Treatment of Early Parkinson's Disease

Part 1

Tanya Simuni^a Kelly E. Lyons^c Rajesh Pahwa^c Robert A. Hauser^d
Cynthia Comella^b Lawrence Elmer^e Daniel Weintraub^f

^aParkinson's Disease and Movement Disorders Center and Department of Neurology, Northwestern University, and ^bDepartment of Neurological Sciences, Rush University Medical Center, Chicago, Ill., ^cParkinson Disease and Movement Disorder Center and Department of Neurology, University of Kansas Medical Center, Kansas City, Kans., ^dParkinson's Disease and Movement Disorders Center and Departments of Neurology, Pharmacology and Experimental Therapeutics, University of South Florida, Tampa, Fla., ^eCenter for Neurological Disorders and Department of Neurology, University of Toledo, Toledo, Ohio, and ^fDepartments of Psychiatry and Neurology, University of Pennsylvania, Philadelphia, Pa., USA

Key Words

Parkinson's disease • Dopamine agonists • Monoamine oxidase B inhibitors • Levodopa

Abstract

The management of early Parkinson's disease (PD) involves the treatment of motor symptoms and, increasingly, non-motor symptoms. Given the fast pace of clinical research in PD, clinicians are faced with the challenge of integrating the latest findings into the ongoing care of individual PD patients. Part 1 of this 2-part article reviews motor symptom efficacy data for the newest PD treatment options, as well as for established therapies. Safety and tolerability data are also reviewed. Part 2 of the article reviews key findings relevant to the assessment of potential neuroprotective therapies and the treatment of non-motor symptoms.

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Introduction

The treatment options for Parkinson's disease (PD) are rapidly expanding. The American Academy of Neurology published evidence-based practice parameters of selected topics in the management of PD in 2006 [1–3]; however, the review did not include the management of early PD since there were no major changes since the last guidelines. Evidence-based treatment guidelines for early PD were published by the American Academy of Neurology in 2002 [4] and the Movement Disorder Society in 2005 [5], but since then new drugs and formulations have become available for the management of the disease.

PD is a multifaceted disorder comprised of both motor and non-motor symptoms at all stages of the disease. This review seeks to integrate data from the newest treatment options with data from established therapies, so as to provide an up-to-date evidence-based reference for clinicians treating early PD. This article will be presented in 2 parts: a review of the efficacy and safety of treatments for PD motor symptoms (part 1) and a review of key clinical trials examining potential neuroprotective therapies for PD and non-motor manifestations of PD (part 2). The following text is part 1.

Treatment of Motor Symptoms

The cardinal motor symptoms of PD include bradykinesia, tremor and rigidity, and even in early disease these symptoms can interfere with daily functioning. The Unified Parkinson's Disease Rating Scale (UPDRS) is the most commonly used scale to assess the severity of PD symptoms. It evaluates mentation (part I), activities of daily living (ADL; part II) and motor function (part III), and the scores from these subsections are summed to determine the total UPDRS score. Part IV of the UPDRS measures complications of therapy, such as dyskinesia, 'off' periods and sleep disturbance, and is often used in trials of adjunct therapy. Of note, the UPDRS is currently undergoing a revision to accommodate advances in the field [6].

UPDRS ADL and motor scores reflecting treatment effects from large, randomized, placebo-controlled, multicenter trials of L-dopa (levodopa), monoamine oxidase type B (MAO-B) inhibitors and dopamine agonists (DAs) in subjects with early-stage PD are summarized in table 1 and will be discussed here. Although anticholinergics and amantadine are also possible treatment options in early PD, they will not be included in this review due to a lack of comparable efficacy data.

L-Dopa

L-dopa is the most effective pharmacological treatment for PD [4, 19]. Since the long-term use of L-dopa is associated with motor complications (motor fluctuations and dyskinesia) [4, 19], the use of other treatment options in an effort to delay the start of L-dopa therapy is often preferred, especially in younger patients.

The ELLDOPA study [7], a 42-week, multicenter, randomized, double-blind trial, compared daily L-dopa to placebo in PD subjects who did not yet need antiparkinsonian medication and were not likely to require medication over the 9 months following enrollment. Patients were randomized to treatment with daily L-dopa dosages of 150 (n = 92), 300 (n = 88) and 600 mg (n = 91) or placebo (n = 90). After 42 weeks, which included a 2-week washout period, the change from baseline in UPDRS total scores was significantly less in each L-dopa group compared to the placebo group. Relative to baseline, UPDRS total scores worsened by 7.8 points in the placebo group and by 1.9 points in the 150 and 300 mg/day L-dopa groups, and improved by 1.4 points in the 600 mg/day L-dopa group ($p < 0.001$ for the dose-response trend; primary outcome). The changes from baseline in UPDRS motor and ADL scores, respectively, were a 5.2- and 2.3-

point worsening in the placebo group, a 1.4- and 0.5-point worsening in the 150 mg/day L-dopa group, a 1.4- and 0.4-point worsening in the 300 mg/day L-dopa group, and a 1.4- and 0.3-point improvement in the 600 mg/day L-dopa group. Although the highest L-dopa dose was the most efficacious, it also resulted in a significantly greater incidence of dyskinesia compared to placebo (16.5 vs. 3.3%). The lower L-dopa dose groups experienced rates of dyskinesia similar to the placebo group. The other adverse events that were significantly more common in the 600 mg/day L-dopa group compared to the placebo group were nausea (31.9 vs. 13.3%), infection (6.6 vs. 1.1%), hypertension (5.5 vs. 1.1%) and headache (13.2 vs. 3.3%). For the 300 and 150 mg/day L-dopa groups, the incidences of nausea (26.1 and 16.3%, respectively) and headache (5.7 and 7.6%, respectively) were notably higher than in the placebo group. L-dopa treatment was associated with a significantly lower incidence of fracture and leg pain compared to placebo.

MAO-B Inhibitors

Selegiline

Oral selegiline has been shown to reduce 'off' time in advanced PD patients [19], and is approved at doses up to 10 mg/day as an adjunctive treatment to L-dopa [19]; however, several clinical trials have shown that selegiline also has symptomatic effects as monotherapy in early PD [4, 5].

DATATOP [8], a multicenter, randomized, double-blind, placebo-controlled trial, is the largest of the selegiline studies in early PD patients, and compared 399 PD subjects taking 10 mg/day oral selegiline to 401 subjects on placebo. Some subjects in both groups were taking concomitant tocopherol, but this was shown to have no effect [20]. Subjects were either de novo (had never been treated; 61%) or had stopped all antiparkinsonian medications prior to the study. After approximately 12 months of follow-up, significantly fewer subjects in the selegiline group (24%) required rescue L-dopa therapy than in the placebo group (44%, $p < 0.001$; primary outcome). At both 1 month and 3 months, the selegiline group had improved from baseline in UPDRS total, motor and ADL scores, while the placebo group had worsened ($p < 0.01$ for all between-group comparisons). At 3 months, the selegiline and placebo groups, respectively, showed a 1.5-point improvement and 1.6-point worsening in UPDRS total scores, a 0.8-point improvement and 1.1-point worsening in UPDRS motor scores, and a 0.3-point improvement and 0.6-point worsening in UPDRS ADL scores ($p < 0.001$ for all between-groups comparisons). Of the

most common adverse events, dry mouth was the only one that occurred at a significantly greater rate in the selegiline group compared to the placebo group.

Rasagiline

Rasagiline is approved at doses up to 1 mg/day as monotherapy and as an adjunct to L-dopa [21]. The monotherapy indication was based in part on the TEMPO study [9], which was a randomized, double-blind, placebo-controlled, 26-week trial comparing 1 mg/day rasagiline ($n = 134$), 2 mg/day rasagiline ($n = 132$) and placebo ($n = 138$) in early PD patients who had not been previously exposed to antiparkinsonian medications other than anticholinergics. At 26 weeks, significantly less worsening of UPDRS total scores was observed with both rasagiline doses compared to placebo; those treated with 1 mg/day rasagiline experienced a 4.2-point improvement relative to placebo and those treated with 2 mg/day rasagiline had a 3.6-point benefit relative to placebo ($p < 0.001$ for both comparisons; primary outcome). A significant benefit of rasagiline was also shown on the UPDRS motor subscale, with the 1 mg/day group showing a 2.7-point benefit relative to placebo and the 2 mg/day group showing a 1.7-point benefit relative to placebo ($p < 0.001$ for both comparisons). On the UPDRS ADL subscale, smaller though still significant benefits were observed, with the 1 and 2 mg/day rasagiline groups showing a 1.0- and 1.2-point benefit, respectively, relative to placebo ($p < 0.001$ for both comparisons). Of the most common adverse events, asthenia was the only one that occurred with a significantly different incidence between the placebo (10.9%) and rasagiline (4.5%) groups.

Selegiline and rasagiline may increase the risk of a hypertensive crisis if used in combination with tyramine-containing foods (e.g. fermented cheese, aged meats) or amine-containing medications (e.g. over-the-counter cough/cold medicines) [21, 22]. Selective MAO inhibitors become non-selective at doses greater than those recommended, and an elevated risk of severe CNS toxicity associated with hyperpyrexia and death has been reported with the use of non-selective MAO inhibitors in combination with tricyclic antidepressants [21, 22]. While the use of rasagiline or selegiline in combination with any agent that increases brain serotonin levels (especially tricyclic antidepressants as well as serotonin and mixed serotonin/noradrenaline reuptake inhibitors) is not contraindicated, caution is advised when an agent with serotonergic properties is used in combination with MAO-B inhibitors.

Dopamine Agonists

DAs can be separated into 2 classes, ergot derived and non-ergot derived. Both classes are efficacious in early PD; however, ergot-derived DAs (e.g. pergolide, bromocriptine, cabergoline) have been associated with valvular heart disease [23, 24], resulting in safety concerns about the ergot class as a whole and prompting the recent removal of pergolide from the US market. The non-ergot DAs approved for early PD include pramipexole, ropinirole and the rotigotine transdermal patch.

Pramipexole

Pramipexole is an orally administered DA approved for early and advanced PD at doses up to 4.5 mg/day [25]. Shannon et al. [10] reported a 31-week, multicenter, randomized, double-blind study of pramipexole ($n = 164$) versus placebo ($n = 171$) in early PD patients. Subjects were allowed concomitant selegiline. The mean daily maintenance dosage of pramipexole for this flexible-dosage study was 3.8 mg, and about two thirds of subjects in each group were taking selegiline. After 31 weeks, the pramipexole group showed improvement in UPDRS motor scores relative to baseline (14.1 post- vs. 18.8 pretreatment) whereas the placebo group had worsened slightly (20.1 post- vs. 18.8 pretreatment), resulting in a significant between-group difference ($p < 0.001$; primary outcome). Similar results were observed for UPDRS ADL scores (also a primary outcome), with pramipexole treatment resulting in an improvement relative to baseline (6.4 post- vs. 8.2 pretreatment) and placebo treatment resulting in a worsening relative to baseline (8.7 post- vs. 8.3 pretreatment; $p < 0.001$ for the between-group comparison).

The Parkinson Study Group [11] reported a 10-week, multicenter, randomized, double-blind, fixed-dosage study of pramipexole 1.5 ($n = 54$), 3.0 ($n = 50$), 4.5 ($n = 54$) or 6.0 mg/day ($n = 55$) versus placebo ($n = 51$) in early PD patients. Subjects were allowed concomitant selegiline, anticholinergics, and amantadine. After 10 weeks, all pramipexole treatment groups showed significantly greater improvements in the primary outcome measure of UPDRS total score compared to placebo (mean decrease from baseline of 5.9–7.0 points for the pramipexole groups vs. 0.9 points for the placebo group; $p < 0.005$ for all comparisons).

Ropinirole

Ropinirole is an orally administered DA approved for both early and advanced PD at doses up to 24 mg/day [13]. Adler et al. [12] reported a 6-month, multicenter, ran-

Table 1. Comparison of selected placebo-controlled monotherapy trials in early PD

Study	n	Drug	Daily dosage, mg	Study duration	Age years	Disease duration years	Medication status at entry
L-dopa							
PSG [7] (ELLDOPA) 2004	361	carbidopa/levodopa	37.5/150 75.0/300 150.0/600	9-week TP 31-week MP 2-week washout	64 64 65	0.5 0.7 0.5	de novo and not likely to need medication during study
MAO-B inhibitors							
PSG [8] (DATATOP) 1989	800	selegiline	10	3 months	61	2.1	de novo (61%); remaining subjects stopped PD medication
PSG [9] (TEMPO) 2002	404	rasagiline	1 2	1-week TP 25-week MP	62 60	0.9 1.2	de novo except anticholinergics
Dopamine agonists							
Shannon et al. [10] 1997	335	pramipexole	3.8	7-week TP 24-week MP	63 (all subjects)	1.8 (all subjects)	selegiline permitted; other PD medication stopped
PSG [11] 1997	264	pramipexole	1.5 3.0 4.5 6.0	6-week TP 4-week MP	60 62 63 63	1.8 2.0 1.9 2.2	selegiline, anticholinergics, amantadine permitted; dopaminergic medication stopped
Adler et al. [12] 1997	241	ropinirole	15.8 (without selegiline) 15.5 (with selegiline)	24 weeks	65 59	1.6 2.5	selegiline permitted; other PD medication stopped
Brooks et al. [13, 14] 1998	63	ropinirole	7.4	12 weeks	59	2.3	selegiline, anticholinergics, amantadine permitted; dopaminergic medication stopped
PSG [15] ^c 2003	242	rotigotine	2 (24 h) 4 (24 h) 6 (24 h) 8 (24 h)	4-week TP 7-week MP	62 61 61 61	1.2 1.5 1.2 1.1	selegiline, anticholinergics, amantadine permitted; other PD medication stopped
Watts et al. [16] 2007	277	rotigotine	5.7 (24 h)	3-week TP 24-week MP	62	1.3	anticholinergics, MAO-B inhibitors, amantadine permitted; dopaminergic medication stopped
Giladi et al. [17, 18] 2006	561	rotigotine or ropinirole	8 ^b (24 h) or 14.1	4-week TP 33-week MP 13-week TP 24-week MP	61.1 61.6	1.4 1.3	anticholinergics, MAO-B inhibitors, amantadine permitted; dopaminergic medication stopped

The studies selected were conducted in early-stage PD patients, did not allow adjunctive L-dopa treatment (with the exception of Adler et al. [12]), and are published and/or described in detail within the prescribing information for each drug.

PSG = Parkinson Study Group; TP = titration phase; MP = maintenance phase; UPDRS III = motor subscale of the UPDRS; UPDRS II = activities of daily living subscale of the UPDRS; n.r. = not reported.

Baseline UPDRS III	Baseline UPDRS II+III	Baseline UPDRS total	Primary end point or outcome	Treatment effect (UPDRS III)	Treatment effect (UPDRS II and III)	Treatment effect (UPDRS total)
18.6 18.9 20.5	n.r.	27.2 27.5 29.4	change in UPDRS total score	-3.8 ^{a, b} -3.8 ^{a, b} -6.6 ^{a, b}	n.r.	-5.9 ^{a, b} -5.9 ^{a, b} -9.2 ^{a, b}
16.8	n.r.	25.3	L-dopa rescue	-1.9 ^{a, b}	n.r.	-3.1 ^{a, b}
17.9 18.0	n.r.	24.7 25.9	change in UPDRS total score	-2.7 -1.7	n.r.	-4.2 -3.6
18.8	n.r.	n.r.	change in UPDRS II and UPDRS III	-6.0 ^{a, b}	n.r.	n.r.
n.r.	n.r.	29.0 28.3 27.3 32.9	change in UPDRS total score	n.r.	n.r.	-5.2 -5.1 -5.9 -5.2
19.1 16.7	n.r.	n.r.	% change in UPDRS III	-4.7 ^{a, b} (all ropinirole patients)	n.r.	n.r.
18.6	n.r.	n.r.	% change in UPDRS III and % responders (≥30% improvement in UPDRS III)	4 ^{a, b}	n.r.	n.r.
19.8 20.0 19.8 17.4	26.7 27.5 27.2 23.8	n.r.	change in UPDRS II and III	-0.9 -1.9 -3.9 -3.8	-0.9 -2.8 -4.8 -5.2	n.r.
n.r.	29.9	n.r.	change in UPDRS II and III and % responders (≥20% improvement in UPDRS II and III)	n.r.	-5.3	n.r.
23.8 23.2	33.2 n.r.	n.r. n.r.	% responders (≥20% improvement in UPDRS II and III)	-3.1 ^{a, b} n.r.	-5.0 ^{a, b, d} -8.8 ^{a, b}	n.r. n.r.
^a Using the published report, value was calculated by subtracting the change from baseline in the placebo group from the change from baseline in the active group. ^b Approximate values.				^c Results from the full study population (n = 316) are reported in the prescribing information [17]. ^d Adjusted treatment effect value reported in the prescribing information is -4.5 [17].		

domized, flexible-dosage, double-blind study of ropinirole (n = 116) versus placebo (n = 125) in early PD patients. Approximately 50% of subjects in each group were taking selegiline. The mean daily dosage of ropinirole at the end of the trial was 15.7 mg/day (15.8 mg/day in subjects not taking selegiline and 15.5 mg/day in subjects taking concomitant selegiline). After 24 weeks of treatment, UPDRS motor scores improved by 24% in the ropinirole group (score of 13.4 post- vs. 17.9 pretreatment), whereas the placebo group worsened by 3% (score of 17.9 post- vs. 17.7 pretreatment; $p < 0.001$; primary outcome). After 6 months of double-blind medication, 11% of ropinirole-treated subjects and 29% of placebo-treated subjects required L-dopa rescue therapy, which was a significant treatment difference in favor of ropinirole that was independent of selegiline use.

Similarly, Brooks et al. [14] reported a 12-week multicenter, randomized, flexible-dosage, double-blind study of ropinirole (n = 41) versus placebo (n = 22) in early PD patients. Subjects were allowed to continue taking stable doses of selegiline, anticholinergics and amantadine. The mean daily dose of ropinirole was 7.4 mg. After 12 weeks of treatment, the ropinirole group showed improvement in UPDRS motor scores of 43.4% relative to baseline, whereas the placebo group had improved by 21.0% ($p = 0.018$; primary outcome). Subjects classified as responders (those who experienced a $\geq 30\%$ improvement relative to baseline in UPDRS motor scores) comprised 71% of the ropinirole group compared to 41% of the placebo group ($p = 0.021$; primary outcome).

A 24-hour extended-release formulation of ropinirole has been approved by the FDA. Results from a trial comparing the extended release formulation of ropinirole (once-daily dosing) to the immediate release formulation (3 times a day dosing) in early PD patients have been reported [26]. The 36-week trial was a multicenter, randomized, double-blind, cross-over study (n = 161) with a 12-week titration phase followed by three 8-week maintenance periods using ropinirole doses up to 24 mg/day. Subjects were randomized to 1 of 4 ropinirole treatment sequences, 2 of which began with titration of extended-release ropinirole while the other 2 began with titration of immediate-release ropinirole. At the end of the titration phase (12 weeks), UPDRS motor scores had improved by 10.4 points in the extended-release ropinirole groups and by 8.9 points in the immediate-release ropinirole groups, which did not represent a clinically significant difference between the 2 preparations [26]. The extended-release groups had higher mean daily ropinirole doses (18.0 mg/day) than the immediate-release groups (7.0 mg/

day) at the end of the titration phase due to differing titration schedules rather than reduced potency of the extended-release formulation; however, the UPDRS motor improvements achieved during titration were maintained during the rest of the trial, which included treatment switches to the closest dose of the alternative formulation. The side-effect profiles of the immediate-release and extended-release preparations of ropinirole were similar, and patients may be switched directly from the immediate-release to the extended-release preparation (the initial switch dose of extended-release ropinirole should closely match the total daily dose of immediate-release ropinirole). Extended-release ropinirole is approved for management of early and advanced PD in the dosage range of 2–24 mg/day.

Rotigotine

Rotigotine is the first DA delivered through a transdermal system. For early PD, rotigotine is currently approved at doses up to 6 mg/24 h in the US [17] and at doses up to 8 mg/24 h in the EU [27]. Watts et al. [16] reported a 27-week, multicenter, randomized, double-blind, flexible-dose study of the rotigotine transdermal patch up to 6 mg/24 h (n = 181) and placebo (n = 96) in early PD patients. Amantadine, anticholinergics, and MAO-B inhibitors were allowed if maintained at stable doses for at least 4 weeks prior to study entry. The mean daily dosage of rotigotine was 5.7 mg/24 h. At the end of the maintenance phase, treatment with rotigotine resulted in a 4.0-point improvement in combined UPDRS ADL and motor scores, while the placebo group demonstrated a 1.3-point worsening ($p < 0.001$; primary outcome), representing a 5.3-point adjusted treatment effect. Improvement in UPDRS motor scores accounted for the majority of the benefit from rotigotine, as the mean change from baseline to end point was 3.5 points, whereas the mean improvement from baseline to end point in UPDRS ADL scores was 0.3 points. Subjects classified as responders (those who experienced a $\geq 20\%$ improvement relative to baseline in combined UPDRS ADL and motor scores) comprised 48% of the rotigotine group compared to 19% of the placebo group ($p < 0.001$; primary outcome).

Similarly, the Parkinson Study Group [15] reported results from the US and Canadian portion (n = 242) of an 11-week, multicenter, randomized, double-blind study in early PD patients that compared the rotigotine transdermal patch 2, 4, 6 or 8 mg/24 h (n = 195) to placebo (n = 47). Subjects had not yet received dopaminergic therapy, though amantadine, anticholinergics and MAO-B inhibitors were allowed if maintained at stable doses for at least

4 weeks prior to study entry. At end point, significant treatment effects in combined UPDRS ADL and motor scores (primary outcome) were observed in the 6 and 8 mg/24 h rotigotine groups (a 4.8- and 5.2-point improvement relative to placebo, $p = 0.001$ and $p < 0.001$, respectively). As in the Watts et al. [16] trial, improvement in UPDRS motor scores accounted for the majority of the benefit from rotigotine treatment, with a nearly 4-point treatment effect in the 6 and 8 mg/24 h groups. Treatment effects of rotigotine, as measured by the UPDRS ADL subscale, ranged from a benefit of 0.4 points in the 2 mg/24 h group to 1.6 points in the 8 mg/24 h group relative to placebo. When the complete population of this trial was examined ($n = 316$) [17], similar results for combined UPDRS ADL and motor scores were observed; however, in addition to the 6 and 8 mg/24 h groups, 4 mg/24 h rotigotine showed significant benefit relative to placebo [17]. Mean improvements in combined UPDRS ADL and motor scores from baseline to the end of treatment were 3.5, 4.5, 6.3 and 6.3 points in the 2, 4, 6 and 8 mg/24 h rotigotine groups, respectively, while the placebo group improved by 1.4 points relative to baseline, yielding treatment effects of 2.1–5.0 points in favor of rotigotine.

A third randomized, double-blind, multicenter, flexible-dose trial was conducted in early PD patients using rotigotine up to 8 mg/24 h ($n = 215$), placebo ($n = 118$) or ropinirole up to 24 mg/day ($n = 228$) [18]. Amantadine, anticholinergics and MAO-B inhibitors were allowed if maintained at stable doses for at least 4 weeks prior to study entry. Subjects were titrated to the optimal effective dose over a period of up to 13 weeks (4 weeks for rotigotine and up to 13 weeks for ropinirole), which was followed by a 24- to 33-week maintenance phase (minimum duration of 33 weeks for rotigotine and 24 weeks for ropinirole). The mean daily dose of rotigotine was just less than 8 mg/24 h [17] and 92% of subjects were titrated to this maximum daily dose [18]. For the ropinirole group, the median dose was 14.1 mg/day, and 26% of subjects received the maximum dose of 24 mg/day [18]. Rotigotine treatment resulted in a significantly greater proportion of responders (defined as those with a $\geq 20\%$ improvement in combined UPDRS ADL and motor scores) than placebo treatment (52 vs. 30%; $p < 0.001$; primary outcome). Rotigotine-treated subjects showed significantly greater mean improvement in combined UPDRS ADL and motor scores (primary outcome) from baseline to the end of treatment (7.2 points) than placebo-treated subjects (mean improvement of 2.2 points; $p < 0.001$). UPDRS motor scores were improved by 5.2 points with rotigotine

and by 2.1 points with placebo, while UPDRS ADL scores were improved by 2.1 points in rotigotine subjects and 0.1 points in placebo subjects. Ropinirole treatment also resulted in significant treatment benefits, yielding a greater proportion of responders than placebo (68 vs. 30%; $p < 0.001$) and greater combined UPDRS ADL and motor score improvements relative to placebo (11.0 vs. 2.2 points; $p < 0.001$).

At the time of this manuscript's preparation, the rotigotine patch – Neupro® – was voluntarily recalled in the US secondary to a manufacturing problem. While this recall does not affect patients using this patch in countries outside the US (as a modified manufacturing process has been approved in Europe), it is uncertain how long the recall will last and whether this will affect the long-term prospects for using this compound in the US patient population.

Challenges in Comparing Efficacy among Agents

Large multicenter, randomized, double-blind, placebo-controlled trials examining the effects of L-dopa [7], selegiline [8], rasagiline [9], pramipexole [10, 11], ropinirole [12, 14] and rotigotine [15, 16, 18] in the treatment of early PD have been conducted. Although it is tempting to compare the results of these trials, it is important to appreciate that direct comparisons in most cases cannot be made; however, considering the data in terms of both the similarities and differences between these independent clinical trials and their resulting data sets can help guide clinical judgments.

In the studies considered here (table 1), PD patients enrolled were of similar age (59–65 years), similar disease duration (0.5 to <3 years) and similar disease severity as reflected in baseline UPDRS motor scores (17–23 points) and UPDRS total scores (25–33 points); however, study duration, concomitant medication use and outcome measures varied. The follow-up duration in these trials ranged from 10 to 42 weeks. Some studies enrolled predominantly untreated PD patients, some studies allowed for selegiline, amantadine and anticholinergic use, while other studies required the discontinuation of all antiparkinsonian medications. Although all of the studies utilized the UPDRS, the results were presented in different ways. For example, within the DA class, data were reported as UPDRS total scores (Parkinson Study Group pramipexole study), percentage change from baseline in the UPDRS motor subscale (ropinirole studies), and combined UPDRS ADL and motor scores (rotigotine studies). In addition, some studies reported absolute scores, some reported mean change from baseline scores, and others

reported mean change from baseline scores adjusted for various baseline conditions. Thus, direct comparisons of efficacy between these independent clinical trials in early PD are confounded by variations in study design and outcome measure reporting. Even so, some generalizations about the outcomes of these trials can be made. Considering the available UPDRS motor data gathered between about 3 and 6 months from the key trials, L-dopa was able to confer the greatest treatment effect over placebo, followed by the DAs and then MAO-B inhibitors (the MAO-B inhibitors selegiline and rasagiline provide about a 2- to 3-point improvement over placebo, DAs provide up to a 6-point improvement over placebo, and L-dopa can confer an almost 7-point improvement over placebo).

Several multicenter, randomized, double-blind studies have compared the long-term efficacy and the development of motor complications in subjects initiating dopaminergic therapy with either a DA or L-dopa [28–30]. In studies of pergolide [28], pramipexole [29] and ropinirole [30], L-dopa consistently demonstrated greater efficacy in UPDRS ADL, motor and total scores than the DAs, but the DA groups consistently showed a delay in the development of motor complications compared to L-dopa. Recent analyses have demonstrated that the benefit of initial DA treatment in delaying the development of motor complications is due to their ability to delay the introduction of L-dopa [31, 32], and exploratory analyses suggest that the benefit of delayed motor complications can be maintained over the long term [33]. Thus, treatment initiation with a DA is often preferred in early PD, especially in younger individuals requiring long-term treatment.

The best way to assess comparative efficacy is through head-to-head comparator trials, although such trials are generally lacking within the DA class. Among the DAs reviewed here, post hoc analyses of the rotigotine trial in early PD that included an active comparator arm with ropinirole indicated that rotigotine treatment up to 8 mg/24 h has a similar benefit as ropinirole treatment up to 12 mg/day as assessed by mean change in combined UPDRS ADL and motor scores [34]. Though further head-to-head trials may provide some clinical guidance, individual patient response and tolerance will ultimately determine the proper treatment choice. Thus, potential adverse effects and patient compliance are issues to be considered in addition to efficacy for the optimal management of the PD patient.

Adverse Effects and Tolerability of Dopamine Agonists

A randomized comparative study with different DAs would be required to accurately compare efficacy and adverse effect profiles; however, in the absence of such a study, comparison of data pooled from multiple individual trials may be informative. One such analysis was performed by Etminan et al. [35], who compared adverse effects of ropinirole and pramipexole using meta-analyses of placebo-controlled or L-dopa-controlled trials. In the analysis of placebo-controlled trials in early PD (which consisted of 3 ropinirole trials with mean doses of 15.5 [12], 7.4 [13, 14] and 5.3 mg/day [36] and 3 pramipexole trials with doses of ≤ 6 [11], 3.8 (mean) [10] and ≤ 4.5 mg/day [37]), ropinirole was associated with a higher risk of hypotension and somnolence relative to placebo than pramipexole, and pramipexole was associated with a higher risk of hallucinations relative to placebo than ropinirole. Interestingly, recent studies in advanced PD with a 24-hour formulation of ropinirole demonstrated less prominent side effects of hypotension and sedation relative to the short-acting ropinirole formulation [38].

With consideration to the variables and limitations of the available data, the adverse effect profiles of pramipexole, ropinirole and rotigotine from pooled trials in early PD were compared qualitatively (tables 2 and 3). The profiles of the most common adverse events (table 2) are similar among the different DAs, with nausea, somnolence and dizziness among the most frequently reported adverse events in each active treatment group. For rotigotine, there is an additional risk of application-site skin reactions following transdermal patch administration. It should be noted that dopaminergic adverse events (table 3) may occur with greater frequency during dose escalation than during maintenance treatment. For example, 1 of the ropinirole studies reported that the incidence of nausea peaked during the titration phase (weeks 1–4) then dropped to levels similar to placebo by the end of the 12-week study [12]. Similarly, the incidence of vomiting and other dopaminergic-related adverse events was highest during the titration phases of the rotigotine trials [40].

Dopaminergic side effects were among the most common adverse events leading to study discontinuation for each drug. For ropinirole-treated patients, the adverse events that most frequently led to discontinuation were nausea (6.4%), dizziness (3.8%), aggravated PD (1.3%), hallucinations (1.3%), somnolence (1.3%), vomiting (1.3%) and headache (1.3%) [13]. For pramipexole, hallucinations (3.1%), dizziness (2.1%), somnolence (1.6%), extrapyramidal syndrome (1.6%), headache (1.3%) and con-

Table 2. Frequent adverse events in DA trials in early PD ($\geq 10\%$ in active group and more frequent than control)

	Placebo (n = 147)	Ropinirole (n = 157)	Placebo (n = 235)	Pramipexole (n = 388)	Placebo (n = 289)	Rotigotine (n = 649)
Mean dose		approx. 13.5 mg/day ^a		approx. 3.7 mg/day ^b		5.2 mg/24 h ^c
Trial dose range		≤ 24 mg/day		≤ 6 mg/day		≤ 8 mg/24 h
Nausea	22	60	18	28	15	38
Somnolence	6	40	9	22	16	24
Dizziness	22	40	24	25	11	18
Vomiting	7	12	–	–	2	12
Syncope	1	12	–	–	–	–
Fatigue	4	11	–	–	–	–
Viral infection	3	11	–	–	–	–
Dyspepsia	5	10	–	–	–	–
Insomnia	–	–	12	17	5	10
Asthenia	–	–	12	14	–	–
Constipation	n.r.	n.r.	6	14	–	–
ASR	n/a	n/a	n/a	n/a	14	37
Headache	–	–	–	–	10	13

Values are percentages, unless otherwise indicated, and are rounded to the nearest whole number. ASR = Application site reaction; n.r. = not reported; n/a = not applicable. – = Indicates adverse events that had an incidence of $<10\%$ in the active treatment group or occurred with less or equal frequency than in the placebo. Adverse event data sources: Mirapex® (pramipexole dihydrochloride) prescribing information [25]; Requip® (ropinirole hydrochloride) prescribing information [13]; Neupro® (rotigotine transdermal system) prescribing information [17].

^a Value was calculated using published mean dose data at end point for each trial as follows: $\{(7.4 \text{ mg/day} \times 41 [13, 14]) + (15.7 \text{ mg/day} \times 116 [12])\}/157$.

^b Value was calculated using mean dose data from the Mirapex® (pramipexole dihydrochloride) new drug application submitted to the FDA [39] as follows: $\{(3.77 \text{ mg/day} \times 229 \text{ male subjects}) + (3.57 \text{ mg/day} \times 126 \text{ female subjects})\}/355$ (the number of subjects entering the maintenance phase of each trial [10, 11] and study 21 [39]).

^c Value reported in [40].

fusion (1%) were most commonly associated with discontinuation [25]. Patients treated with the rotigotine transdermal patch discontinued most commonly due to skin reaction (5%), nausea (2%), vomiting (1%), insomnia and somnolence (each $<1\%$) [17, 40]. It should be noted that these studies typically excluded patients with significant cognitive impairment and psychiatric symptoms, so the safety profiles of these drugs in those patient populations may differ.

Patient Compliance

The extent to which a patient takes their actual dosage compared to the prescribed regimen denotes compliance [41]. In early PD, the long duration of responses to L-dopa and DAs may disguise the effects of non-compliance, but as the disease advances, missed doses may lead to a worsening of PD symptoms. Therefore, to ensure that the patient achieves their optimal clinical response, drug compliance is critical.

Leopold et al. [42] performed a compliance study in 40 PD patients who were taking at least 1 antiparkinsonian medication 3 times or more daily. During the 4-week study, only 4 of 39 patients had complete compliance (no missed, extra or mistimed doses). Although 24% of patients acknowledged missing doses, the computerized monitoring system recorded that 51% missed at least 1 dose per week and 21% missed 3 or more doses per week. Mistimed doses were recorded in 82% of patients. No consistent factors that could predict non-compliance were identified, although the leading reasons that patients gave for non-compliance were that they were too busy or forgot and that they left home without their medication. In another study, Grosset et al. [43] reported 54 PD patients taking a total of 117 PD medications per day. Approximately 80% of patients were reported to have satisfactory compliance ($>80\%$ total compliance), though timing compliance was as poor in this group as it was in patients who had poor total compliance. Poor compli-

Table 3. Dopaminergic-related adverse events from dopamine agonist trials in early PD

	Placebo (n = 147)	Ropinirole (n = 157)	Placebo (n = 235)	Pramipexole (n = 388)	Placebo (n = 289)	Rotigotine (n = 649)
Mean dose		~13.5 mg/day ^a		~3.7 mg/day ^b		5.2 mg/day ^c
Trial dose range		≤24 mg/day		≤6 mg/day		≤8 mg/24 h
Nausea	22	60	18	28	15	38
Somnolence	6	40	9	22	16	24
Dizziness	22	40	24	25	11	18
Vomiting	7	12	3	2	2	12
Syncope	1	12	1	1	1	1
Orthostatic hypotension	5	6	9	8	3	2
Hallucination	1	5	3	9	1	2

Values are percentages, unless otherwise indicated, and are rounded to the nearest whole number. Adverse event data sources: Mirapex® (pramipexole dihydrochloride) prescribing information [25] and [39] (for vomiting and syncope); Requip® (ropinirole hydrochloride) prescribing information [13]; Neupro® (rotigotine transdermal system) prescribing information [17] and Schwarz Pharma data on file (for syncope and hypotension).

^a Value was calculated using published mean dose data at end point for each trial as follows: $\{(7.4 \text{ mg/day} \times 41 [13, 14]) + (15.7 \text{ mg/day} \times 116 [12])\}/157$.

^b Value was calculated using mean dose data from the Mirapex® (pramipexole dihydrochloride) new drug application submitted to the FDA [39] as follows: $\{(3.77 \text{ mg/day} \times 229 \text{ male subjects}) + (3.57 \text{ mg/day} \times 126 \text{ female subjects})\}/355$ (the number of subjects entering the maintenance phase of each trial [10, 11] and study 21 [39]).

^c Value reported in [40].

ance was associated with younger patients, more tablets required per day, higher depression scores and worse quality of life.

Other studies spanning several therapeutic areas have also shown that simpler drug regimens are associated with improved compliance and outcomes [44–46]. In a review of 5 PD studies that compared sustained-release L-dopa to immediate-release L-dopa, an increase in positive health outcomes was associated with the less-frequent dosing schedule [46]. Similarly, the once-daily rotigotine patch, extended-release formulations of other DAs (when available) and once-daily rasagiline may have a positive impact on compliance and patient health in PD. In addition to more easily administered medications, strategies that may improve patient compliance include: involving patients in making therapy decisions, providing educational materials (video, leaflets, etc.) and using physical reminders (alarms, charts, etc.).

Switching between DAs

Although overall efficacy and adverse effects are generally similar among DAs, individual patients may respond differently to the drugs or exhibit better compliance with a particular drug. Therefore, physicians may

Table 4. Proposed DA switching guidelines in early PD: initial dosages (reprinted with permission from [55])

Bromo- crriptine	Pergolide ^a	Pramipexole (salt)	Ropinirole	Rotigotine ^b
<i>Daily dose, mg/day</i>				
3	0.375	0.375	1.5	2
5	0.5	0.5	2	2
7.5	0.75	0.75	3	4
10	1	1	4	4
15	1.5	1.5	6	6
20	2	2	8	6–8
30	3	3	12	6–8

The dose-based recommendations above represent the best estimate of an initial starting dose for conversion; adjustments for individual patient conditions and subsequent response may be required. Not all available tablet strengths are included for every drug. Adapted from Grosset et al. [47] and Schwarz Pharma data on file.

^a Because pergolide has recently been withdrawn from the US market, it is anticipated that patients currently treated with that agent will require a treatment switch, and it is therefore included here.

^b Rotigotine has been studied in doses up to 8 mg/24 h in early PD patients, although in the US rotigotine is approved up to 6 mg/24 h in patients with early PD.

consider switching patients from one DA to another. Several studies have been conducted in an effort to provide guidelines on the dose equivalence of DAs and the best method to perform a switch (i.e. overnight or gradually over days or weeks) [47–54], and though these studies are often limited by open-label designs and/or small sample sizes, they provide the basis for the dose-based conversion chart that was originally proposed by Grosset et al. [47] and adapted recently by Chen [55] (table 4). It is important to note, however, that clinicians should rely on more than a conversion chart when determining an initial switch dose, considering individual patient attributes such as the reason for the switch, disease stage, adequacy of PD symptom control, current and prior side effects, and concomitant medications. In all cases, patients need to be closely monitored after a switch, as dose adjustments upwards or downwards may be needed to achieve optimal symptom control.

Conclusions

The availability of recently developed treatments for early PD may assist clinicians in providing the best possible individualized care. As new treatments and reformulations of existing therapies become available, the ongoing care of the individual patient must be reassessed. Switching or adding therapies to a treatment regimen

may be necessary to provide optimal motor symptom control, tolerability and compliance as the patient progresses to the more advanced stages of the disease.

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