Yahr MD (1994) A multicentre double-blind placebo-controlled trial of pergolide as an adjunct to Sinemet in Parkinson's disease. Mov Disord 9: 40–47

Pezzoli G, Martignoni E, Pacchetti C, Angeleri VA, Lamberti P, Muratorio A, Bonuccelli U, De Mari M, Foschi N, Cossutta E, Nicoletti F, Giammona F, Canesi M, Scarlato G, Caraceni T, Moscarelli E (1994) Pergolide compared with bromocriptine in Parkinson's disease: a multicentre, crossover, controlled study. Mov Disord 9: 431–436

Pezzoli G, Martignoni E, Pacchetti C, Angeleri V, Lamberti P, Muratorio A, Bonuccelli U, De Mari M, Foschi N, Cossutta E (1995) A crossover, controlled study comparing pergolide with bromocriptine as an adjunct to levodopa for the treatment of Parkinson's disease. Neurology 45[Suppl 3]: S22–S27

Cabergoline

Ahlskog JE, Wright KF, Muenter MD, Adler CH (1996) Adjunctive cabergoline therapy of Parkinson's disease: comparison with placebo and assessment of dose responses and duration of effect. Clin Neuropharmacol 19: 202–212

Clarke CE, Deane KH (2001a) Cabergoline for levodopa-induced complications in Parkinson's disease. In: The Cochrane Library, Issue 2, 2001. Update Software, Oxford

Clarke CE, Deane KH (2001b) Cabergoline versus bromocriptine for levodopa-induced complications in Parkinson's disease. In: The Cochrane Library, Issue 2, 2001. Update Software, Oxford

Destee A, Schneider E, Gershanik O, Dom R, Tichy J, Korczyn AD, Caraceni T, Lakke JPWF, Szczudlik A, Lees A, Chousa C, Kostic V, CBG Study Group (1996) Efficacy and tolerability of cabergoline compared to bromocriptine in patients suffering from levodopa associated motor complications (not on treatment with DA-agents). Mov Disord 11[Suppl 1]: 269

Gershanik O, Dom R, Tichy J, Ziegler M, Schneider E, Korczyn AD (1994a) Multicenter, multinational double-blind study of the activity and tolerability of cabergoline vs bromocriptine in parkinsonian patients suffering from L-dopa associated motor complications, not on treatment with dopamine agonist agents. Farmitalia Carlo Erba; Clinical Reference 40 1994. Cited in: Clarke and Deane (cabergoline) (2001b)

Gershanik O, Dom R, Ziegler M, Schneider E, Korczyn AD, Nappi G (1994b) Multicenter, multinational double-blind study of the activity and tolerability of cabergoline vs bromocriptine in parkinsonian patients suffering from L-dopa associated motor complications on treatment with dopamine agonist agents. Farmitalia Carlo Erba; Clinical Reference 41 1994. Cited in: Clarke and Deane (cabergoline) (2001b)

Hutton JT, Koller WC, Ahlskog JE, Pahwa R, Hurtig HI, Stern MB, Hiner BC, Lieberman A, Pfeiffer RF, Rodnitzky RL, Waters CH, Muenter MD, Adler CH, Morris JL (1996) Multicentre, placebo controlled trial of cabergoline taken once daily in the treatment of Parkinson's disease. Neurology 46: 1062–1065

Inzelberg R, Nisipeanu P, Rabey JM, Orlov E, Catz T, Kippervasser S, Schechtman E, Korczyn AD (1996) Double-blind comparison of cabergoline and bromocriptine in Parkinson's disease patients with motor fluctuations. Neurology 47: 785–788

Korczyn A, Stern G, Parkes D et al. (1994) Multicentre, multinational double blind study of the activity and tolerability of cabergoline vs bromocriptine in Parkinsonian patients suffering from L-dopa associated motor complications. FCE Report 21336/736i 1994. Cited in: Clarke and Deane (cabergoline) (2001b)

Lieberman A, Imke S, Muenter M, Wheeler K, Ahlskog JE, Matsumoto JY, Maraganore DM, Wright KF, Schoenfelder J (1993) Multicenter study of cabergoline, a long-acting dopamine receptor agonist, in Parkinson's disease patients with fluctuating responses to levodopa/carbidopa. Neurology 43: 1981–1984

Miguel F, Obeso JA, Olive Plana JM, Tolosa E, Villaueva Eusa JA, Dubini A et al. (1993) Double-blind parallel group study of the efficacy and tolerability of the cabergoline vs placebo in Parkinsonian patients with motor fluctuations. FCE Report: 21336/722i, Clinical Reference 293. Cited in: Clarke and Deane (cabergoline) (2001a)

Musch B (2001) The long-acting dopamine agonist (DA) cabergoline (CBS) in the treatment of early Parkinson's disease (PD). J Neurol Sci 187[Suppl 1]: S241

Rinne UK, Bracco F, Chouza C, Dupont E, Gershanik O, Marti Masso JF, Montastruc JL, Marsden CD, Dubini A, Orlando N, Grimaldi R (1997) Cabergoline in the treatment of early Parkinson's disease: results of the first year of treatment in a double-blind comparison of cabergoline and levodopa. The PKDS009 Collaborative Study Group. Neurology 48: 363–368

Rinne UK, Bracco F, Chouza C, Dupont E, Gershanik O, Marti Masso JF, Montastruc JL, Marsden CD (1998) Early treatment of Parkinson's disease with cabergoline delays the onset of motor complications. Results of a double-blind levodopa controlled trial. The PKDS009 Study Group. Drugs 55[Suppl 1]: 23–30

Schneider E, Gershanik O, Dom R, Tichy J, Korczyn AD, Caraceni T, Lakke JPWF, Szczudlik A, Lees A, Chousa C, Kostic V, CBG Study Group (1996) Efficacy and tolerability of cabergoline compared to bromocriptine in patients suffering from levodopa associated motor complications (on treatment with DA-agents). Mov Disord 11[Suppl 1]: 269

Steiger MJ, El-Debas T, Anderson T, Findley LJ, Marsden CD (1996) Double-blind study of the activity and tolerability of cabergoline versus placebo in parkinsonians with motor fluctuations. J Neurol 243: 68–72

Yanagisawa N, Kowa H, Mizuno Y, Kanazawa I, Ogawa N, Nakashima M (1996) The clinical evaluation of CG-101 (Cabergoline) in Parkinson's disease patients with L-DOPA. A multicentred phase III double-blind comparative study vs. bromocriptine mesilate. J Clin Therapeut Med 12: 12. Cited in: Clarke and Deane (cabergoline) (2001b)

Ropinirole

Adler CH, Sethi KD, Hauser RA, Davis TL, Hammerstad JP, Bertoni J, Taylor RL, Sanchez-Ramos J, O'Brien CF (1997) Ropinirole for the treatment of early Parkinson's disease. The Ropinirole Study Group. Neurology 49: 393–399

Brooks DJ, Abbott RJ, Lees AJ, Martignoni E, Philcox DV, Rascol O, Roos RA, Sagar HJ (1998) A placebo-controlled evaluation of ropinirole, a novel D2 agonist, as sole dopaminergic therapy in Parkinson's disease. Clin Neuropharmacol 21: 101–107

Brunt C, Aitken C (1996) On behalf of the 043 Study Group. A double-blind comparative study of ropinirole versus bromocriptine in the treatment of parkinsonian patients not optimally controlled on L-dopa. J Neurol 243[Suppl 2]: S38

Brunt ER, Korczyn AD, Lieberman A, Stocchi F, Nagy Z, Sethi K (1999) The long term efficacy of ropinirole as an adjunct to L-dopa. Neurology 52[Suppl 2]: A408–A409

Brunt ER, Brooks DJ, Korczyn AD, Montastruc JL, Stocchi F (2002) On behalf of the 043 Study Group. A six-month multicentre, double-blind, bromocriptine-controlled study of the safety and efficacy of ropinirole in the treatment of patients with Parkinson's disease not optimally controlled by L-dopa. J Neural Transm 109: 489–502

Canesi M, Antonini A, Mariani C, Tesei S, Zecchinelli AL, Barichella M, Pezzoli G (1999) An overnight switch to ropinirole in patients with Parkinson's disease. J Neural Transm 106: 925–929

Canesi M, Antonini A, Mariani C, Pezzoli G (2000) Overnight switch to ropinirole improves activities of daily living in Parkinson's disease patients. Neurology 54[Suppl 3]: A280

Clarke CE, Deane KHO (2001a) Ropinirole for levodopa-induced complications in Parkinson's disease. The Cochrane Library, Issue 2, 2001. Update Software, Oxford

Clarke CE, Deane KHO (2001b) Ropinirole versus bromocriptine for levodopa-induced complications in Parkinson's disease. The Cochrane Library, Issue 2, 2001. Update Software, Oxford

De Lucia D, Fratta M, Terracciano M, Quarantiello M (2001) Low incidence of dyskinesia in early Parkinson's disease treated with ropinirole (abstract). Parkinson Rel Disord 7[Suppl]: S54

Im JH, Ha JH, Cho IS, Lee MC (2003) Ropinirole as an adjunct to levodopa in the treatment of Parkinson's disease: a 16-week bromocriptine controlled study. J Neurol 50: 90–96

Korczyn AD et al. (1990) Anti-Parkinson efficacy (L-dopa sparing effect) of ropinirole versus placebo as adjunct therapy in Parkinsonian patients not optimally controlled in L-dopa. SmithKline Beecham Pharmaceuticals Report No: MY-1002/SKF-101468/2/CPMS-034. Cited by Clarke and Deane (ropinirole) (2001)

Korczyn AD, Brooks DJ, Brunt ER, Poewe WH, Rascol O, Stocchi F (1998) Ropinirole versus bromocriptine in the treatment of early Parkinson's disease: a 6-month interim report of a 3-year study. 053 Study Group. Mov Disord 13: 46–51

Korczyn AD, Brunt ER, Larsen JP, Nagy Z, Poewe WH, Ruggieri S (1999) A 3-year randomized trial of ropinirole and bromocriptine in early Parkinson's disease. The 053 Study Group. Neurology 53: 364–370

Kreider MS, Knox S, Gardiner D, Wheadon DE (1996) The efficacy of ropinirole, a non-ergoline D2 agonist, as an adjunct to L-dopa (DCI) in patients with Parkinson's disease. Mov Disord 11[Suppl 1]: 156

Lang AE, Rascol O, Brooks DJ, Clarke CE, De Deyn PP, Korczyn AD, Abdalla M (2002) The development of dyskinesias in Parkinson's disease (PD) patients receiving ropinirole and given supplemental L-Dopa (abstract). American Academy of Neurology, 54th Annual Meeting, Denver (abstract S11.005)

Lieberman A, Olanow C, Sethi K, Swanson P, Waters CH, Fahn S, Hurtig H, Yahr M (1998) A multicenter trial of ropinirole as adjunct treatment for Parkinson's disease. Neurology 51: 1057–1062

Murayama S (1996) Clinical evaluation of ropinirole hydrochloride (SK&F 101468) in patients with Parkinson's disease: a double-blind comparative study vs bromocriptine mesilate. Yakuri to-chiryo (Japan Pharmacol Therapeut) 24[Suppl 11]: 221–289

Murayama S, Narabayashi H, Kowa H et al. (1996) Clinical evaluation of ropinirole hydrochloride (SK&F 101468) in patients with Parkinson's disease. A double-blind comparative study vs. bromocriptine mesilate. SmithKline Beecham Pharmaceuticals, CPMS 080. Cited in Clarke and Deane (ropinirole) (2000b)

Perez-Aharon J, Abbott RJ, Playfer JR, Foster J, Wells TJ, Brooks D, Spokes G, Segar H, Korczyn AD (1994) Ropinirole, a placebo-controlled study of efficacy as adjunct therapy in parkinsonian patients not optimally controlled on L-dopa (abstract). Neurology 44[Suppl 2]: 244

Rakshi JS, Pavese N, Uema T, Ito K, Morrish PK, Bailey DL, Brooks DJ (2002) A comparison of the progression of early Parkinson's disease in patients started on ropinirole or L-dopa: an ^{18}F-dopa PET study. J Neural Transm 109: 1433–1443

Rascol O, Lees AJ, Senard JM, Pirtosek Z, Montastruc JL, Fuell D (1996) Ropinirole in the treatment of levodopa-induced motor fluctuations in patients with Parkinson's disease. Clin Neuropharmacol 19: 234–245

Rascol O, Brooks DJ, Brunt ER, Korczyn AD, Poewe WH, Stocchi F (1998) Ropinirole in the treatment of early Parkinson's disease: a 6-month interim report of a 5-year levodopa-controlled study. 056 Study Group. Mov Disord 13: 39–45

Rascol O, Brooks DJ, Korczyn AD, De Deyn PP, Clarke CE, Lang AE (2000) A five-year study of the incidence of dyskinesia in patients with early Parkinson's disease who were treated with ropinirole or levodopa. 056 Study Group. N Engl J Med 342: 1484–1491

Reichmann H, Lachenmayer L (2000) Langzeitstudie zum Nachweis der Wirksamkeit und Dyskinesieprophylaxe von Ropinirol. Nervenarzt 71: 1012–1014

Ropinirole 043 Study Group (1996) A double-blind comparative study of ropinirole vs bromocriptine in the treatment of parkinsonian patients not optimally controlled on L-dopa. Mov Disord 11[Suppl 1]: 188

Schrag A, Brooks DJ, Brunt E, Fuell D, Korczyn A, Poewe W, Quinn NP, Rascol O, Stocchi F (1998) The safety of ropinirole, a selective nonergoline dopamine agonist, in patients with Parkinson's disease. Clin Neuropharmacol 21: 169–175

Schrag A, Keens J, Warner J (2002) Ropinirole for the treatment of tremor in early Parkinson's disease. Eur J Neurol 9: 253–257

Sethi KD, O'Brien CF, Hammerstad JP, Adler CH, Davis TL, Taylor RL, Sanchez-Ramos J, Bertoni JM, Hauser RA (1998) Ropinirole for the treatment of early Parkinson disease: a 12-month experience. Ropinirole Study Group. Arch Neurol 55: 1211–1216

Whone AL, Watts RL, Stoessl AJ, Davis M, Reske S, Nahmias C, Lang AE, Rascol O, Ribeiro MJ, Remy P, Poewe WH, Hauser RA, Brooks DJ (2003) Slower progression of Parkinson's disease with ropinirole versus levodopa. The REAL-PET study. Ann Neurol 54: 93–101

Wheadon DE, Wilson-Lynch K, Gardiner D, Kreider MS (1996) The efficacy and safety of ropinirole in early parkinsonian patients not receiving dopaminergic therapy in a multi-center double-blind trial. Ropinirole, a non-ergoline D2 agonist, is effective in early parkinsonian patients not treated with L-dopa (abstract). Neurology 46: A159

Pramipexole

Ahlskog JE, Maraganore DM, Uitti RJ, Uhl GR (2002) Brain imaging to assess the effects of dopamine agonists on progression of Parkinson disease (letter). JAMA 288: 311

Albin RL, Nichols TE, Frey KA (2002) Brain imaging to assess the effects of dopamine agonists on progression of Parkinson disease (letter). JAMA 288: 311–312

Barone P, Bressman SB (2001) Pramipexole without levodopa as early treatment for Parkinson's disease: long-term follow-up of 717 patients. Neurology 56[Suppl 3]: A343

Barone P, Bressman SB, Musch B (2001) Pramipexole (PPX) without levodopa (LD) as early treatment of Parkinson's disease (PD): a long-term follow-up of 717 patients (abstract). Parkinson Rel Disord 7[Suppl]: S52

Guttman, M. and the International Pramipexole-Bromocriptine Study Group (1997) Double-blind comparison of pramipexole and bromocriptine treatment with placebo in advanced Parkinson's disease. Neurology 49: 1060–1065

Hubble JP, Koller WC, Cutler NR, Sramek JJ, Friedman J, Goetz C, Ranhosky A, Korts D, Elvin A (1995) Pramipexole in patients with early Parkinson's disease. Clin Neuropharmacol 18: 338–347

Lieberman A, Ranhosky A, Korts D (1997) Clinical evaluation of pramipexole in advanced Parkinson's disease: results of a double-blind, placebo-controlled, parallel-group study. Neurology 49: 162–168

Mizuno Y, Yanagisawa N, Kuno S, Yamamoto M, Hasegawa K, Origasa H, Kowa H The Japan Pramipexole Study Group (2003) Randomized, double-blind study of pramipexole with placebo and bromocriptine in advanced Parkinson's disease. Mov Disord 18: 1149–1156

Molho ES, Factor SA, Weiner WJ, Sanchez-Ramos JR, Singer C, Shulman L, Brown D, Sheldon C (1995) The use of pramipexole, a novel dopamine (DA) agonist, in advanced Parkinson's disease. J Neural Transm [Suppl] 45: 225–230

Marek K, Seibyl J, McDermott M, Fahn S, Lang A (2002) Brain imaging to assess the effects of dopamine agonists on progression of Parkinson disease (letter). JAMA 288: 312–313

Möller JC, Oertel WH (2000) Pramipexole in the treatment of advanced Parkinson's disease. Eur J Neurol 7[Suppl 1]: 21–25

Morrish PK (2002) Brain imaging to assess the effects of dopamine agonists on progression of Parkinson disease (letter). JAMA 288: 312

Musch B, Barone P, Bressman SB (2001) Pramipexole (PPX) without levodopa (LD) as early treatment of Parkinson's disease (PD): a long-term follow-up of 717 patients. J Neurol Sci 187[Suppl 1]: S241

Parkinson Study Group (1997) Safety and efficacy of pramipexole in early Parkinson disease. A randomized dose-ranging study. JAMA 278: 125–130

Parkinson Study Group (2000a) Pramipexole vs levodopa as initial treatment for Parkinson disease: a randomized controlled trial. Parkinson Study Group. JAMA 284: 1931–1938

Parkinson Study Group (2000b) A randomized controlled trial comparing pramipexole with levodopa in early Parkinson's disease: design and methods of the CALM-PD Study. Clin Neuropharmacol 23: 34–44

Parkinson Study Group (2002) Dopamine transporter brain imaging to assess the effects of pramipexole vs levodopa on Parkinson disease progression. JAMA 287: 1653–1661

Pinter MM, Pogarell O, Oertel WH (1999) Efficacy, safety and tolerance of the non-ergoline dopamine agonist pramipexole in the treatment of advanced Parkinson's disease: a double-blind, placebo-controlled, randomised, multicentre study. J Neurol Neurosurg Psychiatry 66: 436–441

Pinter MM, Rutgers AW, Hebenstreit E (2000) An open-label, multicentre clinical trial to determine the levodopa dose-sparing capacity of pramipexole in patients with idiopathic Parkinson's disease. J Neural Transm 107: 1307–1323

Pogarell O, Gasser T, van Hilten JJ, Spieker S, Pollentier S, Meier D, Oertel WH (2002) Pramipexole in patients with Parkinson's disease and marked drug resistant tremor: a randomised, double blind, placebo controlled multicentre study. J Neurol Neurosurg Psychiatry 72: 713–720

Reichmann H, Brecht MB, Kraus PH, Lemke MR (2002) Pramipexol bei der Parkinson-Krankheit. Nervenarzt 73: 745–750

Rektorová I, Rektor I, Bareš M, Dostá V, Ehler E, Fanfrdlová Z, Fiedler F, Klajblová H, Kulišt'ák P, Ressner P, Svátová J, Urbánek K, Velísková J (2003) Pramipexole and pergolide in the treatment of depression in Parkinson's disease: a national multicentre prospective randomized study. Eur J Neurol 10: 399–406

Shannon KM, Bennett JP, Friedman JH (1997) Efficacy of pramipexole, a novel dopamine agonist, as monotherapy in mild to moderate Parkinson's disease. The Pramipexole Study Group Neurology 49: 724–728

Tan EK, Ondo W (2000) Clinical characteristics of pramipexole-induced peripheral edema. Arch Neurol 57: 729–732

Weiner WJ, Factor SA, Jankovic J, Hauser RA, Tetrud JW, Waters CH, Shulman LM, Glassman PM, Beck B, Paume D, Doyle C (2001) The long-term safety and efficacy of pramipexole in advanced Parkinson's disease. Parkinson Rel Disord 7: 115–120

Wermuth L, and Danish Pramipexole Study Group (1993) Pramipexole – a new dopamine agonist: a double-blind, placebo-controlled, randomized study in advanced Parkinson's disease (abstract). Can J Neurol Sci 20[Suppl 4]: S238

Wermuth L, and the Danish Pramipexole Study Group (1998) A double-blind, placebo-controlled, randomised, multi-center study of pramipexole in advanced Parkinson's disease. Eur J Neurol 5: 235–242

α-Dihydroergocryptine

Albanese A, Colosimo C (2003) Dihydroergocriptine in Parkinson's disease: clinical efficacy and comparison with other dopamine agonists. Acta Neurol Scand 107: 349–355

Battistin L, Bardin PG, Ferro-Milone F, Ravenna C, Toso V, Reboldi G (1999) Alpha-dihydroergocryptine in Parkinson's disease: a multicentre randomized double blind parallel group study. Acta Neurol Scand 99: 36–42

Bergamasco B, Frattola L, Muratorio A, Piccoli F, Mailland F, Parnetti L (2000) Alpha-dihydroergocryptine in the treatment of de novo parkinsonian patients: results of a multicentre, randomized, double-blind, placebo-controlled study. Acta Neurol Scand 101: 372–380

Jörg J (1998) Therapie des Morbus Parkinson mit α-Dihydroergocryptin in der neurologischen Praxis. Ergebnisse einer Anwendungsbeobachtung. Akt Neurol 25: 198–201

Martignoni E, Pacchetti C, Sibilla L, Bruggi P, Pedevilla M, Nappi G (1991) Dihydroergocryptine in the treatment of Parkinson's disease: a six months' double-blind clinical trial. Clin Neuropharmacol 14: 78–83

Martucci N, Fabbrini G, Levi Minzi A, Pedevilla M (1989) La diidroergocriptina nella terapia del Morbo di Parkinson. Giorn Neuropsicol 4[Suppl]: 37–39

Piolti R, Bergamasco B, Scarzella L, Scarzella R, Rivoira M, Apollonia I, Frattola L (1989) Diidroergocriptina versus bromocriptina nella terapia dei pazienti parkinsoniani "de novo". Giorn Neuropsicofarmacol 4: 27–31

Piribedil

Lebrun-Frenay C, Borg M (2002) Choosing the right dopamine agonist for patients with Parkinson's disease. Curr Med Res Opin 18: 209–214

Millan MJ, Cussac D, Milligan G, Carr C, Audinot V, Gobert A, Lejeune F, Rivet JM, Brocco M, Duqueyroix D, Nicolas JP, Boutin JA, Newman-Tancredi A (2001) Antiparkinsonian agent piribedil displays antagonist properties at native, rat, and cloned, human α_2-adrenoceptors: cellular and functional characterization. J Pharmacol Exp Ther 297: 876–887

Ziegler M, Rondot P (1999) Activité du piribédil dans la maladie de Parkinson. Étude multicentrique. Presse Med 28: 1414–1418

Ziegler M, Castro-Caldas A, Del Signore S, Rascol O (2003) Efficacy of piribedil as early combination to levodopa in patients with stable Parkinson's disease: a 6-month, randomized, placebo-controlled study. Mov Disord 18: 418–425

Authors' address: Prof. Dr. P. Riederer, Clinical Neurochemistry, Clinic for Psychiatry and Psychotherapy, University of Würzburg, Füchsleinstrasse 15, D-97080 Würzburg, Germany, e-mail: peter.riederer@mail.uni-wuerzburg.de