Current Status of Symptomatic Medical Therapy in Parkinson's Disease

Stewart A. Factor

Department of Neurology, Emory University School of Medicine, 1841 Clifton Road NE, Atlanta, Georgia 30329

Summary: Symptomatic medical therapies for Parkinson's disease (PD) have been disease modifying and have led to improvement in daily function, quality of life, and survival. For 40 years, these therapies have been primarily dopaminergic, and currently include the dopamine (DA) precursor levodopa (LD), DA agonists, catechol-*O*-methyltransferase (COMT) inhibitors, and monoamine oxidase (MAO) inhibitors. The roles of all these classes of agents have evolved, with significant changes occurring since the early 2000s. This article reviews the current literature for each of these classes of drugs, with a focus on efficacy and place in the therapeutic scheme. Levodopa is no longer considered to be toxic and, thus, its early use is not only appropriate but recommended.

Ergot agonists are no longer in use, and new agents administered in patch form or subcutaneous injections have been approved. The COMT inhibitor tolcapone, with its significant efficacy, has been reintroduced, and two new MAO inhibitors have been approved. Selected safety issues are discussed, including the incidence of melanoma in relation to LD; pathological gambling and DA agonists; hepatic toxicity of tolcapone; and the tyramine or so-called cheese reaction with MAO B inhibitors. The article closes with a discussion of future directions and new drugs under development. **Key Words:** Parkinson's disease, symptomatic therapy, levodopa, dopamine agonists, COMT inhibitors, MAO inhibitors.

INTRODUCTION

Parkinson's disease (PD), unlike some other neurodegenerative diseases, has benefited significantly from the development over 40 years of numerous symptomatic medical therapies aimed at the dopamine (DA) system. These have clearly been disease modifying, and have improved daily function, quality of life, and survival. It all began with the approval of levodopa (LD) in 1970, followed by the development of numerous DA agonists, monoamine oxidase (MAO) inhibitors, and catechol-*O*-methyltransferase (COMT) inhibitors.

The roles of all these classes of agents have evolved, with significant changes occurring in the last 5 years. For example, the concept of LD as a potentially toxic agent has changed, particularly with the completion of the ELLDOPA trial (Earlier Versus Later Levodopa Therapy in Parkinson Disease), and, although some DA agonists have been removed from the market, others with new forms of delivery have gained approval. We have also

acquired new knowledge on the efficacy and safety of the COMT inhibitor tolcapone, which has been reintroduced to the medical community, and new MAO inhibitors have surfaced as potentially useful agents in early and advanced PD.

This review will provide a comprehensive look at where we stand in 2008 with regard to these four classes of drugs with an emphasis on efficacy and emerging safety issues. Anticholinergics and amantadine remain available, the former used mainly in younger patients for tremor and dystonia and the latter for treatment of early disease and dyskinesia; however, because little has changed regarding their use, these two will not be discussed.

DOPAMINE PRECURSOR THERAPY: LEVODOPA

Levodopa (L-3,4-dihydroxyphenylalanine) currently remains the cornerstone of symptomatic therapy for PD. The history of the discovery of DA and LD is of great interest, but is beyond the scope of this article (for a review, see Factor¹ and Hornykiewicz^{2,3}). The discovery led to a Nobel prize for Arvid Carlsson in 2000. Levo-

Address correspondence and reprint requests to: Stewart A. Factor, D.O., Emory University School of Medicine, Department of Neurology, 1841 Clifton Road NE, Atlanta, GA 30329. E-mail: sfactor@emory.edu.

dopa has been considered the most potent symptomatic therapy. However, the concern that LD may be toxic to dopaminergic neurons and thus might lead to more rapid nigral degeneration—a controversy for 25 years—had an impact on its use, and typically physicians treating PD tried to delay its use for as long as possible. But the data from cell culture animal and human research indicate that, at least at this point, there is no support for the notion that LD is toxic,^{1,4,5} and thus there should be no concern about toxicity when considering therapy in PD patients. The most recent question is whether LD is neuroprotective and, if so, should patients be treated very early in the disease course?

In the early 1960s, the effectiveness of LD was questioned and its use was nearly abandoned. It was the seminal work of Cotzias et al.,^{6,7} who persevered with the use of high-dose oral LD, that dramatically changed the landscape of PD treatment, and Yahr et al.⁸ completed the first double-blind, parallel group study in 1969. Levodopa was ultimately approved by the U.S. Food and Drug Administration (FDA) for use in PD in 1970, 60 years after its discovery and more than 10 years after the realization that DA depletion was the key abnormality in PD.⁹ In 1973, the combined use of a peripheral aromatic amino acid decarboxylase inhibitor with LD was reported by Cotzias. This approach resulted in a decrease in peripheral metabolism of LD to DA and fewer peripheral adverse effects (e.g., hypotension, nausea, and vomiting).^{10,11} The trade name for the resulting levodopa-carbidopa combination drug, Sinemet, carries the meaning “without vomiting.” Controlled-release formulations were tested in the 1980s to treat fluctuations in response, and the fourth formulation, Sinemet CR4, was approved in the United States in 1991.^{12–15}

Levodopa has its drawbacks, however, which may relate to the pulsatile drug delivery. These include late complications such as motor fluctuations and dyskinesias. Ahlskog and Muentert¹⁶ compared recent literature with older studies and found that the rate is probably 35% to 40% at 4 to 6 years of disease duration, with an increasing frequency of 10% per year, so that nearly 90% of patients experience these complications after a decade. Furthermore, 90% of patients with onset of PD under age 40 are fluctuating by 5 years.¹⁷ Recent studies, however, suggest that only a small portion of patients with dyskinesia require medication adjustments, and even fewer (12%) are not well controlled.¹⁸

The initial therapeutic studies of LD in PD were conducted in the 1960s and early 1970s. These studies differed greatly from present-day trials, in that patients enrolled had varying durations of disease, some quite advanced with dementia, and standard rating scales such as the Unified Parkinson's Disease Rating Scale (UPDRS) were not yet devised. Nonetheless, the results were

dramatic.³ The breakthrough report was published in 1967.⁶

In contemporary trials, study populations are more homogeneous, usually including patients with PD < 5 years and nonfluctuators. The ELLDOPA study^{19,20} was a multicenter, placebo-controlled, randomized, double-blind clinical trial that had two objectives. The primary objective was to examine the impact of LD on disease progression, as well as answering the question of neurotoxicity, and the second objective was to serve as a dose-finding, symptomatic study. The study randomized PD patients ($n = 361$) with disease duration of <2 years, Hoehn and Yahr stage of <3, and not likely to require symptomatic therapy within the next 9 months to receive placebo or LD (50 mg, 100 mg, or 200 mg three times a day [t.i.d.]); 311 participants completed the study. The study involved 40 weeks of therapy, including a 3-day taper and a 2-week withdrawal period (final visit, week 42). The primary outcome was the change in severity of PD between baseline and week 42, as measured by the total UPDRS scale.

An [¹²³I] β -CIT single-photon emission computed tomography (SPECT) substudy¹⁹ included 142 subjects where a scan was completed at baseline and week 40. The clinical results demonstrated that LD improved PD in a dose-response pattern beginning at week 9 through the last treatment visit, compared with placebo. The maximum effect was reached at 24 weeks in the 600 mg/day group. The 150 mg/day group returned to baseline at week 27, and the 300 mg/day group at week 40, but the 600 mg/day group remained better than baseline until withdrawal of the drug.

There was a significant difference of 9.2 points in motor UPDRS between the highest dose and placebo. If LD proved toxic, after the 2-week withdrawal, it would be expected that the LD groups would be worse off than the placebo group. The opposite was true, and the higher-dose subjects were less severely impaired after the 2-week withdrawal than the other three groups. None of the active-treatment groups deteriorated to the level of the placebo group after washout. However, the highest dose caused significantly more dyskinesia (16%) than placebo.

The SPECT study did not correlate with clinical results. The reduction in percent uptake of β -CIT was greater in the LD-treated groups than controls, although the difference was not significant; however, when the 19 scans without dopaminergic deficit (SWEDDs) were removed because of the question of appropriate diagnosis, the difference became significant ($p = 0.036$). The study conclusion was that there was no clinical evidence that LD accelerates PD progression. In fact, the results suggested that LD might instead either slow progression of PD, or that it has a persistent pharmacological effect that goes beyond the 2-week washout (i.e., beyond the long-

duration effect). Because there was little deterioration of PD after the first week of withdrawal and a subset of 38 subjects evaluated 4 weeks after washout had no further deterioration, it is unlikely that prolonged washout effect was responsible. The results of the imaging substudy may be explained by the potential capability of LD to downregulate the DA transporter. From the standpoint of symptomatic effects of LD, the results demonstrated a striking dose–response clinical effect, with the 600-mg group maintaining improvement beyond baseline for the entire 9 months.

Several studies have compared DA agonists to LD in early PD to examine symptomatic effects and the time to onset of motor fluctuations and dyskinesia.^{21,22} The CALM-PD study,^{22,23} a parallel-group, double-blind, randomized trial of 301 patients, comprising both clinical and imaging substudies, compared the rates of dopaminergic motor complications and DA transporter ligand uptake (primary endpoints) after initial treatment of early PD with pramipexole or LD. During the first 10 weeks of the study, patients were permitted to adjust the active-treatment drug to one of three possible doses to treat disability, and from week 11 to month 48 were permitted to add open-label LD to treat continuing or emerging disability. After month 24, patients were permitted to alter the dosage of the original active-treatment drug without losing the blind. With regard to efficacy, the mean improvement in UPDRS Motor score was significantly greater in the LD group than in the pramipexole group (9.2 vs 4.5 units; $p < 0.001$). The LD group remained superior even when LD was added to the pramipexole group.

A similar 5-year comparison of ropinirole and LD (the 056 Study) in 268 patients was reported in 2001.²¹ One subject was randomized to LD for every two who were randomized to ropinirole. Open-label LD supplementation was also allowed. UPDRS Motor score improved by 4 points from baseline for LD, compared with ropinirole, indicating that LD treatment was associated with greater therapeutic benefit throughout the 5 years of the study, despite the use of adjunctive LD in the ropinirole group.

These results suggest to some investigators that withholding LD early will end up costing the patient some benefit, and some have now suggested starting LD as early as possible, despite the issues surrounding motor fluctuations and dyskinesia. Neither study examined the use of LD first followed by an agonist and whether that strategy would also diminish fluctuations and dyskinesia, but with superior response. This still needs to be determined.

Thirty years of experience and literature have led to several conclusions regarding LD therapy in PD. Clearly, LD remains the most potent symptomatic therapy for PD. We have learned quite a bit about the nuances of treatment, such that our goals have changed. We now treat

with the lowest effective dose, not the highest tolerated one; we avoid frequent small doses, which add to unpredictable responses; and we have developed adjunctive therapies that complement LD. The outcome is fewer late complications—which is not to minimize these problems. Also, LD is not toxic in PD patients, but instead may actually have neuroprotective effects. Based on the results of recent trials in early disease, particularly the DA agonist comparisons that showed that using a DA agonist first does not provide the benefit LD does, even after LD is added, it appears that earlier use of the drug (as opposed to the past approach of delayed use) may be the most effective strategy. A practice guideline published by the American Academy of Neurology has indicated that using LD as first-line therapy is an acceptable approach.²⁴

Safety issues: malignant melanoma

The connection between LD therapy, PD, and malignant melanoma has been a matter of controversy for three decades. Levodopa is a precursor of DA, and DA has a relationship to neuromelanin in CNS nigral neurons. Dopa quinones, derived from LD, are oxidized to form neuromelanin in these cells.²⁵ Hence, it has been proposed that LD may also affect the activity of melanocytes in the skin, possibly promoting malignant transformation, although this connection has never been proven. This issue seems to emerge once or twice per decade, with more than 40 articles published on the subject,²⁵ and conclusions varying from caution using LD in patients with a history of melanoma to no need for concern have been put forth in response to the coincident occurrence of melanoma and PD. However, two studies have recently demonstrated a small but significant increased relative risk for malignant melanoma and other nonmelanotic skin cancers in PD, but probably not related to LD.^{26,27} It is recommended that PD patients be monitored regularly for skin cancer, but a history of melanoma should not preclude the use of LD.

Safety issues: elevated homocysteine

A recent concern regarding LD therapy relates to its association with elevated levels of homocysteine (HC). Since the late 1990s, several studies have indicated that the LD dose correlates with elevation of HC.²⁸ The relevance of this increase to PD and patient health remains unclear. The concern relates to data suggesting that elevated HC levels increase the risk of stroke, coronary artery disease, and dementia.^{29–31}

HC is metabolized from dietary methionine through two intermediates: *S*-adenosylmethionine (SAM) and *S*-adenosylhomocysteine (SAH). HC is metabolized back to methionine via methylene tetrahydrofolate reductase (MTHFR) or to cysteine via other mechanisms. These enzymatic reactions occur in the presence of cofactors folate, vitamin B₁₂, and vitamin B₆. Deficiency of any of

TABLE 1. Receptor Affinities and Pharmacokinetics of Currently Available Dopamine Agonists

Agent	Receptor Affinities		$T_{\max}$	Elimination Half-life
	Dopamine	Other		
Pramipexole	D3 > D2 >> D4	α_2 adrenergic	<180 min	8–12 h
Ropinirole	D3 > D2 > D4	None	<120 min	6 h
Rotigotine	D3 > D4 > D2 > D1	α_2 adrenergic; 5HT1A	15–18 h	5–7 h
Apomorphine	D2 = D3 = D4 > D1	α_2 adrenergic	<10 min	40 min

$T_{\max}$ = time to mean peak concentration; 5-HT1A = serotonin receptor 1A.

these could lead to elevated HC levels. This is also true for the presence of the C677T MTHFR polymorphism which decreases metabolism of HC. In PD, the conversion of LD to 3-*O*-methyldopa via COMT drives the formation of HC. SAM is the methyl donor for this reaction, yielding SAH, which is rapidly converted to HC.²⁸ The resulting elevation of HC is modest.^{32,33} These elevations are blunted when COMT inhibitors are used as adjunctive therapy.^{34,35} Studies of the risk of stroke in PD have not consistently demonstrated increased risk.²⁸ One study showed that the measure of biomarkers for endothelial function in PD patients with modestly elevated HC levels was normal.³⁶ Hence, the impact of HC changes in PD patients regarding atherosclerotic disease remains to be discerned. The same is true for the relation to dementia.³³

DOPAMINE AGONISTS

Dopamine agonists play a major role in the treatment of PD.³⁷ These drugs bypass the degenerating neurons and directly stimulate the intact, although denervated, postsynaptic receptors in the striatum. This effect was expected to provide an advantage for DA agonists over LD. This idea has been central to PD clinical therapeutic research since the mid-1970s.^{37,38} These drugs are not affected by the pharmacokinetic shortcomings seen with LD. There is no competition with dietary neutral amino acids for absorption in the gut and, in addition, no competition for penetration of the blood–brain barrier. Dopamine agonists have substantially longer elimination half-lives than LD, which allows for more prolonged stimulation of receptors. One DA agonist is in a patch form, which provides stable blood levels.

Dopamine agonists have been used to target specific receptor subtypes, which was hoped to provide more selective therapeutic effects and to eliminate certain adverse effects, although that has not actually been borne out. In fact, it has been suggested that these drugs generate more behavioral adverse effects (including psychosis), greater autonomic problems (such as orthostatic hypotension), and, possibly, more frequent gait disorders (such as freezing). On the other hand, DA agonists may

provide a wider therapeutic window, with a decrease in risk of dyskinesias.^{37,38}

Dopamine agonists have been used in the treatment of PD since 1974.³⁹ Two groups of agonists have been developed: ergot agents and non-ergot agents. The first group includes the first-generation drugs bromocriptine and pergolide, as well as cabergoline. These agents are mentioned here for a historic perspective, because the most significant news in relation to them is that pergolide has been taken off the market, and cabergoline has been relegated to being a drug of last resort because of the potential for developing pulmonary fibrosis and cardiac valvular disease.^{40–42} The primary focus here is on non-ergot drugs, including pramipexole, ropinirole, the new rotigotine patch, and apomorphine, an injectable agent. The pharmacology of these agents varies in relation to their receptor affinities and pharmacokinetics (Table 1).

Pramipexole was the first non-ergot DA agonist approved for use in the United States for early and fluctuating PD in July 1997. It is a synthetic amino-benzothiazole derivative that has both pre- and post-synaptic effects on the D2 subfamily of DA receptors. Pramipexole has a seven-fold higher affinity for D3 than for D2 receptors, and less affinity for D4. It has very low affinity for D1, moderate binding to α_2 adrenoceptor, and low affinity for α_1 and α_{1B} adrenoceptors, acetylcholine receptors, and serotonin receptors.⁴³

Pramipexole causes complete suppression of firing of neurons in the substantia nigra pars compacta and the ventral tegmental area. This is an autoreceptor effect, which results in a decrease in DA metabolism.⁴⁴ Notably, this drug acts as an autoreceptor agonist primarily when the presynaptic DA neurons are intact and there is no denervation of postsynaptic neurons. Once there is degeneration or loss of presynaptic neurons, however, it becomes a potent postsynaptic receptor stimulator, and it was these findings that led to its use in PD. Because of its strong D3 affinity, pramipexole may be effective in the treatment of some patients with depression. Results of clinical trials have supported this notion.^{45–47}

There is no evidence of drug interactions. Only 10% of the drug is metabolized; the rest is excreted unchanged in the urine.⁴⁷ Therefore, hepatic disease is unlikely to af-

fect the levels of pramipexole; however, renal failure may lead to higher plasma levels and possible toxicity. Typical doses range from 1.5 to 4.5 mg/day.

Ropinirole was approved in the United States in September 1997 for early and advanced PD. This drug is a dipropyl-aminoethyl-indole derivative. It specifically binds to the D2 family of receptors and has no affinity for the D1. It has no other significant binding affinities. The affinity of this drug is similar to that of DA for the D2 subfamily, $D3 > D2 > D4$.⁴³ In addition to binding to postsynaptic receptors, ropinirole stimulates presynaptic D2 autoreceptors causing a dose-dependent decrease in whole-brain levels of the two major metabolites of DA, homovanillic acid (HVA) and 3,4-dihydroxyphenylacetic acid (DOPAC), and stops the firing rate of substantia nigral cells in animal models,⁴⁸ making it a full agonist.

Ropinirole is rapidly and fully absorbed, reaching peak levels in 1 to 2 hours and is unaffected by food.⁴⁹ Ropinirole is extensively metabolized by cytochrome P450 1A2 (CYP1A2) in the liver into inactive metabolites. It achieves a steady state within 2 days. Ciprofloxacin inhibits CYP1A2, and thus may increase serum ropinirole concentrations and lead to possible adverse effects. Ropinirole is excreted in the urine, and <10% is excreted intact. Renal failure does not appear to alter the pharmacokinetics of the drug, and no dosage adjustment is necessary in this situation. The effect of dialysis is unknown; however, removal of the drug is unlikely, given its wide volume distribution. Liver failure, however, may lead to higher levels of unmetabolized drug and thus to more adverse effects. No clinically significant interactions have been detected with a variety of commonly used medications. Typical dose ranges are 9 to 24 mg/day.

Rotigotine is the most recently approved non-ergoline DA agonist for early PD (FDA approval in May 2007), and is the first transcutaneous patch. It will likely be approved for advanced PD in 2008. It is an aminotetralin compound with greatest affinity to D3, but is also a full agonist to D2 and D1, and a partial agonist to D4.^{50,51} The affinity for D3 is 10-fold higher than for D2 and 100-fold higher than for D1.⁵² It has antagonistic activity to the α_{2B} adrenoceptor, and agonist activity to 5HT1A and 5HT7.

The patch is a silicone-based transdermal system, to be changed every 24 hours. A steady state of rotigotine levels is reached after 24 hours, and a stable drug level is maintained throughout the 24-hour period that the patch stays affixed to the skin.⁵³ A short elimination half-life (5–7 hours) allows reversal of effects quickly after removal of the patch. Subcutaneous administration prevents first-pass hepatic metabolism, but it can be rapidly metabolized by the liver and by several cytochromes, and it is excreted rapidly through renal and hepatic systems.^{50,51} Three different patches are available: 10 cm²

with 4.5 mg of drug, releasing 2 mg/24 hours; 20 cm² containing 9 mg of drug, releasing 4 mg/24 hours; and 30 cm² containing 14.5 mg of drug, releasing 6 mg/24 hours.

Apomorphine, the oldest of all DA agonists, was initially examined in the United States for PD in 1951,⁵⁴ although it was not approved until 2004. The first and only subcutaneous injection rescue therapy, apomorphine is a non-ergot compound that has full DA receptor agonist properties. Its affinities to D1, D2, and D3 are similar to those of DA (more similar than any other drug in this class).³⁷ It is the only DA agonist with efficacy similar to LD. It also has affinity for α_{1D} , α_{2B} , and α_{2C} adrenoceptors, as well as for multiple serotonin receptors (5-HT1A, 5-HT12A, 5-HT12B, and 5-HT12C).⁵⁵

Apomorphine is extensively metabolized by the liver, which explains why it is not effective when given orally. Higher doses orally lead to nephrotoxicity. The drug is rapidly absorbed after subcutaneous injection and has a half-life of 30 to 60 minutes. The time to mean peak concentration (C_{max}) in the serum (serum T_{max}) is 5 to 45 minutes, with rapid transmission through the blood-brain barrier and T_{max} in the CSF 10 to 20 minutes later.⁵⁵ This explains its rapid effects and its use as a rescue drug in PD.

DA agonists: phase III clinical trial results, early PD

Pramipexole, ropinirole, and rotigotine have been studied in phase III multicenter, randomized, placebo-controlled trials as monotherapy in early PD. These studies have been similar in randomization scheme (1:1 or 2:1), duration (ascending dose phase followed by 6 months of maintenance therapy), and primary endpoints (change in UPDRS part II and part III scores). Each study enrolled 200 to 300 patients.

For pramipexole, Shannon et al.⁵⁶ found a 2.2-point improvement in the Activities of Daily Living (ADL) score over placebo and a 6-point improvement in the Motor score over placebo, both of which were statistically significant and maintained for the entire 6 months with a mean dose of 3.8 mg. More than 80% of participants completed the study. The most common adverse events included nausea (39%), insomnia (25.6%), constipation (17.7%), and somnolence (18.3%); these were significantly more common with active therapy than with placebo. Symptomatic orthostasis was absent. Visual hallucinations occurred in 9.7%, which was significantly greater than placebo.

A 10-week dose ranging study performed by the Parkinson Study Group⁵⁷ evaluated four doses of pramipexole and placebo in a double-blind, parallel group, randomized trial. In all, 264 patients were randomized to receive 1.5 mg, 3 mg, 4.5 mg, or 6 mg of pramipexole or placebo. There was an improvement of

~20% in UPDRS score in all active-treatment groups, with a linear trend between mean response and dosage that was highly significant and in all cases significantly different from placebo. The main difference between 4.5 mg/day and 6 mg/day was a greater frequency of adverse effects at the higher dose. The optimum dosage of pramipexole monotherapy in early PD patients lies between 1.5 mg/day and 4.5 mg/day.

For ropinirole, Adler et al.⁵⁸ found, with an average dose of 15.7 mg/day, a decrease in UPDRS Motor score of 4.7 points in the ropinirole group, compared with the placebo group. This was maintained for 1 year.⁵⁹ The most common adverse effects in this study were nausea (52.6%), dizziness (36.2%), and somnolence (36.2%). Hallucinations occurred in only 1.7% of patients, confusion in 6%, and orthostasis in 6%.

For rotigotine, Watts et al.⁶⁰ found, with a mean dose of 5.7 mg/24 hours, a decrease in UPDRS subtotal score (part II ADL plus part III Motor) of 5.28 points, compared with placebo. The part III Motor score decreased by 3.5 points. The study was completed by 78% of participants. The most common adverse effects were nausea (41%), dizziness (19%), somnolence (33%), and insomnia (9%). Hallucinations and confusion were not reported. A side effect unique to the patch is application skin site reactions (44%).

One study compared rotigotine, ropinirole, and placebo in a study of similar design but with a double-dummy design and a noninferiority analysis.⁶¹ Recruitment yielded a randomization of 215 for rotigotine 8 mg/24 hours, 228 for ropinirole 24 mg/day, and 118 for placebo (a 2:2:1 scheme). Responders, defined as $\geq 20\%$ decrease in combined ADL and Motor subscores of the UPDRS, were seen in 52% of the rotigotine group, 68% of the ropinirole group, and 30% of the placebo group ($p < 0.0001$ for each active treatment *vs* placebo). The absolute decrease in combined scores was 7.2 points for rotigotine, 11 points for ropinirole, and 2.2 points for placebo ($p < 0.0001$ for each *vs* placebo). ADL score decreased by 2.1 for rotigotine, compared with 0.1 for placebo, and the Motor score decreased by 5.2, compared with 2.1 for placebo. Noninferiority was not shown for rotigotine *versus* ropinirole. The two drugs had a similar adverse event profile, although rotigotine resulted in lower levels of nausea, dizziness, and somnolence.

An 11-week dose-finding study similar to that with pramipexole was performed by the Parkinson Study Group,⁵³ in which 242 patients received 2 mg/24 hours, 4 mg/24 hours, 6 mg/24 hours, 8 mg/24 hours of rotigotine, or placebo. There was a significant dose-related improvement (>5 points) in UPDRS ADL and Motor combined scores in the 6 mg/24 h and 8 mg/24 h groups.

Comparisons with levodopa

Several prospective, randomized, double-blind studies have been completed in which DA agonists were used as monotherapy in early PD and the effect was compared with LD. These studies, which used ropinirole and pramipexole, have already been discussed in some detail in the LD section of this article. In both of these studies, LD was given as an open-label supplement, if needed, to either group. In the 5-year 056 Study,²¹ the primary endpoint was the appearance of dyskinesias, as reported on item 32 of the UPDRS. Dyskinesias occurred earlier and more frequently in patients treated with LD. Regardless of LD supplementation, 20% of ropinirole subjects experienced dyskinesia by the end of 5 years, compared with 45% of LD subjects ($p < 0.0001$). There were no differences between the two groups in terms of the occurrence of wearing off.

In the 4-year CALM-PD study,²² which compared pramipexole to LD, 38% of the LD group and 20% of the pramipexole group developed wearing off ($p < 0.01$), and 30% of the LD group and 10% of the pramipexole group developed dyskinesia ($p < 0.0001$).

Phase III clinical trial results in advanced patients

Phase III trials for pramipexole, ropinirole, and rotigotine have been completed in fluctuating PD patients. As with the early PD trials, the methods were similar. These were double-blind, placebo-controlled trials with similar randomization schemes (1:1 or 2:1), duration (ascending dose phase followed by 6 months of maintenance therapy), and primary endpoints (diary measures of daily off times). LD doses could be reduced if needed, and never increased beyond baseline. The subjects had about 6 hours off time per day at baseline.

For pramipexole, Lieberman et al.⁶² enrolled 360 patients, with a maximum dose of 4.5 mg/day. The percentage of off time, comparing the last visit (after 8 months) to baseline, significantly decreased by 31% (actual hour change not given). The LD dose was reduced in the pramipexole group by 27%, compared with 5% in the placebo group. The major adverse events reported included dyskinesia (61.3%), asymptomatic orthostatic hypotension (48.1%), dizziness (36.5%), insomnia (22.7%), hallucinations (19.3%), nausea (17.7%), and symptomatic orthostatic hypotension (16%). Guttman⁶³ reported another large multicenter trial in which 246 subjects were randomized to placebo, pramipexole, or bromocriptine. At an average dose of 3.36 mg/day, pramipexole had a significant improvement in hours on, with an increase of 2.5 hours per day. The relative percentage decrease in off time in the pramipexole group was 45.6%, compared with 5.5% for placebo.

The principal study of ropinirole in advanced patients is that reported by Lieberman et al.,⁶⁴ who randomized 149 patients to ropinirole ($n = 95$) or placebo ($n = 54$);

73% of participants completed the study. Results demonstrated a reduction in LD dose in the ropinirole group of 31%, compared with 6% in the placebo group. Hours off per day were reduced by ~12% (1.9 hours) in the ropinirole group and 5% (.8 hours) in the placebo group. Dyskinesia was the only side effect that was significantly more common in the ropinirole group (33.7%).

For the rotigotine patch, LeWitt et al.⁵⁰ examined the decrease in off time in 351 patients randomized to 8 mg/24 hours, 12 mg/24 hours, or placebo; 74% of participants completed the trial. Reductions of LD were 2.6% (8 mg), 4.5% (12 mg), and 1.8% (placebo). The decrease in off time in the 8 mg/24 hours group compared with placebo was 1.8 hours; for the 12 mg/day, the decrease was 1.2 hours; there was no significant difference between the two active-treatment groups. An notable result was a 29% decrease in off time upon awakening in the 8 mg/24 hours group, and a 23% decrease for the 12 mg/24 hours, compared with 9% for placebo. The primary adverse effects more common in the active-treatment groups were dyskinesia, peripheral edema, and hallucinations. Application skin site reactions (present in >40% of participants) included erythema, pruritus, and dermatitis. Only 1.7% discontinued the study because of these, however.

One study compared rotigotine, pramipexole, and placebo in a study of similar design but with a double-dummy design and a noninferiority analysis.⁶⁵ This study was a shorter, 16-week maintenance phase. The maximum dose was 16 mg/24 hours for rotigotine and 4.5 mg/day for pramipexole. Randomization yielded 204 patients treated with rotigotine, 201 with pramipexole, and 101 with placebo (a 2:2:1 scheme). LD dose was reduced by 3% in the rotigotine group, by 9% in the pramipexole group, and by 2% in the placebo group. The mean change in daily off time, compared with placebo, was -1.58 hours for rotigotine and -1.94 hours for pramipexole ($p < 0.0001$). The difference between active treatments for hours off exceeded the noninferiority margin of 1.2 hours ($p = 0.003$), indicating noninferiority. The drugs were similar in most primary and secondary outcomes. Adverse-effect profiles were similar.

Apomorphine is the only drug used on an as-needed basis, an injection rescue drug to abort off episodes. It requires pretreatment with an antiemetic drug: in Canada and Europe, domperidone is required; in the United States, trimethobenzamide. A review of early, small, double-blind and open-label studies indicates that the drug starts to take effect after 7.5 to 20 minutes, and lasts 20 to 120 minutes with doses of 0.5 mg to 5 mg per injection.⁶⁶ The pivotal, double-blind, placebo-controlled trial that led to FDA approval in the United States was a combined inpatient and outpatient study with 29 patients (20 patients received active drug; 9 received placebo).⁶⁷

In part one, inpatients received escalating doses of apomorphine in a blinded fashion and in a standardized schedule, up to an equivalent response to LD or 10 mg. There was a statistically significant improvement in UPDRS motor scores, compared with placebo ($p < 0.001$). This was followed by a 4-week outpatient, blinded extension. Key findings included decrease in daily off time by 2 hours, reversal of 95% of off times, and mean latency to onset of 22 minutes. This was followed by a second blinded study, which examined 62 patients who received apomorphine for at least 3 months, to evaluate long-term efficacy. Patients, in an outpatient setting, received their usual dose, a dose 2 mg higher, or placebo. Apomorphine improved the off period significantly more than placebo at 10 and 20 minutes after injection ($p < 0.0001$), indicating long-term effectiveness.⁶⁸

Safety issues: excessive daytime somnolence and "sleep attacks"

It has been known for years that some PD patients suffer from excessive daytime sleepiness,⁶⁹ with spontaneous dozing significantly more common in PD patients (49%) than in controls (26%). It was not until 1999, however, after Frucht et al.⁷⁰ reported that eight patients with PD had fallen asleep at the wheel, that concerns about sleep attacks arose. Seven of the eight patients were taking pramipexole, and it was suggested that this drug was the cause. Subsequently, several reports indicated that pergolide and LD could cause the same problems.^{71,72} These reports engendered an unusual amount of interest, response, and controversy.^{72,73} Based on the report by Frucht et al.,⁷⁰ the FDA and health organizations around the world required amendments to package inserts, including a black box warning in the United States with a statement that patients should not drive until "they have gained sufficient experience with [pramipexole] to gauge whether or not it affects their mental and/or motor performance adversely."

Part of the controversy was whether these patients had true sleep attacks, as seen with narcolepsy, or whether these were related to drug-induced somnolence. An additional controversy related to causation. Terminology in the literature indicates two types of episodes: "sleep attacks," occurring without warning and unrelated to somnolence, and "unintended sleep episodes" or "sleep events," which are events with premonitory sleepiness. The term "sudden-onset sleep" covers both groups. Investigations with polysomnography have demonstrated that sleep attacks do occur in both treated and untreated patients, which suggests that this is a disease-related phenomenon.^{74,75}

The frequency of sudden-onset sleep has been examined in several studies. Meindorfner et al.⁷⁶ found, from a questionnaire study, that 8% of 5210 patients experi-

enced at least one episode of sudden-onset sleep; of these, 57% were unintended sleep episodes, and 26% had sleep attacks. Sudden-onset sleep was often reported in association with change in medications and, in half the cases, was due to the addition of DA agonists. A consortium of 18 Canadian trial sites⁷⁷ examined 638 cases with a questionnaire. Excessive daytime sleepiness was present in 51% of patients, but sudden-onset sleep occurred in only 3.8% and actual sleep attacks were reported in only 0.7%. The study failed to show a relationship with any particular group of drugs.

It is clear that excessive daytime sleepiness is a common problem in PD. Sudden-onset sleep of both types does occur, with sleep attacks being much less common. These problems may relate to PD directly, but some data suggest an increased risk with dopaminergic drugs, particularly for unintended sleep episodes.⁷⁸ The data at this point are not reliable enough to establish a direct causal relationship. When therapy with LD or DA agonists is initiated, patients should be advised of the possibility of somnolence and cautioned about the operation of any dangerous machinery, including automobiles.⁷⁹

Safety issues: pathological gambling and related impulse control disorders

Another class of adverse events linked to DA agonists is impulse control disorders (ICD), which are defined as an inability to resist an impulse despite negative consequences.⁸⁰ Such disorders include pathological gambling (PG), compulsive shopping, compulsive eating, hypersexuality, punding, and hedonistic homeostatic dysregulation (also known as dopamine dysregulation syndrome), the last relating to compulsive overmedication use.^{81–84} The focus here will be on PG and compulsive shopping, because these complications are the ones initially thought to be primarily associated with DA agonists. The others have all been clearly associated with LD therapy and are not necessarily new issues in PD.

The understanding of PG and compulsive shopping is beginning to evolve in a manner similar to that of sleep attacks. Initial reports were case series, followed by small, clinic-related, case-control studies, one of which involved consecutive patients.⁸⁵ (Large-scale, prospective, controlled trials have yet to be reported.) Although the first report in 2000 implicated LD in 12 cases of fluctuating PD,⁸⁶ the case series that followed implicated DA agonists and, more specifically, pramipexole.^{87,88} The lifetime prevalence of PG was greater for those prescribed DA agonists (7.2%) than for PD populations with all treatment combinations (3.4%).⁸⁵ Other DA agonists, however, have an equal likelihood of being associated with PG,^{89–91} and it was suggested that the initial association of pramipexole with PG was likely the result of prescribing practices.^{92,93}

Although PG was initially associated with both DA agonist monotherapy and combination DA agonist and LD therapy, more recent reports indicate that it is combined therapy that is most prominently associated with PG.⁹⁴ Although it is reported that PG reverses with decreasing or stopping DA agonists,⁹⁵ this has not been a consistent finding. There are also data supporting an association with LD therapy, amantadine, and (although this is not universally supported) deep brain stimulation surgery.^{86,89,91,92,95} Furthermore, there are increasing data to suggest that PG may be disease-related, with reports of onset without change in medications, lack of relation to agonist dosages, continuing symptoms after stopping DA agonists in a notable portion of cases, spontaneous reversal without medication changes, and particular disease-related risk factors (including young age of onset, longer disease duration, association with prior history of alcoholism and other ICD, mania, executive dysfunction, and novelty seeking).^{80,81,86,90,94,96}

There are also significant psychiatric and motor comorbidities; depression, disinhibition, irritability, appetite changes and mania or hypomania.^{94,97} These have been seen in non-PD cases as well. The motor comorbidity is primarily the presence of motor fluctuations, with symptoms of ICD occurring more commonly in the on state.^{94,97} The younger age of onset is the most predictive risk factor. The suggestion that DA agonists may cause PG is confounded by the fact that young patients are more likely to be initially treated with agonists. In one study examining novelty seeking as a risk factor, those patients with PG had novelty-seeking scores similar to those of the non-PD population, but higher than PD patients without PG. Because novelty-seeking scores are not changed by DA agonists, it is hard to interpret these findings in relation to cause of PG.⁹⁴ For those patients with ICD prior to PD, the behaviors before and during PD were the same.⁹⁰

Small case-control prevalence studies (<300 patients) of ICD estimated a range from 4% to 6% in PD populations and as high as 9% in a population of cases with onset before age 65 years.^{85,90,97} Specifically, PG retrospective reviews estimated a prevalence of 0.4% to 0.5%.^{87,98} Small prospective studies found a 3.4% lifetime prevalence, a 3-month prevalence of 1.7%,⁸⁵ and an active prevalence of 2.2%, with 2.6% subsequent to diagnosis of PD.⁹⁰ The prevalence of compulsive shopping is estimated at 1.5%.^{85, 90} One other small study compared 98 PD patients with 392 non-PD controls and found a prevalence of ICD of 6.1% in the PD group, compared with 0.25% for the control group.⁹¹

With so many unknowns at this point, the cause of these behavioral disturbances and their relation to DA agonists is unclear. ICD may be primarily disease-related, primarily drug induced, an unmasking of premorbid condition with medication, or unrelated to both dis-

ease and treatment. There is a need for a large prospective study to clarify these issues, and one is ongoing now. Still, it is reasonable to inform patients of this potential association when initiating treatment and to recommend to those developing such disturbances to diminish or stop the DA agonist as an initial step in therapy. Careful monitoring is important.

CATECHOL-*O*-METHYLTRANSFERASE (COMT) INHIBITORS

COMT inhibitors were first introduced in the United States in 1997, with the approval of tolcapone. Entacapone followed in 1999. Both were approved for treatment of advanced fluctuating PD, but tolcapone was also approved as an adjunct to LD in nonfluctuating patients. The development of hepatic toxicity in 4 individuals and the death of 3 in 1998, out of 60,000 patients treated, had a significant impact on the use of tolcapone.⁹⁹ These patients were not monitored according to recommendations, and two were maintained on the drug after the diagnosis of hepatitis was made.^{99,100} Nevertheless, these cases resulted in the withdrawal of tolcapone from the market in Europe and Canada and a black-box warning in the United States in 1998 requiring careful liver enzyme monitoring, the patient's signature on a consent form, and the use of tolcapone as a last resort. Several changes occurred in 2006 and 2007 making use of tolcapone easier, based on new safety data. This is discussed below, under safety issues.

COMT inhibitors act peripherally to inhibit metabolism of LD to 3-*O*-methyldopa (3-OMD).¹⁰¹ The impact of this effect is to increase the half-life and bioavailability of LD, significantly increasing the area under the curve. This is done without increasing either C_{max} or T_{max} . The result is to extend the duration of effect of LD.

Tolcapone and entacapone have a number of pharmacological differences. From a pharmacokinetic standpoint, tolcapone has greater bioavailability (68% vs 36%), area under the curve (18.5 $\mu\text{g/mL}$ vs 1.6 $\mu\text{g/mL}$), T_{max} and C_{max} , and COMT enzyme affinity than does entacapone,¹⁰¹ leading to a greater magnitude and duration of COMT inhibition. These findings point to a greater inhibitory effect on the metabolism of LD by tolcapone. It increases LD half-life by 80% (compared with 40% for entacapone), increases LD area under the curve by 80% (compared with 40% for entacapone), and provides a greater decrease in the formation of 3-OMD.¹⁰¹ Dosing differences relate to the duration of inhibitory effect on COMT; tolcapone is given three times a day, whereas entacapone must be given with each dose of LD.

One would expect tolcapone to have twice the effectiveness of entacapone when used to treat fluctuating PD. Although there are some data on the use of COMT

inhibitors in nonfluctuating PD, the effect is modest at best, and the ability of these agents to prevent fluctuations remains as yet unknown.^{102,103} Hence, the primary use of these drugs is in fluctuating patients, and that will be the focus of the discussion here. Ten published placebo-controlled, blinded clinical trials have examined tolcapone and entacapone in advanced PD, five trials for each of the two drugs (summarized in Table 2). The two pivotal studies for each drug are considered in the following sections.

Clinical trials in PD with motor fluctuations

Rajput et al.¹⁰⁴ published the first double-blind, randomized, placebo-controlled, multicenter 12-week trial with three treatment groups: tolcapone 100 mg t.i.d., tolcapone 200 mg t.i.d., and placebo. There were 136 active and 66 placebo patients. Tolcapone 100 mg decreased off time by 32% (2.3 hours), tolcapone 200 mg decreased off time by 48% (3.2 hours), and placebo decreased off time by 20% (1.4 hours) ($p < 0.01$ for the tolcapone 200 mg group). At both tolcapone doses, a significant improvement in investigator global score occurred, as well as a significant decrease in daily LD dose (~ 200 mg) and number of LD doses per day (decreased by ~ 1). The effect of the drug was rapid, and dyskinesia increased in the first 30 days, but was treated effectively with reductions in LD dose.

Baas et al.¹⁰⁵ also reported a double-blind, placebo-controlled trial. Patients were randomized to the same treatment groups: tolcapone 100 mg t.i.d. ($n = 60$), tolcapone 200 mg t.i.d. ($n = 59$), and placebo ($n = 58$). Off time decreased by 26.2% in the 200 mg group, by 31.5% in the 100 mg group, and 10.5% in the placebo group ($p < 0.01$). Levodopa doses dropped 16% for the 100 mg group and 18% in the 200 group, compared with 4% for the placebo group. Dyskinesia developed or worsened in 37% at 100 mg of tolcapone, 52.5% at 200 mg, and in 21% of the placebo group. During these trials a greater than threefold increase in liver transaminase levels was seen in 1.3% of those treated with 100 mg t.i.d. and in 3.7% of those treated with 200 mg t.i.d. This was reversible within 1 to 3 months after drug cessation. Other adverse effects were diarrhea (20%–30%), nausea, somnolence, hallucinations, and orthostatic hypotension.

The Parkinson Study Group reported a double-blind, parallel group, multicenter trial; 103 patients received entacapone (200 mg with each dose of LD) and 102 received placebo for 24 weeks. On time increased by 5% in the entacapone group. Dyskinesias developed in 53% of the entacapone patients, compared with 32% of the placebo patients ($p = 0.002$).¹⁰⁶ In another study (LARGO),¹⁰⁷ rasagiline 1 mg/day (231 patients) was compared with entacapone 200 mg with each dose of LD, up to eight per day (227 patients), and placebo (229 patients) in a double-dummy paradigm; 87% of partici-

TABLE 2. Results From Trials of Tolcapone and Entacapone in Advanced Parkinson's Disease

Study Reference	Increase in On Time, h or %		Decrease in Off Time, h or %		Decrease in Levodopa Dose, mg or %		
	100 mg	200 mg	Placebo	100 mg	200 mg	Placebo	
Tolcapone, 100 or 200 mg vs placebo							
Adler et al. ¹⁴⁵	2.1	2.3	0.3	2.0	2.5	0.3	
Rajput et al. ¹⁰⁴				2.3 (32%)	3.3 (48%)	1.4	186 (23%)
Baas et al. ¹⁰⁵	21%	21%	1%	32%	26%	11%	166 (21%)
Myllylä et al. ¹⁴⁶		34%	-5%		42%	3%	109 (16%)
Kurth et al. ¹⁴⁷		0.3 (4%)	0.4 (6%)		1.3 (19%)	0.4 (5%)	251 (29%)
Entacapone, 200 mg vs placebo							
Parkinson Study Group ¹⁰⁶							207 (24%)
Rinne et al. ¹⁴⁸		1 (5%)					122 (18%)
Rascol et al. ¹⁰⁷		1.4 (15%)	0.2 (2%)		1.3 (24%)	0.1 (2%)	80 (11%)
Fenelon et al. ¹⁴⁹		0.85 (9%)	0.03 (0.3%)		1.2 (21%)	0.4 (7%)	200 (26%)
Poewe et al. ¹⁵⁰		0.7	0.62		0.9	0.5	
		1.7 (17%)	1.0 (10%)		1.6 (26%)	0.9 (13%)	
							100 (12%)
							87 (12%)
							19 (3%)
							32
							10
							54 (9%)
							+15 (2%)
							+5 (+0.7%)
							10
							+27 (+5%)

Across all studies, the indicated 100 or 200 mg refers to a single dose. Tolcapone was 100 or 200 mg, entacapone was only 200 mg per dose (three doses daily for tolcapone; entacapone was given as many times as levodopa). Change in levodopa refer to total daily dose.

pants completed the study. The active-treatment groups were compared with placebo, not each other. The total daily off time decreased by 21% (1.2 hours) for entacapone, which was significantly more than the decrease of 7% (0.4 hours) with placebo, ($p < 0.0001$) with a net change of 0.8 hours. There was no change in on time with troublesome dyskinesia, and the percentage of subjects with dyskinesia as an adverse effect was similar for all three groups. The adverse effects of entacapone are similar to tolcapone, but to a lesser degree.

To summarize the effect of these drugs on fluctuations, tolcapone decreased off time by 1.6 to 3.3 hours and entacapone decreased off time by 0.9 to 1.3 hours. Levodopa dose was decreased by 80 to 251 mg/day for tolcapone and by 19 to 100 mg/day for entacapone (Table 2). Both drugs cause diarrhea but, as expected based on the difference in potency, this adverse effect is more common and severe with tolcapone.

There have been two comparator trials. One small, 3-year, open trial of 25 subjects demonstrated that tolcapone had a greater impact on decreasing duration of off time and LD doses long term.¹⁰⁸ More recently, a 3-week, double-blind study examined 150 advanced PD patients optimized on entacapone therapy and randomized to continued entacapone 200 mg/dose or switched to tolcapone 100 mg t.i.d.¹⁰⁹ On time was increased by ≥ 1 hour in 43% on entacapone and 53% on tolcapone, and by ≥ 3 hours in 13% of entacapone subjects and 25% on tolcapone ($p = 0.02$). Tolcapone increased on time by 1.34 hours, compared with 0.65 hours for entacapone ($p = 0.04$). Adverse events, including dyskinesia ($\sim 30\%$ in each group), were similar for both treatments. These comparator studies confirmed the notion that tolcapone is a more potent agent. The results of the switch study¹⁰⁹ led to the reinstatement of tolcapone on the market in several European countries.

Safety issues: hepatic injury with tolcapone

Liver enzyme monitoring has never been required for entacapone, despite some reports of toxicity.¹¹⁰ In clinical trials for tolcapone, however, there appeared to be a dose-related elevation in liver enzymes up to $\sim 4\%$. It was originally recommended that alanine aminotransferase (ALT) and aspartate aminotransferase (AST) be monitored every 4 weeks in the first 3 months and every 6 weeks for the next 3 months. After the deaths of three elderly women, at 2 to 4 months after initiating tolcapone treatment, were reported through post-marketing surveillance, liver monitoring was required every 2 weeks for 1 year, followed by monthly for 6 months, and then every other month continuously as long as the patient was on the drug. In addition, a consent form was developed for patients to sign before starting on the drug. If the ALT or AST went over the upper limit of normal, the drug was to be stopped and the patient monitored. Recent reports,

however, indicate that with appropriate monitoring the drug can be prescribed safely.

One study examined 2-year data from a central database developed by the manufacturer.¹¹¹ Of 1725 patients, 3.9% had elevations above the upper limit of normal of ALT, AST, or both, and 0.9% had elevations >2 times the upper limit of normal. Most values normalized, despite continuation of the drug (>60% of cases), even in those with >3 times the upper limit of normal. A 7-year post-marketing study found that 224 hepatic events were recorded over 40,000 patient years, but only 22 had documented elevations of liver enzymes, and these were usually transient, asymptomatic, and resolved spontaneously.¹⁰⁰ No additional deaths were reported.

Finally, a prospective, placebo-controlled trial examined the frequency of hepatic events in 677 PD patients (335 received tolcapone 100 mg t.i.d. and LD; 342 received placebo and LD).¹¹² In patients treated for a mean of 216 days and with liver enzymes monitored monthly, 20.2% of the placebo group and 27.5% in the active-treatment group had at least one elevated value above the upper limit of normal; 1.2% placebo and 1.8% active patients had levels >3 times the upper limit of normal, a difference that was not statistically significant. In 97% of the patients, the abnormalities were detected within 6 months of therapy. No patients developed jaundice or hepatic insufficiency, and >60% of the liver enzyme values returned to normal with continuation of the drug.

These data support the notion that liver toxicity with tolcapone is rare and the safety margin is wider than previously believed, although the shortcomings of post-marketing reporting are understood. The change in labeling that occurred in 2006 now states that a baseline ALT/AST test should be done before initiating tolcapone, then every 2 to 4 weeks for 6 months; thereafter, it is at the discretion of the physician. The drug should be stopped if ALT/AST levels reach two times the upper limit of normal. The consent required has been downgraded to an "acknowledgement." These changes reflect a sense of greater safety with the drug, especially with appropriate monitoring, and should improve accessibility to this exceedingly effective and underused drug for patients with advanced PD.

MONOAMINE OXIDASE (MAO) INHIBITORS

Monoamine oxidases are intracellular enzymes (within the outer mitochondrial membrane) that play a major role in oxidative deamination of monoamines such as DA.¹¹³ Type B is the primary form of the enzyme found in the brain, making up ~80% of all MAOs.¹¹³ In the brain, type B is generally extraneuronal, located primarily in astrocytes.¹¹⁴ Inhibition of the enzyme would be expected to enhance the effect of both endogenous and exogenous DA, and this has been a recent focus of symp-

tomatic therapy. Oral selegiline was first approved for treatment of PD in 1989. Although it came to be used primarily in early disease as a potentially neuroprotective agent^{115,116} (a use not discussed here), it was approved for advanced patients with motor fluctuations based on trials examining off time as the endpoint.^{117,118} The symptomatic effects of oral selegiline were thought not only to relate to MAO inhibition but were also thought to be associated with an amphetamine effect (enhancing release of DA), because oral selegiline is metabolized to L-amphetamine via the first pass in the liver. This explains the most serious adverse effect of the drug, insomnia. In studies in platelets, it has been shown that 98% of the enzyme is blocked within 24 hours of ingesting 10 mg.¹¹³

In 2006, two new MAO B inhibitors were approved by the FDA: orally disintegrating selegiline (Zydis, a new formulation of the oral form of selegiline), and rasagiline, which is a novel second-generation agent. Both drugs are irreversible MAO inhibitors, with an effect that lasts until enzyme turnover (which takes ~40 days¹¹⁹). Thus, the functional half-life does not coincide with the pharmacologic half-life. Rasagiline is a more potent inhibitor of MAO type B, and at a dose of 0.5 mg/day the enzyme is fully inhibited in a week.¹²⁰ Rasagiline was approved for early and advanced PD, whereas Zydis selegiline was approved only for treatment of motor fluctuations. Both are given once a day, an advantage for patients that also improves compliance.

The Zydis system for delivery of selegiline eliminates the large first-pass metabolism of the drug, with a 3-fold to 10-fold reduction in the amphetamine effect and with enhanced availability in the brain. It is a freeze-dried tablet that dissolves quickly and is absorbed by the oral mucosa.¹²¹ The Zydis preparation has eight times the bioavailability of oral selegiline, which is reflected in dosing, and it is absorbed 1 hour faster.¹²² The typical dosage is 1.25 or 2.5 mg/day.

Two identical phase III trials examining Zydis selegiline in fluctuating PD patients have been reported. These were 3-month, placebo-controlled trials with a 2:1 randomization scheme examining 1.25 mg/day (first 6 weeks) and 2.5 mg/day (second 6 weeks); the primary outcome was decrease in hours off per day. In the first trial,¹²³ 140 patients with at least 3 hours of off time were randomized. At 6 weeks on 1.25 mg/day, there was a decrease in off time for the active-treatment group of 1.6 hours, compared with 0.5 hours for the placebo controls, and at 12 weeks on 2.5 mg/day the active-treatment group improved by 2.2 hours, compared with 0.6 hours for controls. Dyskinesia-free on time increased on both 1.25 and 2.5 mg/day. This magnitude of effect is similar to that of DA agonists. In the second trial,¹²⁴ 148 patients were enrolled, but the results were negative. At 1.25 mg/day, the active-treatment group had a decrease of off

time of 1.7 hours, compared with 1.5 hours for the placebo group. At 2.5 mg/day, the active-treatment group decreased off time by 1.9 hours and the placebo group decreased it by 1.6 hours. The reason for the conflicting results is not clear. Adverse effects were infrequent, but the most common included dizziness and hallucinations.

Rasagiline blocks 50% to 70% of MAO B in the brain with a single dose of 1 to 2 mg.¹²⁵ Three major clinical trials led to the approval in the United States for both early and advanced PD. The early trial was referred to as TEMPO.¹²⁶ This was a 26-week, double-blind, parallel group study randomizing 404 patients into three groups: rasagiline 1 mg, rasagiline 2 mg, and placebo. At 26 weeks, the adjusted effect size related to placebo for total UPDRS score was -4.2 for 1 mg and -4.6 for 2 mg. For Motor and ADL subscores, respectively, it was -2.71 and -1.04 for 1 mg and -1.68 and -1.22 for 2 mg ($p < 0.001$). When the placebo group was switched to rasagiline 2 mg/day and followed for 6 more months (only 62% completed the entire year), a 2.3-point difference was noted between those receiving 2 mg for 1 year and those receiving 2 mg for 6 months ($p < 0.01$).¹²⁷ Whether this difference represents purely symptomatic benefit or neuroprotection remains to be elucidated.

Two trials examined rasagiline in advanced fluctuating PD, the PRESTO study and the LARGO study.^{107,128} PRESTO was a 26-week, placebo-controlled, double-blind trial in which 472 patients with at least 2.5 hours of off time per day were randomized to rasagiline 0.5 mg, rasagiline 1 mg, or placebo. The primary outcome was change in off time per day. There was a demonstrated decrease of 1.85 hours for 1 mg rasagiline and 1.41 hours for 0.5 mg, compared with 0.9 hours for placebo. This was a net improvement of 0.95 hours for the 1 mg group. For $\sim 30\%$, increase in on time was accompanied by dyskinesia.

LARGO was an 18-week, placebo-controlled, double-blind study in which 687 patients were randomized to rasagiline 1 mg/day, entacapone 200 mg with each LD dose, or placebo. In this study, rasagiline decreased off time by 1.18 hours, entacapone by 1.2 hours, and placebo by 0.4 hours. The net effect for rasagiline was identical to entacapone, a decrease in off time of 0.8 hours. Adverse effects of rasagiline, which were uncommon, included weight loss, vomiting, anorexia, postural hypotension, peripheral edema, depression, dizziness, hallucinations, dyskinesias and sleep disorders; few were significantly more common than controls.

Safety issues: tyramine effect

The main safety concern for the MAO inhibitor class of agents relates to drug interactions. Tyramine is a pressor agent that can generate significant elevations in blood pressure. It is metabolized by MAO and treatment with nonselective MAO inhibitors could lead to accumu-

lation of tyramine and a resultant hypertensive event. Tyramine is present in many foods, including such popular items as chocolate, red wine, and notably in cheese: hence the term "cheese reaction." The use of nonselective MAO inhibitors requires dietary restriction of tyramine to prevent such an effect. Theoretically, with selective MAO-B inhibitors dietary restrictions are not required, because 90% of the MAO in the periphery is type A.¹²⁹ Nevertheless, a warning remains on the label. There were no dietary restrictions in the phase III studies and no episodes of hypertensive crisis to support the warning.

More recently, tyramine challenge studies were conducted with both drugs. Zydys selegiline, at a dose of 1.25 mg/day, was examined with tyramine challenges up to 700 mg for possible elevation of systolic blood pressure of ≥ 30 mm Hg.¹³⁰ Subjects were challenged before treatment and after 14 days of therapy. No difference in blood pressure response was seen with an average threshold dose of 400 mg of tyramine being maintained. For rasagiline, a tyramine challenge study was conducted in 55 patients completing the TEMPO trial and 55 patients completing the PRESTO study.¹²⁹ For the TEMPO study, patients were receiving placebo or rasagiline monotherapy at 2 mg/day. These patients received a 75-mg tyramine challenge. For the PRESTO study, all patients were on LD and various percentages were receiving DA agonists, COMT inhibitors and serotonin reuptake inhibitors along with either rasagiline at 0.5 or 1 mg/day or placebo. They received a 50-mg tyramine challenge. None of the TEMPO subjects developed a hypertensive event; however, an asymptomatic elevation of >30 mm Hg occurred in three LD-treated patients on rasagiline and one on placebo in the PRESTO study. There was no statistically significant difference between rasagiline and placebo patients on blood pressure changes. For those with an elevation in blood pressure, the pattern of change was not typical of a tyramine-evoked event. Therefore, these drugs used at standard, selective doses probably do not require dietary restrictions of tyramine. However, care must be taken with higher doses or when patients are treated with drugs that might alter metabolism of the MAO inhibitor (for Zydys selegiline, those drugs metabolized by CYP2B6 and CYP3A4; for rasagiline, CYP1A6).

Safety issues: serotonin syndrome

The serotonin syndrome occurs when antidepressants (tricyclics or selective serotonin uptake inhibitors) are used in combination with nonselective MAO inhibitors or selective type A inhibitors (serotonin is metabolized by MAO type A). The syndrome develops over hours to days after initiation of combined therapy or after an increase in dose of either agent. Clinical features include motor symptoms, including movement disorders, partic-

ularly myoclonus and tremor, muscle rigidity, hyperreflexia; mental status changes, including agitation, confusion, disorientation and restlessness; and autonomic instability, including low-grade fever, nausea, diarrhea, headache, shivering, flushing, diaphoresis, tachycardia, tachypnea, blood pressure change, and pupillary dilatation.¹³¹ Laboratory changes are usually nonspecific, but can involve small increases in creatine kinase and white blood cell count. Death may ensue because of disseminated intravascular coagulation, myoglobinuria with renal failure, or cardiac arrhythmias. The cause of the serotonin syndrome is related to an excess of serotonin at 5HT1A and 5HT2 receptors. An increase in serotonin activity can also lead to inhibition of dopaminergic neurons in the substantia nigra, among other regions, which may explain the similarities between the serotonin syndrome and neuroleptic malignant syndrome. Treatment involves withdrawal of the causative agents; the syndrome will usually resolve over hours to days.¹³²

There has been some question about the occurrence of serotonin syndrome with the combined use of antidepressants and MAO B inhibitors. The package inserts for all contain a warning. A retrospective study involving oral selegiline¹³³ found that 0.24% of PD patients treated with this combination have symptoms possibly consistent with this syndrome, and 0.04% of patients had a serious disorder. There have been no deaths in PD patients. There are no reports at present regarding Zydys selegiline or rasagiline. Because they are selective type B inhibitors, as is true for oral selegiline, the risk is certainly low. It is recommended that the combination can be used if the benefit outweighs the risk and if appropriate monitoring is in place. If higher doses of the MAO B inhibitors are used, perhaps leading to loss of selectivity, then it is recommended not to use antidepressants concomitantly.

CONCLUSIONS AND FUTURE DIRECTIONS

The four classes of dopaminergic agents are effective in treating motor features of both early and advanced PD, and their roles are evolving. Table 3 summarizes the clinical impact of these drugs. In early disease, MAO inhibitors are least effective, followed by DA agonists; LD remains the most potent agent. In advanced disease, MAO inhibitors and entacapone have the smallest effect on reducing hours off per day, followed by ropinirole, rotigotine, pramipexole, apomorphine, and tolcapone.

These data were gathered through separate clinical trials, so comparisons are imperfect, but a general sense of the order of magnitude of effect can be observed from available data, and clinical experience has supported these conclusions. Because LD is not toxic, its use in early patients can be appropriate, and there is a shift in strategy by many specialists in movement disorders to

TABLE 3. *Changes in Measures for Early and Fluctuating Parkinson's Disease for Nine Drug Treatments, Compared With Placebo*

Drug	Early Parkinson's Disease: Change in UPDRS Motor Points	Advanced Parkinson's Disease: Decrease in Hours Off
Levodopa	9.2	not evaluated
Pramipexole	4.5–6.0	1.9–2.0
Ropinirole	4.7	1.1
Rotigotine patch	3.1–3.5	1.2–1.8
Apomorphine injection	not evaluated	2.0
Zydys selegiline		
1.25 mg	not evaluated	0.2–1.1
2.5 mg	not evaluated	0.3–1.6
Rasagiline		
0.5 mg	not evaluated	0.5
1.0 mg	2.7	0.8–0.95
2.0 mg	1.7	not evaluated
Entacapone	not evaluated	0.4–1.2
Tolcapone		
100 mg	not evaluated	0.9–1.7
200 mg	not evaluated	0.9–2.2

Values are composites from the various trials that provided these measures.

initiate therapy as early as possible. In both early and advanced PD patients, we are provided with a growing variety of pharmacological choices—which is good news for our patients. Practice guidelines from the American Academy of Neurology indicate that the evidence supports many options.^{24,134}

Several key adverse events received significant attention in recent years and can be summarized in the following manner: melanoma (along with other skin cancers) may occur at an increased rate in PD, but there is no evidence to connect it causally with LD. Modest elevations of homocysteine have been seen with LD, but the importance has yet to be determined. Sleep attacks are rare, and probably relate to PD rather than to its treatment. Dopamine agonists cause somnolence, and may increase the likelihood of unintended sleep episodes. Pathological gambling was initially linked to pramipexole, but later shown to occur with all DA agonists and with LD. There is not enough evidence to indicate that this association is actually a reflection of causation. The frequency of hepatic toxicity from tolcapone is probably lower than previously thought, and new, less-restrictive monitoring guidelines reflect that. Newly available MAO type B inhibitors do not appear to cause the “cheese reaction,” and thus no dietary tyramine restrictions are necessary (despite the required warning labels).

The future of symptomatic therapies will likely move

in two directions (for a review, see Colosimo et al.¹³⁵). First, continued refinement of dopaminergic drugs is in progress, for example, a once-daily form of ropinirole has completed phase III trials, and was found to be at least as effective and perhaps safer than the current formulation.¹³⁶ A new DA agonist with D2-D3 and 5HT1A effects has completed phase II trials. A new MAO B inhibitor, safinamide, is about to enter phase III trials. Safinamide is a highly selective and reversible MAO B inhibitor that also appears to have the capability of blocking voltage-dependent sodium and calcium channels and therefore inhibiting glutamate release.^{137–139} Pilot studies have demonstrated improvement in nonfluctuating and fluctuating PD.¹³⁸ Finally, changes in technology may allow the development of an easier and safer way to provide continuous infusions. Subcutaneous apomorphine infusions have been used successfully in the United Kingdom for the treatment of motor fluctuations, but there have been significant technical difficulties and associated cutaneous adverse effects.¹⁴⁰ New delivery devices are being developed. Duodenal infusion of LD in a viscous gel (Duodopa) as monotherapy has been demonstrated to be safe, and has provided significant improvement over various oral combinations.¹⁴¹

The second direction, and one that will probably increasingly dominate the landscape, involves nondopaminergic agents. It is hoped that such agents will prevent complications such as dyskinesia.¹³⁵ The first group of agents, including ones that are closest to approval, are the adenosine A_{2A} antagonists, which are related to caffeine. KW-6002, also known as istradefylline, has completed phase III studies and a new drug application for approval as symptomatic therapy in PD has been submitted. The A_{2A} receptors are colocalized with D2 receptors on medium spiny neurons of the indirect pathway, and antagonists decrease sensitivity to dopaminergic stimulation.¹⁴² One double-blind, placebo-controlled trial demonstrated a decrease in off time by as much as 1.7 hours, compared with placebo, at doses of 20 mg and 40 mg per day.¹⁴³ The drug has the potential to prevent dyskinesia, but does not reverse dyskinesia that is already present.^{142,143} A newer highly selective A_{2A} antagonist, SCH 420814, is currently being examined in phase II trials.

Several other classes of agents are being explored for motor fluctuations and dyskinesia. Based on the effect that amantadine has on dyskinesia, glutamate antagonist drugs, including the AMPA antagonist E2007, are currently in development and in phase II studies in patients with motor fluctuations and dyskinesia. Finally, noradrenergic drugs are being examined, because this neurotransmitter appears to influence motor and affective symptoms.¹³⁵ Both α and β adrenoceptors seem to be important. The drug fipamezole, an α_2 adrenergic receptor antagonist that reduces dyskinesia in MPTP-lesioned

primates,¹⁴⁴ is currently in phase II studies. Its formulation is as an orally disintegrating (Zydis) tablet.

Parkinson's disease therapy has enjoyed an enormous growth and evolution. Eight symptomatic drugs have been approved since 1997, and there is every reason to believe that the next decade will be at least as productive and interesting.

Acknowledgments: Work on this review was supported by the Sartain Lanier Family Foundation.

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