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Dopamine Agonists

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INTRODUCTION

Dopamine agonists (DA) have been used to treat symptoms of Parkinson's disease (PD) since the late 1970s (1). These agents were initially introduced to supplement the beneficial effect and possibly reduce the incidence of long-term complications of levodopa. In the last 30 years, methodical investigations of DA have demonstrated therapeutic benefit in all stages of PD both in combination with levodopa and as monotherapy. More recently, positron emission tomography (PET) and single photon emission computed tomography (SPECT) imaging have demonstrated possible benefit in patients randomized to a DA when compared to subjects receiving levodopa (2–4). Increasingly, clinical, animal model, and cellular data suggest not only a levodopa-sparing effect and a delay in the incidence of motor fluctuations, but also a potential neuroprotective effect (5). A number of hypotheses regarding this phenomenon have been proposed. These include reduction of free radical formation by limiting levodopa exposure or increase in the activity of radical-scavenging systems, perhaps by changing mitochondrial membrane potential. In addition, some investigators suggest that DA may enhance neurotrophic activity. However,

there is currently no evidence of neurological improvement clinically, using trial designs with sufficient duration and washout periods to assess neurological status beyond therapeutic response.

This chapter will review the history of DA usage in the treatment of PD and provide a summary of data concerning efficacy, treatment approaches, and comparison between commonly prescribed DA. In addition, data suggesting long-term favorability when compared to levodopa will be reviewed. Lastly, similarly designed clinical trials will be discussed with direct comparative trials in an effort to better define the relative efficacy of these agents.

DOPAMINE AGONISTS AND DOPAMINE RECEPTORS

The DA most often used in treating symptoms of PD include apomorphine, bromocriptine, cabergoline, lisuride, pergolide, pramipexole, and ropinirole. All of these agents activate D_2 receptors, while pergolide has been shown to be a mild D_1 agonist, and pramipexole may have higher affinity for D_3 (Table 1). Five subtypes of DA receptors have been identified and may be classified into striatal (D_1 and D_2) receptors or cortical (D_3, D_4, and D_5) receptors. The D_{3-5} receptors are present in the limbic system and other dopaminergic pathways. Although the different roles of D_1 and D_2 receptors in regulation of striatal function are more fully outlined elsewhere in this volume, the D_1 receptor ($D_{1,5}$) family is associated with activation of adenylate cyclase, and dopamine and DA activate the D_2 receptor family (D_{2-4}) (6). Postmortem examination of brains of subjects with PD reveal upregulation of striatal D_2 and downregulation of the D_1 receptors. It is postulated that these changes lead to alteration of the indirect D_2-mediated pathway and disinhibition of the subthalamic nucleus. Intracortical inhibition studies comparing apomorphine, a rapid-acting DA, to deep brain stimulation found comparable changes in Unified Parkinson's Disease Rating Scale (UPDRS) and intracortical inhibition with bilateral sub-thalamic nuclei or globus pallidus stimulation or with apomorphine infusion, suggesting a connection between the nigral dopaminergic pathway and the thalamo-cortical motor pathway (7).

Apomorphine

Because of the powerful emetic action of apomorphine, clinical usage of this compound in treating PD has been avoided (8). More recently, this short-acting DA has been developed as injectable and sublingual forms to be used in "rescuing" PD patients from unpredictable off-periods. This therapy may

TABLE 1 Dopamine Agonists in Parkinson's Disease

Dopamine agonist	D_1	D_2	D_3	D_4	D_5	5-HT	NE	ACh
Dopamine	+	++	+++	++	+++	0	0	0
Bromocriptine	−	++	+	+	+	−	+	0
Pergolide	+	+++	+++	+++	+	0	+	0
Pramipexole	0	+++	+++	++	0	+	+	+
Ropinirole	0	+++	+++	0	0	0	0	0

D = dopamine; 5-HT = 5 hydroxytryptamine; NE = norepinephrine; ACh = acetylcholine.
Source: Adapted from Ref. 6.

require initial treatment with domperidone, a peripheral DA receptor blocking antiemetic agent. Dewey et al. (9) demonstrated a 62% improvement in off-state UPDRS scores in subjects with advanced PD 20 minutes after subcutaneously injecting apomorphine in a 2:1 randomized placebo-controlled trial. This agent has been demonstrated to be effective as a subcutaneously administered agent in 30 patients for up to 5 years of therapy (10), and some follow-up studies of up to 8 years have demonstrated long-term persistence of apomorphine efficacy. In a subset of patients who could no longer tolerate subcutaneous injections, an intravenous (IV) preparation is being evaluated. In one study of five subjects with severe subcutaneous nodule formation who were followed for a mean of 7 months (range 0.5–18 months) IV administered apomorphine appeared to produce more consistent motor abilities, allowed for a reduction in oral medications by an average of 59%, and decreased off time from 5.4 to 0.5 hours per day. However, unanticipated intravascular thrombotic complications, secondary to apomorphine crystal accumulation, were seen in two subjects (11).

Bromocriptine

Bromocriptine was first approved in the United States in 1978. This ergot alkaloid is a partial D_2 agonist and a mild adrenergic agonist. It also has mild D_1 and 5-hydroxytryptamine (5-HT) antagonist properties (Table 1). When taken orally, bromocriptine is rapidly absorbed and 90% degraded through first-pass hepatic metabolism. Peak drug levels are achieved in 70–100 minutes, and it has a half-life of 3–8 hours. Less than 5% of the drug is excreted into the urine, and bromocriptine is highly protein bound. The drug is formulated into 2.5 mg scored tablets and 5 mg capsules (1). Dosing titration usually begins at 1.25 mg/day and increases to a recommended

20 mg/day over the course of 7 weeks; however, successful treatment with dosages higher than 60 mg/day has been reported (12) (Table 2).

While the side effects of the various DA are similar, only the ergot-derived compounds have been associated with retroperitoneal fibrosis, a rare but serious condition associated with severe pulmonary and renal complications (13). Erythromelalgia, a painful discoloration of the shins, may also be more prevalent in patients taking ergoline DA. The side effects of nausea, vomiting, sleepiness, orthostatic hypotension, and hallucinations are common to all DA, but in pivotal trials using bromocriptine they were 8–12% more common than in subjects receiving placebo (14) (Table 3).

Bromocriptine has been investigated extensively in de novo and levodopa-treated populations. A recent systematic review of all randomized controlled trials of bromocriptine monotherapy compared with levodopa (LD) monotherapy in PD found that although numerous small trials have been reported, methodological factors or lack of a control population has led to a lack of evidence basis for clinical decisions (15–17). From 1974 to

TABLE 2 Agonist Titration Schedule

Time	Bromocriptine	Pergolide	Pramipexole	Ropinirole
Week 1	1.25 mg qd	0.05 mg qd	0.125 mg tid	0.25 mg tid
Week 2	1.25 mg bid	0.05 mg tid	0.25 mg tid	0.50 mg tid
Week 3	1.25 mg tid	0.10 mg tid	0.50 mg tid	0.75 mg tid
Week 4	2.50 mg tid	0.15 mg tid	0.75 mg tid	1.00 mg tid
Week 5	3.75 mg tid	0.25 mg tid	1.00 mg tid	2.00 mg tid
Week 6	5.00 mg tid	0.50 mg tid		3.00 mg tid
Week 7	5.00 mg qid	0.75 mg tid		4.00 mg tid
Week 8		1.00 mg tid		
Maximum dosage	15.0 mg qid	2.00 mg qid	1.5 mg tid	8.00 mg tid

Source: Adapted Ref. 12.

TABLE 3 Dopamine Agonists in Parkinson's Disease

Dopamine agonist	$t_{1/2}$ (h)	Metabolism	Percentage				
			N	S	H	OH	RPF
Bromocriptine	3–8	Hepatic	37	8	12	44	2–5
Pergolide	27	Hepatic	24	6	14	2	2–5
Pramipexole	8–12	Renal	18	13	19	16	0
Ropinirole	4–6	Hepatic	20	12	15	17	0

N = nausea; S = somnolence; H = hallucinations; OH = orthostatic hypotension; RPF = retroperitoneal or pulmonary fibrosis.
Source: Adapted from Ref. 1. Additional data from published package inserts.

January 1999, six studies randomizing more than 850 patients to a bromocriptine or a levodopa regimen are in the literature, but only two trials were performed according to a double-blind design (16). These studies indicate a reduced frequency of dyskinesias, and there was a trend toward less wearing-off and fewer on-off problems in the bromocriptine group. However, the statistically larger number of dropouts in the bromocriptine group leaves these data subject to varied interpretations. In the treatment of early PD bromocriptine may be beneficial in delaying motor complications and dyskinesias with comparable effects on impairment and disability in those patients who tolerate the drug.

Bromocriptine is well accepted as a treatment in advancing PD. Although numerous studies have demonstrated this benefit in the past, a more recent, well-designed, multicenter trial comparing bromocriptine to placebo in patients with motor fluctuations has been reported. In this 9-month study there was a 14% improvement in UPDRS activities of daily living, and a 23.8% improvement in motor score. The bromocriptine arm also demonstrated a 29.7% reduction in off-time while taking a mean dosage of 22.8 mg/day (18).

Pergolide

Pergolide, an ergoline-derived DA, was approved for usage in the United States in 1989. It is 10 times more potent than bromocriptine. Like bromocriptine, pergolide has high affinity for the D_2 receptor and mild α_2-adrenergic activity, but it does not have 5-HT activity. In addition, pergolide has significant D_3 activity and is the only DA with D_1 agonist activity, although this is mild (1) (Table 1). Pergolide is available in three tablet sizes—0.05, 0.25, and 1.0 mg—and is usually titrated to an effective dosage or an initial maximum dosage of 3 mg daily over the course of 6–8 weeks (12) (Table 2). If clinical benefit is seen at 3 mg daily, this dosage may be increased with disease progression to a typical maximum dosage of 6–8 mg/day. Pergolide is rapidly absorbed from the gut and reaches a peak plasma concentration in 1–3 hours. While the duration of action is typically 4–8 hours, the half-life ranges from 15 to 42 hours, with a mean of 27 hours. Pergolide is highly protein bound, and >50% is excreted through the kidney (1). Side effects associated with pergolide are similar to bromocriptine and include retroperitoneal fibrosis, erythromelalgia, somnolence, orthostatic hypotension, and hallucinations (14,19) (Table 3).

Pergolide has been demonstrated effective in both early- and late-stage PD (20). In an open-label trial, Mizuno et al. demonstrated mild to moderate to marked benefit in 47.5% of patients after 8 weeks of pergolide at dosages up to 5 mg/day (21). Another open-label trial of 20 PD subjects

reported benefit in 7 subjects with a mean dosage of 0.85 mg/day. These subjects were followed for 3 years. By 30 months, 7 subjects required supplementation with levodopa, and by the end of the study the mean dosage of pergolide had increased to 2.15 mg/day (19). A more recent de novo PD study (PELMOPET-trial), with randomization to levodopa or pergolide and concurrently evaluated using PET scanning, suggests a more robust therapeutic effect. In this double-blind study, 294 subjects were randomized to pergolide ($n = 148$) or levodopa ($n = 146$) and treated without levodopa rescue for 36 months (4). An early report indicated that 77 subject (52%) receiving pergolide compared to 90 subjects (61.6%) treated with levodopa completed the study. Mean dosages for pergolide were 3.23 mg/day and for levodopa were 504 mg/day. Although no statistical significance was seen in study completers, differences were noted in change from baseline UPDRS motor score (13.4 ± 8.8 pergolide vs. 18.1 ± 10.1 levodopa). As expected, dyskinesias were three times more frequent and motor complications more severe in the levodopa group as captured by the UPDRS, part IV. In addition, 88 subjects were followed by 18F-Dopa PET scans. Early reports of these results show a decrease in uptake in the putamen of 7.9% in the pergolide group and 14.5% in the levodopa group, but these differences were nonsignificant ($p = 0.288$) (Table 4). Evidence-based treatment data for pergolide therapy in patients with motor fluctuations on levodopa are available. In general, numerous small trials found data similar to those reported by Olanow et al. (22). In this report of a 24-week, double-blind trial of 377 subjects randomized to pergolide (189) or placebo (187), significant improvements were seen in motor scores and off-time, and levodopa dosages were reduced by approximately 25% in the pergolide group (Table 5).

A review comparing efficacy data in adjunct therapy trials of pergolide and bromocriptine found that pergolide was superior to bromocriptine in

TABLE 4 Relative Potencies of Dopamine Agonists in Early Parkinson's Disease

	Effective dose (mg/d)	Relative potency	Relative dose range	UPDRS III Benefit vs. levodopa	UPDRS III monoRx
Bromocriptine	15–60	1:1	15–60	n/a	+ 0.2
Pergolide	1.5–8	10:1	15–80	+ 3.0 vs − 2.5[a]	n/a
Pramipexole	1.5–4.5	10:1	15–45	− 3.4 vs − 7.3[b]	− 6.0
Ropinirole	9–24	2:1	18–48	− 0.8 vs − 4.8[c]	− 4.5

[a] 36-month study.
[b] 23-month study.
[c] 40-month study.

TABLE 5 Relative Potencies of Dopamine Agonists in Advanced Parkinson's Disease

	Effective dose (mg/d)	LD↓ (mg/d)	Off-time decrease (%)	UPDRS III Benefit
Bromocriptine	22.6	ns-30%	0–30	− 3.0 (24%)
Pergolide	2.9	235 (20%)	32	n/a (35%)
Pramipexole	3.4	(22%)	15	− 4.0 (35%)
Ropinirole	7.5–24	191 (25%)	7	n/a

regard to improvements in motor function and activities of daily living (23). In addition, more patients reported a "marked" or "moderate improvement" with pergolide than with bromocriptine. However, no significant difference in motor fluctuations, dyskinesias, levodopa dose reduction, dropouts, or adverse events was found.

Pramipexole

Pramipexole was approved for use in the United States in July 1997. It is a synthetic, nonergot DA. Like the ergot-derived DA, this agent is active at the D_2, D_3, and D_4 receptors. Pramipexole also has affinity for α- and β-adrenoreceptors, acetylcholine receptors, and 5-HT receptors (Table 1). The drug is available in 0.125, 0.25, 0.5, 1.0, and 1.5 mg tablets, and the usual dosage is 3.0 mg/day over 5 weeks (12) (Table 2). When ingested, this drug reaches peak plasma levels within 1–3 hours and has an elimination half-life of 8–12 hours. The agent is excreted mostly unchanged in the urine, and <20% of pramipexole is protein bound. Pivotal trials with pramipexole report nausea, vomiting, somnolence, and orthostatic hypotension 0–13%, higher than in subjects randomized to placebo (14) (Table 3). A condition described as an "unexpected sleep episode" has been described and has also been seen with other dopamine agents (24,25). In addition, pathological gambling has been reported (26,27).

Pramipexole has been thoroughly studied in de novo and adjunctive populations. Three major trials have evaluated the effectiveness of pramipexole as monotherapy in early PD (28–31). A large dose ranging trial ($n = 264$) conducted by the Parkinson Study Group found that most patients tolerated dosages of 6 mg or less of pramipexole. In this 10-week study, 98% (placebo), 81% (1.5 mg/day), 92% (3.0 mg/day), 78% (4.5 mg/day) and 67% (6.0 mg/day) of subjects tolerated drug to study conclusion (28). A 20% benefit in motor score was seen in all active treatment groups, and it was determined that the optimum dosage range was 1.5–4.5 mg/day. In a 6-month study, 335 subjects were randomized to pramipexole ($n = 164$)

or placebo ($n = 171$). Investigators reported a greater than 20% improvement in the UPDRS activities of daily living and motor scores in the active treatment group (29). Side effects in these investigations included nausea, somnolence, dizziness, and hallucinations (Table 4).

The Parkinson Study Group reported data comparing pramipexole to levodopa in early PD (CALM-PD) (2,29,30). In this trial, 301 subjects were randomized to pramipexole or placebo and were followed for 4 years. At the conclusion of the trial, 52% of pramipexole and 74% of levodopa subjects reached the primary endpoint of motor complications. Furthermore, dyskinesias (25% vs. 54%) and wearing off (47% vs. 67%) were present in a greater percentage of patients initiated with levodopa. However, UPDRS assessments found significantly greater improvements (approximately 4 points) in subjects receiving levodopa (30). Eighty-two subjects in the CALM-PD cohort also underwent sequential SPECT imaging with β-CIT to assess striatal uptake of this dopamine transporter molecule (2). Comparisons between the pramipexole ($n = 42$) and the levodopa ($n = 40$) groups found statistically significant differences ranging from 6.4 to 9.5% in transporter uptake at 22, 34, and 46 months, suggesting less decline in the subjects receiving the dopamine agonist (Table 4). This study differs from the PELMOPET study comparing pergolide to levodopa in that supplemental levodopa was allowed at the discretion of the investigator in either group. The dosages of pramipexole averaged 2.78 mg/day, with 48% of subjects receiving a levodopa supplement of a mean dosage of 264 mg/day, while 36% of the levodopa-treated subjects required levodopa supplementation with a mean dosage of 509 mg/day.

Two large, randomized clinical trials using pramipexole in levodopa-treated patients have demonstrated significant benefit in off time (31% and 15%), activities of daily living (22% and 27%), motor scores (25% and 35%), and levodopa dosage reduction (27%) (18,31). The mean dosage of pramipexole was 3.36 mg/day, and side effects including dyskinesias, orthostatic hypotension, dizziness, insomnia, hallucinations, nausea, confusion, and headache were seen (18,31) (Table 3).

Ropinirole

Ropinirole was approved in the United States in September 1997. This DA is a nonergot compound with affinity for the D_2 family of receptors, but not the D_1 or D_5 receptors. In addition, unlike pergolide or pramipexole, ropinirole lacks affinity for adrenergic, cholinergic, or serotonergic receptors (Table 1). This drug is also rapidly absorbed from the gut with peak plasma concentrations occurring in 1–2 hours and is 40% protein bound (1). The elimination half-life is 6 hours, and the P450 CYP1A2 hepatic enzyme

pathway metabolizes the drug. Because of this, patients given ciprofloxacin may have an increase in serum ropinirole concentrations. Because of the difference in potency, when compared to pramipexole and pergolide, this agent is often underdosed. Ropinirole is available in 0.25, 0.5, 1.0, 2.0, 3.0, 4.0, and 5.0 mg tablets and is usually titrated to 12 mg/day over a 7-week period. Clinical improvement is usually not seen until patients are taking 6 mg/day (12) (Table 2). Side effects are similar to those seen with the other DA and include nausea, somnolence, hallucinations, and orthostatic hypotension (Table 3).

Ropinirole has been tested extensively in early and advanced PD populations, and its development closely mirrors that of pramipexole. Adler et al. randomized 241 untreated subjects to ropinirole ($n = 116$) or placebo ($n = 125$) arms in a 24-week trial (32). Responders were defined as subjects achieving at least a 30% improvement in UPDRS total and motor scores, the primary outcome variables. In addition, subjects were assessed for time to levodopa initiation and with a clinical global improvement scale. With an average dosage of 15.7 mg daily, 47% of ropinirole subjects were identified as responders, while only 20% of subjects responded in the placebo arm. The mean changes in UPDRS of 24% in the ropinirole group and 3% in the placebo group reached statistical significance. Time to levodopa significantly differed, with 11% of ropinirole subjects and 29% of placebo subjects requiring additional therapy. Requirement for levodopa therapy for the ropinirole subjects was 16, 27, and 40% at 1, 2, and 3 years, respectively (1).

Studies have also been completed in de novo patients randomized to ropinirole or placebo (ropinirole 056 study) and followed by PET scanning (REAL-PET) (3,33). The 5-year clinical trial randomized 268 subjects to ropinirole ($n = 179$) or placebo ($n = 89$) in a 2:1 fashion, allowing add-on levodopa at the discretion of the investigator. Eighty-five subjects in the ropinirole group (47%) and 45 subjects in the levodopa group (51%) completed the study. In the ropinirole group 29 of the 85 patients (34%) received no levodopa supplementation at 5 years. The analysis of the time to dyskinesia showed a significant difference in favor of ropinirole, and at 5 years the cumulative incidence of dyskinesias, regardless of levodopa supplementation, was 20% in the ropinirole group and 45% in the levodopa group. The mean daily dose by the end of the study was 16.5 mg of ropinirole. The average dosage for levodopa supplementation was 427 mg/day. The subjects randomized to levodopa received an average of 753 mg/day. Recently, the results of a PET analysis comparing ropinirole to levodopa have been reported (REAL-PET) (3). This 2-year randomized trial found a statistically significant difference in striatal uptake when comparing ropinirole 13% to levodopa 20%. Clinical evaluation of these subjects found that 14% of the ropinirole group vs. 8% of the levodopa group required

levodopa, while only 3% of subjects on ropinirole and 27% on levodopa developed dyskinesias. Lang et al. (34) reviewed ropinirole data to assess whether the development of dyskinesias in subjects exposed to early DA monotherapy would have sustained benefit compared to levodopa, a gradual return to the dyskinesia of those receiving early levodopa, or a rapid return to the dyskinesias of levodopa subjects (34). In this review, no differences were seen between groups, and a parallel rate of sustained efficacy without dyskinesia was seen. A 6-month, placebo-controlled trial of 149 subjects with advanced PD randomized to ropinirole ($n = 95$) or placebo ($n = 54$) followed for levodopa dosage and off-time reduction was conducted. In this study, levodopa dosage was reduced an average of 31% in ropinirole subjects compared to 6% in placebo subjects. Off-time was reduced by 12% in the ropinirole group and 5% in the placebo group, a difference in off-time of slightly over one hour per day (36).

Other Dopamine Agonists

Cabergoline is a once-daily, ergot-derived, dopamine agonist available in the United States for the treatment of hyperprolactinemia. It has been demonstrated to be effective in PD, but is prohibitively expensive in the United States. Cabergoline has been evaluated in de novo and advanced PD populations. In a double-blind, 2:1 placebo-controlled trial of 188 subjects taking levodopa, the addition of cabergoline allowed for an 18% reduction in levodopa, with a 16% improvement in motor scores (37). Clarke and Deane have compared cabergoline to bromocriptine in a meta-analysis of five randomized, double-blind, parallel group studies in 1071 patients (35). Cabergoline produced benefits similar to bromocriptine in off-time reduction, motor impairment and disability ratings, and levodopa dose reduction over the first 3 months of therapy. Dyskinesia and confusion were increased with cabergoline, but otherwise the frequency of adverse events and withdrawals from treatment were similar with the two agonists.

Rotigotine is a novel DA that is unique in that it is delivered through a skin patch transdermal system. In one multicenter phase II b trial, 316 patients were randomized to placebo or active drug in a 1:4 ratio and followed by UPDRS for 4 weeks (38). In this dose-finding study, statistical improvement in UPDRS activity of daily living and motor scores were seen at 9, 13.5, and 18 mg/day. No changes were seen with placebo or at 4.5 mg/day. Positive responder rates (>20% UPDRS change) increased with dosage; responder rates were as follows: placebo, 29%; 4.5 mg, 38%; 9 mg, 45%; 13.5 mg, 57%; 18 mg, 53% (daily dosages) (38).

COMPARISONS BETWEEN DOPAMINE AGONISTS

At this time 15 comparative trials between DA are known: Tan and Jankovic have summarized these studies and report conversion factors of 10:1 for bromocriptine to pergolide, 1:1 for pergolide to pramipexole, 1:6 for pergolide to ropinirole, and 10:6 for bromocriptine to ropinirole (6). Hanna et al. followed 21 stable subjects on pergolide switched safely to pramipexole in a 1:1 ratio (39). Although not statistically significant, levodopa dosages were reduced by 16.5%, and 13 of the 21 (62%) subjects reported improvement with the change in regimen. Hauser et al. reported conversion of stable subjects on levodopa and pramipexole to levodopa and ropinirole in a 1:3 mg ratio. A gradual transition was somewhat better tolerated when compared to rapid change (40). However, the difficulties reported by subjects in retrospect may have been improved with a higher conversion factor for ropinirole.

Although there are obvious difficulties when making direct comparisons in studies to determine dosage equivalence, a reasonable equation of relative DA potency would suggest bromocriptine ($\times 10$) = pergolide = pramipexole = ropinirole ($\times 6$) on a milligram-to-milligram basis. Using the least potent and longest prescribed DA, a dosing equivalence range may provide a useful measure of the treatment dosing spectrum using these agents (Table 4). Using these assumptions, dosing ranges appear to be higher in the ergot-related compounds, suggesting a longer treatment horizon. However, at higher prescribed amounts, the dosing curves for these agents tend to become more level, and the linear improvement seen at midrange dosages may not be present at higher doses. Perhaps a better measure of treatment response is to review similar trials of DA therapy. In the early PD population, UPDRS data in similar, placebo-controlled studies using pramipexole and ropinirole found remarkably similar benefit (Table 4). Another potential comparison perspective is to evaluate trials comparing two active interventions with the DA and levodopa. In the imaging trials for pergolide, pramipexole, and ropinirole, subjects treated with the agonist demonstrated similar, but less, benefit than those with levodopa. It is unfortunate that the levodopa supplementation in the pramipexole and ropinirole trials limited long-term monotherapy assessment, so extensive direct comparisons cannot be made, but in general the three trials produced similar benefit when compared to levodopa response.

Because the data in the PELMOPET, CALM-PD, and 056/REAL-PET trials represent, perhaps, the most rigorous and careful information gathered about these compounds, it is useful to compare them as closely as possible (2–4,31,33) (Table 4). Clinically, subjects treated with pergolide at

an average dosage of 3.23 mg/day demonstrated a motor scale decline of 3 points over 36 months, while subjects randomized to levodopa still demonstrated benefit of 2.5 points in the same time interval. Although the DA/levodopa trials using pramipexole and ropinirole allowed for levodopa supplementation and had different durations, it is interesting to note that, like the 5.5 point difference seen in the PELMOPET trial, the differences between pramipexole (-3.4) and levodopa (-7.3) at 23.5 months (difference $= 3.9$ points) and ropinirole (-0.8) and levodopa (-4.8) at 60 months (difference $= 4$ points) are highly similar. Furthermore, the small differences between the PELMOPET (5.5 UPDRS motor points) and the CALM-PD (3.9 points) and 056 (4.0) trials may be explained by the levodopa supplementation allowed in the latter studies. The functional imaging data from these investigations are also similar for dosages of 3.23, 2.78, and 16.5 mg/day for pergolide, pramipexole, and ropinirole, respectively (Fig. 1). F-dopa PET demonstrates ropinirole striatal decline 65.0% of levodopa at 24 months and pergolide striatal decline 54.5% of levodopa at 36 months. SPECT imaging with β-CIT demonstrates 52.6%, 55.6%, and 62.7% pramipexole to levodopa decline at 22, 34, and 46 months of treatment. The imaging impact of added levodopa in the pramipexole and ropinirole groups is unknown.

In summary, similar designs between pergolide, pramipexole, and ropinirole demonstrate similar benefits in terms of levodopa dosage reduction, levodopa percent reduction, treatment responders, and decrease in off-time in adjunctive therapy trials (Tables 3, 4). In these studies subject selection, methodological design, and data collected differed to the point that trends are less reliable than in the early patient studies, but in general similar improvements in all variables were seen.

TREATMENT WITH DOPAMINE AGONISTS

Initiation of Therapy in a New-Onset PD Patient

DA provide substantial improvement in PD symptoms while delaying the development of early morning foot dystonia, motor fluctuations, and dyskinesias (41). In addition, similar trials comparing DA (pergolide, pramipexole, ropinirole) to levodopa in a randomized fashion suggest possible long-term benefit by functional imaging measures (42). In a clinical setting of a 30-year-old patient, it is quite compelling to delay levodopa therapy in favor of DA because of the potentially long clinical horizon (43). Conversely, in an 80-year-old patient with other health concerns, treatment with levodopa may be better tolerated. The decisions regarding initial therapy in the 50 years between these two examples is dependent on the
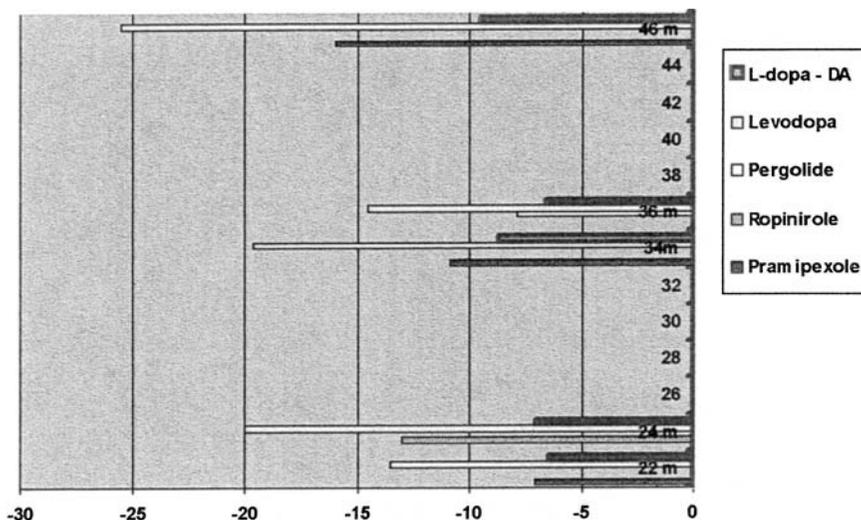
FIGURE 1 Dopamine agonist imaging data. Striatal decline by F-dopa and β-CIT in Parkinson's disease.

health of the patient, the relationship of the physician and the patient, the side effect profiles of the DA and levodopa, and, unfortunately, the cost of the drug (Table 2).

Dopaminergic medications carry similar side effect profiles, including nausea, sleepiness, confusion, orthostatic hypotension, and hallucinations (Table 3). Besides these problems, lower extremity edema, hair loss, and weight gain have also been seen with DA, and the ergoline derivatives bromocriptine, cabergoline, and pergolide also carry a slight risk of erythromelalgia (a reddish discoloration of the legs), and pulmonary and retroperitoneal fibrosis has been reported in 2–5% of subjects exposed to these agents (1). With the exception of nausea, DA are more likely than levodopa to cause these clinical difficulties, and discussion of the potential side effects at the time of prescribing will greatly aid in the tolerance of any new pharmacological agent. Because the statistical spectrum of side effects of these agents are quite similar but vary from patient to patient, it is important for any patient to understand that if he or she does not tolerate the first DA, there is no reason to expect that the other DA will not provide benefit.

Lastly, the nonergoline agonists pramipexole and ropinirole have been associated with "unexpected sleep episodes," and although this problem has been reported with pergolide and levodopa, it remains difficult to refute the observation that this symptom had not been reported prior to the use of pramipexole and ropinirole (24,25). In general, patients reporting excessive daytime sleepiness should be monitored closely with the increase of any dopaminergic therapy, especially in the first 3 months after the change.

Initiation of DA therapy is somewhat dependent on the needs and emotional state of the patient (44). Each of the DA requires a titration period of 4–8 weeks (Table 3). In the healthy patient seeking to improve quickly, initiation of a rapidly titratable agent may be preferred, while the more slowly titrated schedules may suit the needs of a patient reluctant to take any drugs. However, each patient should be reminded that the differences in titration time usually are less than 3 weeks, a brief period of time in the context of a 20-year treatment horizon (Table 2).

Initiation of Dopamine Agonists as Adjunctive Therapy

The initiation of therapy in the early patient is somewhat arbitrary with the exception of pramipexole and renal metabolism vs. the other DA and hepatic metabolism. With advancing PD, the addition of a DA should minimize the risk of aggravating further symptoms of nausea, sleepiness, orthostatic hypotension, and other problems (45) (Table 3).

CONCLUSIONS

The development of DA, particularly pergolide, pramipexole, and ropinirole, has gradually shifted treatment paradigms in PD. In the last 20 years, many parkinsonologists have moved from using DA as adjunctive therapy to levodopa to initiating antiparkinsonian therapy with one of these agents in otherwise healthy subjects (41). More recently, imaging data with SPECT and PET scanning have produced debate regarding the possible "neuroprotective" advantages of DA when compared to levodopa (2–4). In this regard some have questioned whether these agents should be initiated sooner in the disease course, perhaps before obvious disability develops. Regardless of when DA therapy is initiated, each patient benefits from the choice of several agents for treating the symptoms of PD, and it is the responsibility of the physician to provide the information regarding the reasons for using this class of drugs and for choosing one agent over another.

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