Inhibitors of monoamine oxidase (MAO) with selectivity and specificity for MAO type B prolong the activity of both endogenously and exogenously derived dopamine, making them an option either as monotherapy in early Parkinson's disease or as adjunctive therapy in patients treated with levodopa who are experiencing motor complications. In addition to symptomatic benefits, experimental data suggest that MAO-B inhibitors may be neuroprotective through MAO-B inhibition and other mechanisms that have yet to be clearly defined. The two available MAO-B inhibitors approved for use in the United States, rasagiline and selegiline, each provide symptomatic relief as monotherapy and as adjunctive therapy, and have shown potential disease-modifying effects in experimental models and clinical studies. Selegiline in a conventional tablet formulation is less bioavailable than rasagiline, resulting in limited potency. It also has amphetamine metabolites that may produce adverse effects and interfere with any putative disease-modifying effects. The oral disintegrating tablet formulation of selegiline allows pregastric absorption, minimizing first-pass metabolism, thereby increasing selegiline bioavailability and reducing the concentration of amphetamine metabolites. Rasagiline, more potent than selegiline, exhibits disease-modifying effects in experimental models and lacks amphetamine metabolites. Both the symptomatic and potential disease-modifying effects of rasagiline are under investigation. A third agent with MAO-B inhibition properties, safinamide, is in phase III development. Although not yet approved, safinamide may offer the added advantage of combined MAO-B and dopamine reuptake inhibition. 

Key Words: disease modification, monoamine oxidase, MAO type B, MAO-B inhibitors, neuroprotection, Parkinson's disease, rasagiline, safinamide, selegiline.

inhibitor rasagiline, recently approved by the United States Food and Drug Administration, are compatible with a neuroprotective effect.\textsuperscript{2}

**Dopaminergic Therapy**

Levodopa remains the most effective agent for symptomatic treatment of Parkinson's disease, providing benefit to virtually all treated patients.\textsuperscript{1} (For more specifics on the diagnosis and symptoms of Parkinson's disease, see the accompanying article in this supplement by Dr. Mark Lew.\textsuperscript{5}) However, levodopa does not ameliorate nonmotor symptoms, such as dementia, and is associated with long-term development of motor complications such as dyskinesia (involuntary movements) and motor fluctuations including an end-of-dose "wearing off" phenomenon, variability of response (unpredictable "on-off" phenomenon), and "delayed-on" or "no-on" episodes (dose failures). Levodopa-induced dyskinesias typically develop with motor fluctuations (periods of off) and become more severe as the disease progresses and with increases in levodopa dosages. Dyskinesia typically occurs during "on" periods, and patients frequently cycle between "on" periods with dyskinesia and "off" periods during which their voluntary movements are profoundly impaired. To extend its efficacy and decrease motor complications, levodopa may be augmented with a dopamine agonist or catechol-O-methyltransferase (COMT) inhibitor, but ultimately the therapeutic window for levodopa narrows as its efficacy shortens and its adverse effects, including dyskinesias, become less tolerable.\textsuperscript{1}

Dopamine agonists provide effective relief of parkinsonian symptoms either as first-line therapy in early Parkinson's disease or as an adjunct to levodopa. With longer half-lives than levodopa, dopamine agonists theoretically provide more sustained and predictable enhancement of dopaminergic function, which in part may be responsible for delaying levodopa-induced motor complications. Nonetheless, dopamine agonists are less potent than levodopa, do not target all Parkinson's disease symptom domains, and are accompanied by significant adverse effects of their own, including nausea, neuropsychiatric effects (hallucinations, psychosis, and impulse control disorders such as pathologic gambling, compulsive shopping, and hypersexuality), orthostatic hypotension, sedation, and agonist-specific effects such as ankle edema and erythromelalgia.\textsuperscript{1, 5}

Both levodopa and dopamine agonists have been associated with another idiosyncratic nonmotor adverse effect, that of punding, a disorder characterized by the compulsive performance of repetitive, mechanical tasks such as assembling, disassembling, collecting, or sorting objects.\textsuperscript{6}

A link between levodopa therapy and melanoma has been suggested, but those analyzing the clinical data have concluded that although there is an increased frequency of melanoma associated with Parkinson's disease, the evidence supporting a causal role for levodopa is weak.\textsuperscript{7, 8}

Imaging studies do not prove or refute a disease-modifying or neuroprotective effect of levodopa. In the Comparison of the Agonist Pramipexole versus Levodopa on Motor Complications in Parkinson Disease–\textsuperscript{2}β-Carboxymethoxy-3β(4-iodophenyl)tropane (CALM-PD-CIT) study, 82 treatment-naïve patients with early Parkinson's disease were randomly assigned to receive pramipexole or levodopa for 4 years.\textsuperscript{9} After 46 months of treatment, single-photon emission computed tomography revealed that patients assigned to the pramipexole group had a 16% reduction in the decline of striatal uptake of \textsuperscript{\textit{β}}-CIT compared with 25.5% in the levodopa group. \textsuperscript{β}-CIT is a measure of the density of dopamine transporters on postsynaptic dopamine terminals.

Similarly, in the ReQuip as Early Therapy versus L-Dopa–Positron Emission Tomography (REAL-PET) study, 162 treatment-naïve patients were randomly assigned to dopaminergic therapy with ropinirole or levodopa.\textsuperscript{10} After 2 years, patients treated with ropinirole had a 13.4% reduction in putamen \textsuperscript{18}Ffluorodopa uptake, a marker for the capacity of dopaminergic neurons to store levodopa or dopamine. Levodopa-treated patients experienced a 20.3% reduction. These findings have been interpreted to be suggestive of a neuroprotective effect of dopamine agonists or a neurotoxic effect of levodopa on dopaminergic neurons.\textsuperscript{11} Based on these findings, it appears that dopaminergic therapy alleviates motor symptoms in Parkinson's disease, but it remains unclear if it offers neuroprotection. (For additional information on the overall management of Parkinson's disease, please see the companion article in this supplement by Drs. Jack Chen and David Swope.\textsuperscript{12})

**Monoamine Oxidase-B Inhibitors**

The central pathology of Parkinson's disease is progressive deterioration of the melanin-
containing dopaminergic neurons in the substantia nigra pars compacta, resulting in a depletion of dopamine along the nigrostriatal pathway. The primary rationale for using selective MAO-B inhibition in Parkinson’s disease is that it enhances striatal dopaminergic activity by inhibiting the metabolism of dopamine, thereby improving Parkinson’s disease motor symptoms.\(^{13, 14}\)

Two isoforms of MAO have been identified: MAO-A and MAO-B. The B type is the predominant MAO isoenzyme in the human brain.\(^{15}\) It helps to break down dopamine into 3,4-dihydroxyphenylacetic acid and homovanillic acid, and also deaminates β-phenylethylamine, an endogenous amine that stimulates dopamine release and inhibits neuronal dopamine uptake. The MAO-A isoform, the predominant isoform in the intestinal tract, plays a critical role in deactivating circulating catecholamines and dietary vasopressors such as tyramine and, to a lesser extent, assists with the breakdown of neurotransmitters in the brain. Although inhibition of brain MAO-A may be useful for the treatment of psychiatric illness, peripheral inhibition of MAO-A may induce an acute syndrome characterized by hypertension, headache, nausea, palpitations, and tachycardia when tyramine or other amines such as levodopa are ingested along with an MAO-A inhibitor.

Since certain cheeses contain high amounts of tyramine, this syndrome is often called the “cheese reaction.”

Due to the role of MAO-A in the breakdown of serotonin, MAO-A inhibitors may also promote a centrally mediated, possibly life-threatening, serotonin syndrome when administered with selective serotonin reuptake inhibitors (SSRIs) or other serotonin-enhancing drugs. Serotonin syndrome is characterized by the following symptoms: restlessness, hallucinations, loss of coordination, rapid heart beat, sudden changes in blood pressure, increased body temperature, overactive reflexes, nausea, vomiting, and diarrhea. Consequently, nonselective MAO inhibitors are contraindicated in levodopa-treated patients with Parkinson’s disease. However, selective MAO-B inhibitors increase synaptic dopamine concentrations without significantly affecting MAO-A activity, making them a feasible option for the treatment of Parkinson’s disease motor symptoms.\(^{16}\)

A second, and to some extent theoretical, rationale for the use of selective MAO-B inhibitors in patients with Parkinson’s disease is that they may modify disease activity or be neuroprotective. Monoamine oxidase-B is responsible for the biotransformation of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) into 1-methyl-4-phenylpyridium ion (MPP\(^+\)), a potent parkinsonism-inducing neurotoxin.\(^{17}\) The discovery that MAO-B inhibition attenuates MPP\(^+\)-induced toxicity helped generate the hypothesis that MAO-B inhibitors modify the underlying processes of Parkinson’s disease. This hypothesis was first tested in the Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism (DATATOP) trial, a double-blind, randomized, placebo-controlled study of L-deprenyl (selegiline) and tocopherol (vitamin E) in patients with early Parkinson’s disease.\(^{18}\)

Pharmacology of Monoamine Oxidase-B Inhibitors

Two selective MAO-B inhibitors are currently available: selegiline and rasagiline. Selegiline, the prototype for selective MAO-B inhibitors, is a propargyl amphetamine derivative that undergoes extensive first-pass hepatic metabolism to three metabolites: desmethylselegiline, L-methamphetamine, and L-amphetamine. Selegiline has relatively low absolute bioavailability (~10%),\(^{19, 20}\) and its amphetamine metabolites are potentially neurotoxic and possibly associated with adverse cardiovascular and psychiatric effects.\(^{21–24}\) There is some evidence that selegiline loses selectivity for MAO-B at higher doses, resulting in potentially dangerous cheese reactions.\(^{25}\) In subjects receiving selegiline 12 mg/day transdermally (to circumvent first-pass metabolism), a tyramine challenge consistently provoked a cheese reaction.\(^{26}\)

A new orally disintegrating tablet (ODT) formulation of selegiline dissolves on contact with saliva and is absorbed mostly in the buccal region. Because it is absorbed presystemically, first-pass metabolism is minimized, and compared with the conventional formulation, bioavailability of selegiline is increased and metabolite concentrations are reduced. Consequently, selegiline 10-mg conventional tablets and 1.25-mg ODTs produce similar plasma selegiline concentrations, although the areas under the curve of desmethyl-selegiline and the amphetamine metabolites are about 10 times lower with ODTs than with conventional tablets.\(^{27, 28}\)

The second-generation MAO-B inhibitor rasagiline is a nonamphetamine, secondary cyclic benzylamine propargylamine pharmacophore that undergoes first-pass metabolism to the inactive metabolite aminodind.\(^{16}\) Rasagiline is devoid of amphetamine metabolites, has an
MONOAMINE OXIDASE-B INHIBITION IN PARKINSON'S DISEASE

Fernandez and Chen

approximate bioavailability of 36% (more than 3-fold greater than that of conventional selegiline), and in animal experiments was 3–15-fold more potent than selegiline in inhibition of MAO-B in the brain. Animal experiments suggest that rasagiline loses some of its specificity for MAO-B at higher doses; however, clinical data show no evidence of cheese reactions. Rasagiline is effective both as monotherapy and as an adjunct to levodopa.

Selegiline

Efficacy

The DATATOP trial examined the effects of selegiline, tocopherol, their combination, and placebo on progression of disability in 800 patients with early, untreated Parkinson's disease. Selegiline was associated with an approximate 9-month delay in the emergence of disability requiring levodopa therapy, representing a 57% reduction in the risk of starting levodopa during the first year of treatment. In an extension of DATATOP, 368 patients from the original DATATOP study who started levodopa therapy were given the option to continue selegiline as adjunctive therapy or be switched to matching placebo. During a mean follow-up of 2 years, patients treated with selegiline were significantly less likely to experience the on-off phenomenon or freezing of gait, but significantly more likely to experience dyskinesia. Selegiline did not improve the wearing-off phenomenon. However, patients receiving selegiline did have significantly lower Unified Parkinson's Disease Rating Scale (UPDRS) total, activities of daily living (ADL), and motor scores, and levodopa dosages and dopamine agonist use were significantly reduced in the selegiline group. In DATATOP and its extension study, it was impossible to distinguish between potential disease-modifying (i.e., neuroprotective) and symptomatic benefits of treatment.

The DATATOP results, along with those from several earlier studies, demonstrated a modest symptomatic benefit with selegiline; however, a 782-patient clinical trial conducted by the Parkinson's Disease Research Group of the United Kingdom (PDRG-UK) found that the addition of selegiline to ongoing levodopa therapy provided no additional clinical benefit and was, in fact, associated with increased motor complications and increased mortality. However, a 157-patient, randomized, placebo-controlled Swedish study of selegiline's long-term effects when used in early Parkinson's disease either as monotherapy or in combination with levodopa showed that at 7 years, selegiline-treated patients had slower disease progression than their placebo-treated counterparts as measured by UPDRS score. This outcome was found for the selegiline monotherapy group as well as the selegiline-levodopa combination group. In general, the benefits of selegiline should be weighed against the potential risks.

Neuroprotective Potential

Selegiline, in addition to its symptomatic effects, has shown neuroprotective effects in several preclinical experiments. In animal models of MPTP-induced parkinsonism, pretreatment with selegiline prevented neurodegeneration in MPTP-treated rodents and nonhuman primates. In vitro, selegiline reduced oxidative stress associated with MAO-B–mediated dopamine metabolism and glutamate-induced toxicity. Selegiline has shown a capacity to prevent apoptosis by altering expression of the genes for pro- and antiapoptotic proteins, with the result that mitochondrial integrity is preserved during oxidative stress. However, selegiline's amphetamine metabolites, L-amphetamine and L-methamphetamine, have proven neurotoxic in vitro and in vivo models. These neurotoxic effects may neutralize the neuroprotective effects of selegiline that have been observed in experimental models and may also compromise its safety in patient populations.

Safety

Throughout the DATATOP study, no significant differences were noted between selegiline and placebo in the frequency of adverse events, serious adverse events, cardiovascular adverse events, treatment discontinuations, or mortality. However, long-term postmarketing data have revealed that psychiatric and vasoreactive adverse effects (e.g., hallucinations and orthostatic hypotension) are frequently reported in patients treated with selegiline, particularly in combination with levodopa. Moreover, the PDRG-UK study found that combined levodopa and selegiline was accompanied by a substantial increase in motor adverse effects and a 60% increase in mortality during a mean follow-up of 5.6 years. However, a population-based survey of more than 12,000 patients with Parkinson's disease in the United Kingdom found a nonsignificant 14% increase in the risk of
mortality among patients treated with selegiline monotherapy and a nonsignificant 10% increase in patients treated with combined levodopa-selegiline therapy.47 These safety issues have been attributed in part to the amphetamine metabolites of selegiline and potential cardiovascular effects.48 In rats, long-term oral administration of selegiline decreased systolic and diastolic blood pressure and mean arterial pressure. Administration of L-methamphetamine induced profound depressor response, reduced carotid blood flow, and increased carotid vascular resistance.48 In human volunteers, administration of amphetamine and methamphetamine was associated with reductions in systolic blood pressure.49 In two studies involving a total of 45 patients with Parkinson's disease, severe orthostatic hypotension occurred during head-tilt tests in 15 patients treated with levodopa plus selegiline, including four who experienced loss of consciousness with unrecordable blood pressure. Normal protective increases in pulse rate and plasma noradrenaline concentrations were impaired in these patients. Cardiovascular adverse events in these studies may be attributed at least in part to a toxic effect of selegiline's amphetamine metabolites. In a study to evaluate the effect of selegiline on blood pressure in patients with advanced Parkinson's disease, 14 patients receiving long-term selegiline underwent an orthostatic test before and after selegiline withdrawal. After a 4-week washout from selegiline, orthostatic changes were diminished compared with those before washout. This suggests that selegiline treatment enhances orthostatic hypotension.50

Currently, selegiline may be recommended (AAN support level C; Table 1) as adjunctive therapy for patients with Parkinson's disease who are receiving optimized dopaminergic treatment and are experiencing motor complications.51 The ODT formulation of selegiline was developed in an effort to improve selegiline's efficacy:safety ratio. Because selegiline ODT is absorbed in the mouth and first-pass hepatic metabolism is minimized, higher selegiline concentrations in the brain are achieved and a 3–10-fold reduction in the generation of L-amphetamine and L-methamphetamine metabolites occurs. This makes a 4- or 5-fold reduction in selegiline dosage possible.

The published clinical data on selegiline ODT's efficacy and safety are limited to small studies of levodopa-treated patients experiencing motor fluctuations. In a 12-week trial, 140 patients with significant daily "off" time despite optimized treatment with levodopa were randomly assigned to receive selegiline ODT 1.25 mg/day or placebo for 6 weeks, after which patients in the selegiline ODT group were switched to 2.5 mg/day for another 6 weeks (Figure 1).52 The mean percentage reductions in

<table>
<thead>
<tr>
<th>Support Level</th>
<th>Definition</th>
<th>Evidence Requirement</th>
<th>Drug Recommendations*</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Established as effective, ineffective, or harmful for the given condition in the specified population</td>
<td>At least two consistent class I studies</td>
<td>Entacapone and rasagiline should be considered to reduce “off” time</td>
</tr>
<tr>
<td>B</td>
<td>Probably effective, ineffective, or harmful for the given condition in the specified population</td>
<td>At least one class I study or two consistent class II studies</td>
<td>Pramipexole, ropinirole, and tolcapone should be considered to reduce “off” time. Tolcapone should be used with caution and requires monitoring due to potential hepatotoxicity</td>
</tr>
<tr>
<td>C</td>
<td>Possibly effective, ineffective, or harmful for the given condition in the specified population</td>
<td>At least one class II study or two consistent class III studies</td>
<td>Apomorphine, cabergoline, and selegiline may be considered to reduce “off” time. Sustained-release carbidopa-levodopa and bromocriptine should not be used to reduce “off” time</td>
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<td>U</td>
<td>Data inadequate or conflicting given current knowledge; treatment is unproven</td>
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*Information on pergolide was omitted because the drug was discontinued in the United States due to cardiac valvulopathy.

Adapted from reference 52.
“off” time at weeks 4–6 and 10–12 were 9.9% and 13.2%, respectively. The reduction in “off” time at weeks 10–12 was significantly superior compared with placebo (-7%, p<0.001). Dyskinesia-free “on” time was significantly improved with selegiline ODT compared with placebo. A limitation of the study was the lack of a conventional selegiline arm, which would have made it easier to gauge the relative efficacy of the two selegiline formulations. The most frequent drug-related adverse events associated with selegiline ODT were dizziness (six cases) and dyskinesia, hallucinations, headache, and dyspepsia (four cases each). No significant differences were noted between selegiline ODT and placebo with respect to total adverse effects, serious adverse effects, or treatment discontinuations.

Selegiline ODT 2.5 mg was assessed in an open-label extension study. The 254 patients in this study had completed either of two large, phase III, double-blind studies. Patients were evaluated for “off” time, as well as for safety end points (which included a cohort that received 1.25-mg ODT). The mean reductions in “off” time were 9.4% (1.6 hrs) for patients previously given selegiline ODT, 6.0% (1.2 hrs) for patients who switched to selegiline ODT from placebo, and 8.1% (1.4 hrs) overall. No severe adverse events were attributed to selegiline ODT or required discontinuation of the drug.

Rasagiline
Efficacy

The efficacy of rasagiline monotherapy was examined in the Rasagiline (TVP-1012) in Early Monotherapy for Parkinson’s (TEMPO) study, a randomized, double-blind, placebo-controlled study comparing early versus delayed initiation of rasagiline in patients with Parkinson’s disease who had not yet required dopaminergic therapy. A total of 404 patients received rasagiline 1.0 or 2.0 mg/day or placebo for 6 months, after which the placebo group (the delayed-start group) was switched to rasagiline 2.0 mg/day for the remainder of the study. After 6 months, the adjusted treatment effect for total UPDRS score was -4.2 units for rasagiline 1.0 mg and -3.56 units for rasagiline 2.0 mg versus placebo (p<0.001 for each comparison). Patients receiving active treatment showed significant improvements in Parkinson’s Disease Quality of Life Scale scores compared with the placebo group, particularly in items assessing self-image or sexuality and Parkinson’s disease symptoms. The effect size for rasagiline treatment was modest but similar to that observed with a group receiving levodopa 150 mg–carbidopa 37.5 mg (in three divided doses) in the Early versus Late Levodopa in Parkinson Disease (ELLDOPA) study. After 1 year of treatment, mean adjusted effect size for total UPDRS score was -2.3 units for the early-start rasagiline 2.0-mg group versus the delayed-start group. The effect size was -1.82 units for the rasagiline 1.0-mg group compared with the delayed-start group (Figure 2).

These results suggest that rasagiline, in addition to its symptomatic benefits, may alter the course of Parkinson’s disease. If the benefits of treatment were exclusively symptomatic, then delaying treatment would not be expected to have a long-term negative effect on outcomes. Patients in the delayed-start group should “catch up” to patients receiving rasagiline throughout the study. This was not the case, as differences in UPDRS-rated progression favored the early treatment arm throughout the study. In view of these findings, investigators initiated the Attenuation of Disease Progression with Azilect Once Daily (ADAGIO) study, a multicenter, multinational, long-term, prospective, double-blind, placebo-controlled, delayed-start trial. Begun in 2005, the ADAGIO study will further investigate potential disease-modifying effects of rasagiline in patients with early Parkinson’s disease. Preliminary results are anticipated in 2009.

Rasagiline is currently recommended (AAN support level A; Table 1) for adjunctive therapy in patients with Parkinson’s disease to reduce “off” time associated with motor fluctuations. The efficacy and safety of adjunctive rasagiline were demonstrated in the Parkinson’s Rasagiline:}
Efficacy and Safety in the Treatment of “Off” (PRESTO) and the Lasting Effect in Adjunct Therapy with Rasagiline Given Once Daily (LARGO) studies. In the PRESTO study, 472 patients with Parkinson’s disease with 2.5 hours or more of daily “off” time despite optimized dopaminergic treatment were randomly assigned to rasagiline 0.5 mg/day, rasagiline 1.0 mg/day, or placebo for 26 weeks. The mean daily “off” time decreased from baseline by 1.41 hours (23%) for the rasagiline 0.5-mg arm, by 1.85 hours (29%) for the rasagiline 1.0-mg arm, and 0.91 hour (15%) for the placebo arm. Both rasagiline dosages improved Clinical Global Impression (CGI) ratings, UPDRS ADL scores during “off” time, and UPDRS motor scores during “on” time compared with placebo. Patient-rated quality of life, assessed using the Parkinson’s Disease Quality of Life scale summary score, showed a nonsignificant trend toward improvement in the rasagiline 0.5-mg group.

In the LARGO study, rasagiline was compared with the COMT inhibitor entacapone and placebo. In this double-blind, multicenter trial, 687 patients with Parkinson’s disease who had motor complications despite optimized levodopa-carbidopa treatment were randomly assigned to receive rasagiline 1.0 mg/day, entacapone 200 mg with each levodopa dose, or placebo for 18 weeks. Rasagiline was associated with a significant 0.78-hour reduction in daily “off” time compared with placebo (-1.18 vs -0.4 hrs, p=0.0001); entacapone was associated with a 0.80-hour reduction versus placebo (-1.20 hrs, p<0.0001). Both treatments increased daily “on” time without troublesome dyskinesia by an average of 0.85 hour compared with placebo. Improvements in CGI ratings were significant with rasagiline (-0.86, p<0.0001) and entacapone (-0.72, p=0.0002) compared with placebo (-0.37). Rasagiline and entacapone were associated with significant improvements in UPDRS scores for ADL and motor function during “on” time. However, only rasagiline was associated with significant improvements in UPDRS-rated freezing of gait, postural instability and gait disturbance, and motor performance during “off” periods.

These trials demonstrate that rasagiline improves clinical outcomes in patients with early Parkinson’s disease and reduces “off” time in patients with moderate-to-severe Parkinson’s disease who are experiencing motor fluctuations despite optimized levodopa therapy. As adjunctive therapy, once-daily rasagiline simplifies treatment and is at least as effective as entacapone at reducing “off” time. Subanalyses of the TEMPO and PRESTO trials revealed no significant effect of age on efficacy, suggesting similar efficacy in patients aged 70 years or older and those younger than 70 years.

Neuroprotective Potential

Rasagiline, in addition to its symptomatic benefits, has shown neuroprotective effects in several preclinical experiments. In animal models of MPTP-induced parkinsonism, pretreatment with rasagiline inhibited degeneration of dopaminergic nigral cells from MPTP-treated mice and nonhuman primates. In non-Parkinson’s disease models, rasagiline has shown neuroprotective effects in experimental focal ischemia in rats, postnatal anoxia in rats, hypoxia in rats, amyotrophic lateral sclerosis in mice, and closed-head injury in mice. Rasagiline prevented stroke and improved stroke outcomes in stroke-prone hypertensive rats, also, it reduced paraventricular hypothalamic neurodegeneration and prevented ventricular

Figure 2. Unified Parkinson’s Disease Rating Scale (UPDRS) scores for three rasagiline dosage groups. (A) Total unadjusted UPDRS score by visit for the 371 patients included in the efficacy cohort, last observation carried forward for any missing data. (B) Unadjusted UPDRS score by visit for the 249 patients who completed 52 weeks of treatment without starting additional therapy. Data are mean scores; error bars are ± standard error. (Adapted with permission from reference 56.)
In experimental models of Parkinson's disease, rasagiline protected dopaminergic cells and cerebellar granule cells from challenges with 6-hydroxydopamine, N-methyl-(R)-salsonol, and N-morpholino sydonime. Rasagiline protected cultured cells against glutamate-induced toxicity, which has been implicated in Parkinson's disease-induced neurodegeneration. Rasagiline has also shown neuroprotective effects against a variety of insults in cultured nerve growth factor–differentiated rat pheochromocytoma PC-12 cells, fetal human and rat mesencephalic neurons, rat hippocampal neurons, and rat cerebellar granule cells.

Rasagiline-mediated neuroprotection in the MPTP model was directly attributable to inhibition of MAO-B, which is known to mediate the biotransformation of MPTP into the neurotoxin MPP+. However, rasagiline exhibits neuroprotective effects not related to MAO-B inhibition. This is apparent from experiments showing that the S-enantiomer of rasagiline, which is 1000 times less active than the R-isomer as an MAO-B inhibitor, is nevertheless neuroprotective in cell lines under a variety of challenges. Rasagiline has also been neuroprotective at concentrations below the threshold for MAO-B inhibition and in cell lines not expressing MAO-B. The neuroprotective effects of rasagiline are dose dependent and are more pronounced than those of selegiline. Moreover, the rasagiline metabolite aminoindan, unlike the amphetamine metabolites of selegiline, is not neurotoxic, thus, it is unlikely to confound any neuroprotective effects of rasagiline. In fact, aminoindan has shown neuroprotective activity in some specific cellular systems, although not in others.

The mechanisms whereby rasagiline exerts neuroprotective effects appear to be multifactorial, with antiapoptotic and antioxidant mechanisms playing central roles. Rasagiline has been shown to prevent apoptosis by preserving mitochondrial membrane integrity. During mitochondrial-induced apoptosis, a neurotoxic challenge alters mitochondrial membrane permeability in such a way as to open the mitochondrial permeability transition pore complex. Rasagiline binds to this complex, preventing induction of proapoptotic catalysts (caspase 3, glyceraldehyde-3-phosphate dehydrogenase, mitochondrial cytochrome C, and polyadenosine 5′-diphosphate-ribose polymerase). Rasagiline activates antiapoptotic proteins such as Bcl-2, Bcl-XL, and protein kinase C, and also downregulates proapoptotic proteins such as Bad and Bax.

Rasagiline has been shown to increase expression of glial cell line–derived neurotrophic factor, a selective neurotrophic factor that promotes the survival of dopaminergic neurons, and to suppress oxidative stress in dopaminergic neurons by increasing expression of antioxidant enzymes such as superoxide dismutase and catalase.

### Safety

Rasagiline, unlike selegiline, is not a propargyl amphetamine derivative, and therefore, amphetamine-like adverse effects are eliminated. The overall rates of adverse events did not differ significantly between active treatment and placebo in the TEMPO or LARGO studies. Adverse events were more frequent with rasagiline than with placebo in the PRESTO study (p=0.02), but events occurring more often with rasagiline were primarily gastrointestinal and dose related.

In the TEMPO, LARGO, and PRESTO studies, no significant differences were noted between rasagiline and placebo with respect to serious adverse events or treatment discontinuations. Rasagiline and placebo did not significantly differ in their effect on blood pressure or pulse rate, with the exception of a slight but statistically significant increase in standing systolic blood pressure with rasagiline 2.0 mg/day in the TEMPO study. Adverse events typically associated with dopaminergic therapy (e.g., dizziness, postural hypotension, confusion, hallucinations, and somnolence) were no more common with rasagiline than with placebo.

In the PRESTO study, the occurrence of dyskinesia was significantly greater with rasagiline 1.0 mg than with placebo; however, no patient discontinued treatment due to dyskinesia.

Melanoma was diagnosed in one patient in the TEMPO study and in three in the PRESTO study. All had been randomly assigned to rasagiline, but the diagnosis was made before the start of treatment in one patient. The PRESTO investigators concluded that melanoma in these patients was more likely to be related to an increased risk in patients with Parkinson's disease in general than to a specific treatment effect. (This conclusion, in fact, reflects those of more recent examinations of the association between melanoma and Parkinson's disease.)

Substudies of the TEMPO and PRESTO trials...
(TEMPO, PRESTO, and LARGO were conducted without dietary tyramine restrictions) found no significant effect of tyramine challenge on blood pressure parameters in patients receiving rasagiline alone or as adjunctive therapy, nor did rasagiline adversely affect UPDRS-rated cognitive function, behavior, or mood.

Age had no effect on the tolerability of rasagiline versus placebo in the TEMPO and PRESTO studies. Serious adverse events—orthostatic hypotension (during monotherapy) and hallucinations—occurred more frequently in patients aged 70 years or older, but this was irrespective of whether they received active treatment or placebo.

Results of a Parkinson Study Group investigation found that the rate of serotonin syndrome in patients treated with selegiline and an SSRI was 0.24%, with 0.04% experiencing a serious reaction. In the PRESTO trial with rasagiline, however, no significant difference was noted in adverse-event rates between rasagiline-treated patients receiving concomitant SSRIs and those not receiving SSRIs. Likewise, in a more recent safety analysis of 316 patients (23.2%) with Parkinson's disease who took an antidepressant concomitantly with rasagiline in a total cohort of 1361 patients with Parkinson's disease who ever took rasagiline in controlled clinical trials, no unexpected adverse events or any evidence of serotonin toxicity was noted. The most common antidepressant exposures were to amitriptyline, sertraline, paroxetine, trazodone, and citalopram.

Rasagiline is metabolized through the cytochrome P450 (CYP) 1A2 pathway; hence, a CYP1A2 inhibitor such as ciprofloxacin, fluvoxamine, or cimetidine may increase rasagiline concentrations, whereas potent CYP1A2 inducers such as omeprazole may reduce rasagiline concentrations. The clinical significance of these interactions has not been determined. Rasagiline does not inhibit or induce the CYP1A2, 2A6, 2C9, 2C19, 2D6, 2E1, 3A4, or 4A pathways; hence, it is not likely to affect substrates of these CYP isoenzymes.

Overall, rasagiline has been well tolerated in clinical trials and has not been associated with increased risk of vasoreactive and psychiatric adverse effects, a finding that distinguishes rasagiline from both selegiline and dopaminergic therapies. The long-term safety and tolerability of rasagiline will require confirmation by results of ongoing long-term clinical studies.

**Safinamide**

Currently in phase III development, safinamide is an α-aminoamide derivative that may combine MAO-B inhibition with dopamine reuptake inhibition. In a recently reported phase III trial, 270 patients with early Parkinson's disease who were receiving a stable dose of a dopamine agonist were randomly assigned to add safinamide 50–100 mg/day, safinamide 150–200 mg/day, or placebo to their ongoing therapy. Addition of safinamide 50–100 mg was associated with significantly greater improvement in UPDRS part III motor scores compared with placebo (6.0 vs 3.6 units, p=0.0419). Improvements in UPDRS part II ADL scores were also superior with safinamide 50–100 mg (-2.2+ vs -1.2+, p=0.0248). Compared with dopamine agonist monotherapy, addition of safinamide was associated with improvements in measures of cognitive function (including working memory), strategic target detection, and auditory number sequencing. Safinamide 150–200 mg conferred no additional benefit compared with the 50–100-mg doses. Adverse effects were similar in the safinamide and placebo groups. A 1-year extension of this study is ongoing, and a second phase III trial of safinamide in patients with moderate-to-severe Parkinson's disease who are experiencing motor fluctuations despite levodopa therapy was begun in November 2006. Safinamide may represent an alternative to currently available therapies as an adjunct to levodopa or dopamine agonists in patients with Parkinson's disease.

**Conclusion**

The possibility of neuroprotection features prominently in the most recent practice parameter of the AAN. Although it concludes that no treatment has yet been shown conclusively to be neuroprotective, it points out that the effect of rasagiline in a delayed-start study was compatible with a neuroprotective effect. This underscores the potential of MAO-B inhibition to help reach the goal of neuroprotection in Parkinson's disease. The second-generation MAO-B inhibitor rasagiline, which has greater potency and less potential for toxicity than selegiline, is a safe, effective option for the management of Parkinson's disease symptoms in early and advanced Parkinson's disease and in treated and untreated patients, irrespective of age. In addition, the new selegiline ODT formulation
allows pregastric absorption of the agent, thus minimizing first-pass metabolism, and thereby increasing selegiline bioavailability and reducing the concentration of amphetamine metabolites. However, selegiline ODT monotherapy in patients with early Parkinson's disease has not yet been studied.

Recent developments in the use of selective MAO-B inhibitors (particularly rasagiline and selegiline ODT) as a treatment option in patients with Parkinson's disease represents an important step. Clinicians should be aware of these developments (e.g., symptomatic effects, safety) concerning MAO-B inhibitors. Each of these agents has a role in the management of Parkinson's disease. Rasagiline should be a consideration for the management of patients throughout the disease spectrum, from early to advanced disease (levodopa-treated patients with motor fluctuations). Since no data are available for selegiline ODT in early Parkinson's disease, it should only be considered for management of levodopa-treated patients experiencing motor fluctuations. Additional delineation or refinement of the role of MAO-B inhibitors in the management of Parkinson's disease are anticipated with the completion of the ADAGIO disease modification study.

References


