Early Pharmacologic Treatment in Parkinson's Disease

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Abstract

Early treatment of Parkinson's disease (PD) affords an opportunity to forestall clinical progression. Levodopa is the most effective treatment for PD motor signs and symptoms, but its use is associated with the development of motor fluctuations and dyskinesias. Because of this, levodopa use is commonly withheld until the patient experiences functional disability. Other medications are available for the treatment of early PD and can be initiated at or near the time of diagnosis. Monoamine oxidase type B (MAO-B) inhibitors provide mild symptomatic benefit, delay the need for levodopa, are very well tolerated, and may provide long-term disease-modifying effects. Dopamine agonists provide moderate symptomatic benefit, delay the need for levodopa, and cause fewer motor complications than levodopa. Compared with levodopa, however, dopamine agonists cause more somnolence and sudden-onset sleep as well as impulse control disorders. The treatment of early PD depends in part on the individual patient's anticipated risk of side effects and the degree of motor improvement required. Physicians should also consider the early use of MAO-B inhibitors in light of their very good tolerability and the recent evidence suggesting long-term disease-modifying effects.

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For author information and disclosures, see end of text.

Introduction

The devastating impact of Parkinson's disease (PD) on the lives of patients is well known and widespread. Up to 1 million people in the United States are believed to have PD, with onset typically occurring in patients over the age of 50 years.[1] For many years, first-line pharmacologic treatment of PD consisted of levodopa to increase brain dopamine concentrations. It is administered with a dopa decarboxylase inhibitor (DDI) to minimize adverse effects (eg, nausea) by limiting the peripheral metabolism of levodopa.[2] Nevertheless, levodopa treatment is associated with significant adverse events, specifically motor fluctuations and dyskinesias (even when accompanied by a DDI), and is commonly withheld until functional disability emerges and the benefits of treatment outweigh the side effects. Delaying treatment, however, means that the potential benefits that may accrue as a result of early treatment, whether in terms of reducing symptoms or even slowing disease progression, are largely missed.

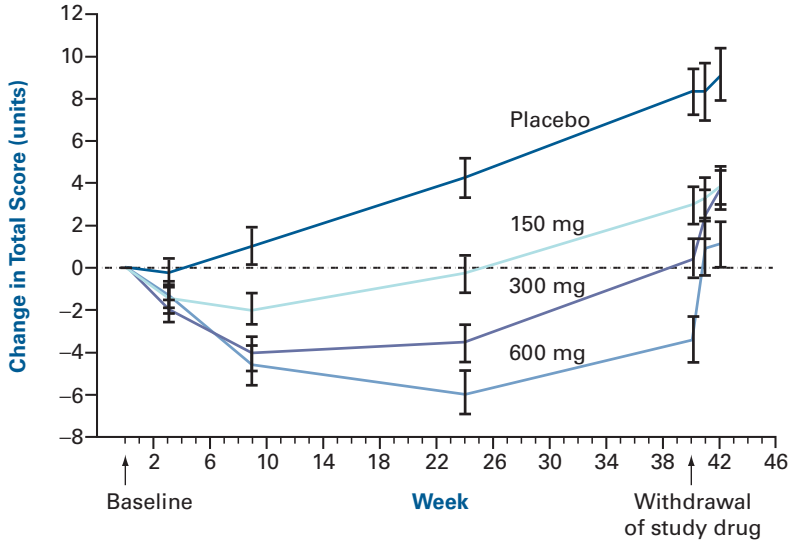
Emerging clinical trial data point to the potential of certain agents to delay functional symptoms and possibly slow the evolution of PD. Early treatment of PD offers the opportunity to forestall clinical progression.[3] The implications of slowing disease progression are enormous, comprising additional time in the lives of PD patients in which symptoms are reduced and the descent into profound morbidity is, at least for a time, delayed. Early treatment of PD may decrease the costs of treatment with consequent effects on the economic burden to patients, families, and the larger society.[4] The potential to reduce symptoms and the possibility of slowing disease progression is contingent upon an understanding of the relative benefits of pharmacologic therapies in the context of early PD treatment. The present article will review pharmacologic options for early treatment of PD and discuss the relevant clinical guideline recommendations.

Neuroprotection/Disease Modification

Ideally, early treatment of PD would confer a neuroprotective effect. Limited evidence has hinted at the possibility of a neuroprotective effect with several agents for the treatment of PD, but none have been definitively proven to possess such properties.

The notion of neuroprotection is distinct from that of disease modification in that the former implies an alteration of the pathophysiology of the disease, whereas the latter implies an effect

Figure 1. Change in UPDRS from Baseline to Week 42 in the ELLDOPA Study[7]



ELLDOPA indicates Earlier versus Later Levodopa Therapy in Parkinson's Disease; UPDRS, Unified Parkinson's Disease Rating Scale.
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upon clinical outcome without necessarily affecting the disease pathophysiology.[5] That said, a definitive and clinically practical means of measuring neuroprotection remains an area of considerable debate. A slowed rate of neuron loss is the most accurate method of doing so, but this is not currently possible in PD.[6]

Secondary means of measuring neuroprotection involve applying clinical assessment instruments to evaluate the change in various domains of PD deterioration, including motor impairment, disability, and quality of life. Other potential markers for neuroprotection include time to a given event (eg, delay of levodopa initiation, death), radionuclide positron emission tomography (PET), or single photon emission computed tomography (SPECT).[5,6] None of these approaches, however, have been validated as a reliable means of measuring neuroprotection.

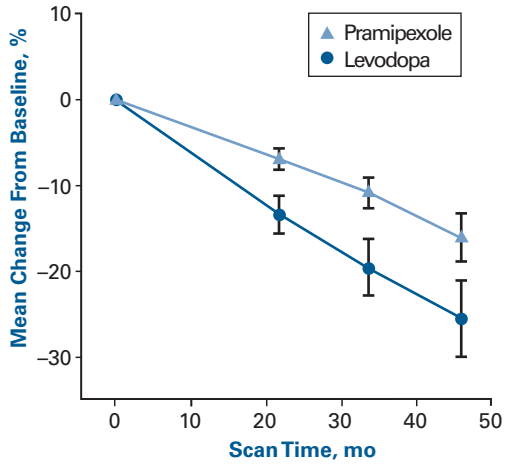
Levodopa

The key clinical trial examining possible neuroprotective or disease-modifying properties of levodopa is the Earlier versus Later Levodopa Therapy in Parkinson Disease (ELLDOPA) study, conducted by the Parkinson Study Group.[7] This was a randomized, double-blind trial in 361 patients with early PD. Patients received 1 of 3 doses of levodopa/carbidopa (150/37.5 mg, 300/75 mg, or 600/150 mg given in 3 divided doses) or placebo for 40 weeks followed by a 2-week washout period.[7] The primary outcome of the study was change in Parkinson's severity from baseline to week 42, as measured by the Unified Parkinson's Disease Rating Scale (UPDRS).[7] A preplanned substudy was also conducted; at baseline and week 40, SPECT with radiolabeled 2beta-carbomethoxy-3beta-(4-[125I]iodophenyl)tropane (ß-CIT) was used to determine the effect of treatment on dopamine-transporter density. ß-CIT uptake is a potential biomarker for dopamine neuronal status.

The results showed that treatment with levodopa was significantly better than placebo at reducing worsening of Parkinson's symptoms in a dose-dependent manner (**Figure 1**). Patients given placebo experienced a gradual worsening from baseline in UPDRS scores. All 3 levodopa doses were associated with rapid improvement; scores did not return to baseline values until approximately week 25 with the 150-mg dose, week 38 with the 300-mg dose, and week 41 with the 600-mg dose (ie, with the 600-mg dose, a week after cessation of therapy during which the UPDRS scores rapidly deteriorated).[7] At week 42 (following a 2-week washout), patients in all 3 levodopa groups demonstrated significantly less (P <.001) worsening of symptoms from baseline to end point compared with those given placebo.

In apparent contrast to these results, the dopamine transporter substudy showed that patients given levodopa experienced a greater decrease in ß-CIT uptake than patients given placebo, a difference that was significant (P = .036) when 19 patients in the study who proved not to have a dopaminergic deficit were excluded.[7] The implications of these data are uncertain. At face value, the clinical results are consistent

Figure 2. Change from Baseline in ß-CIT Striatal Uptake[8]



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with a neuroprotective effect of levodopa, but the imaging results suggest a possible neurotoxic effect. However, it is possible that neither of these 2 interpretations is correct. A 2-week washout of levodopa may be insufficient to resolve all symptomatic benefit (due to the "long-duration response"), and the difference in outcome between placebo and levodopa groups might disappear if the subjects were followed for a longer time. In addition, it may be that levodopa affects dopamine transporter imaging, either through a pharmacologic or compensatory mechanism, thereby rendering this imaging modality invalid as a measure of disease progression. Thus, it is possible that levodopa has no effect on the rate of progression of the underlying disease.

Dopamine Agonists

A limited number of studies have sought to evaluate possible neuroprotective effects of dopamine agonists in the treatment of PD. ß-CIT imaging was used in a subset of subjects participating in the CALM-PD (Comparison of the Agonist Pramipexole With Levodopa on Motor Complications of Parkinson's Disease) study, conducted by the Parkinson Study Group prior to the ELLDOPA study. This study in 82 patients with early PD compared initial treatment with pramipexole to initial treatment with levodopa/carbidopa.[8] The primary outcome was change in SPECT-evaluated ß-CIT striatal uptake at 46 months. Disease severity was also evaluated using the UPDRS prior to each imaging interval when patients had been off the study drug for 12 hours.[8] At 46 months, the rate of decline in ß-CIT striatal uptake was significantly less in the pramipexole group compared with the levodopa group; the decline from baseline was 16.0% versus 25.5%, respectively (P = .01)[8] (**Figure 2**). However, at 22 months, patients assigned to initial treatment with levodopa had significantly better total and motor UPDRS scores than patients given pramipexole (P = .02 and P = .04, respectively). Significant superiority in UPDRS scores was no longer present at 34 months or 46 months.[8]

The REAL-PET (Requip as Early Therapy versus L-dopa–PET) study included 186 patients with early PD and compared the dopamine agonist ropinirole to levodopa over 2 years; the primary outcome was change in dopamine terminal function evaluated by PET imaging.[9] At 2 years, the imaging data showed significant decline with ropinirole compared with levodopa.[9] However, mean UPDRS motor scores worsenend by 0.70 from baseline to year 2 in the ropinirole group compared with an improvement of 5.64 in the levodopa group. Ropinirole also produced less dyskinesia and was associated with a longer time to the onset of dyskinesia.

The Parkinson's Disease Research Group of the United Kingdom (UK-PDRG) undertook a randomized, open-label trial in 782 patients with early PD that compared levodopa/DDI versus levodopa/DDI + the monoamine oxidase type B (MAO-B) inhibitor selegiline (deprenyl) versus bromocriptine over a study period of 5 years.[10] The outcome measures were mortality, disability measured with both the Hoehn and Yahr scale and the Webster scale, and adverse events. Bromocriptine was associated with fewer motor complications compared with levodopa/DDI as well as levodopa/DDI + selegiline, but bromocriptine-treated patients returned to baseline disability scores approximately 3 years after initiating therapy, which was 1 year earlier than those treated with levodopa.[10] Mortality rates were similar between groups.

Cabergoline was studied in a 3- to 5-year double-blind trial in 412 patients with early PD. Cabergoline monotherapy was first compared with levodopa, and then the combination of cabergoline and levodopa (once UPDRS scores decreased 30% below baseline) was compared with higher-dose levodopa monotherapy.[11] Cabergoline monotherapy was associated with less than half the rate of motor complications compared with levodopa, although the cabergoline + levodopa combination (ultimately involving 65% of the initial cabergoline monotherapy patients) was not better than levodopa alone for motor complications.[11]

Thus, the dopamine agonists appear to be associated with a lower incidence of dyskinesia but levodopa provides greater symptomatic benefit. In imaging studies, the dopamine ago-

nists pramipexole and ropinirole were associated with slower decline compared with levodopa, but this may be a function of greater compensatory or pharmacologic changes with levodopa compared with dopamine agonists and not a true indicator of disease progression.

Monoamine Oxidase Type B Inhibitors

Two Cochrane review publications analyzed clinical trial data with MAO-B inhibitors—primarily selegiline (deprenyl)—in early PD. A full discussion of these results is located below, but overall, the meta-analyses found that MAO-B inhibitors were effective in reducing motor fluctuations and disability, were neutral with regard to mortality, and reduced the need for levodopa. However, MAO-B inhibitors were not clearly associated with slowing disease progression.[12,13]

The effects of selegiline therapy on newly diagnosed PD were assessed in a double-blind, placebo-controlled study in 157 patients.[14] Patients were randomly assigned to receive either selegiline 10 mg or placebo once daily until levodopa therapy became necessary. Thereafter, selegiline (or placebo) was withdrawn for an 8-week washout period to evaluate the possible symptomatic effect of selegiline. Compared with placebo, selegiline therapy significantly delayed the need for levodopa (P = .028). However, after the washout period, no significant differences in worsening of disability were observed between the 2 groups, suggesting that besides having a slight symptomatic effect, selegiline may also have neuroprotective effects.

In the second phase of the study, 140 patients received selegiline 10 mg or placebo once daily in combination with individually tailored levodopa therapy.[15] Compared with placebo, selegiline slowed the progression of disease disability as measured by UPDRS total score (P = .003), motor score (P = .002), and activities of daily living score (P = .0002). After 5 years, the mean dose of levodopa was 19% higher for those given placebo compared with those given selegiline (P = .0002). Patients given selegiline had total UPDRS scores 26% better than those given placebo, and the mean difference in UPDRS total score was approximately 10 points. Results from both phases of this study, which comprised 7 years in total, suggest that selegiline delays the clinical progression of the signs and symptoms of PD. Two 5-year studies in patients with early PD reported similar results, suggesting an increasing benefit with selegiline over time.[16,17]

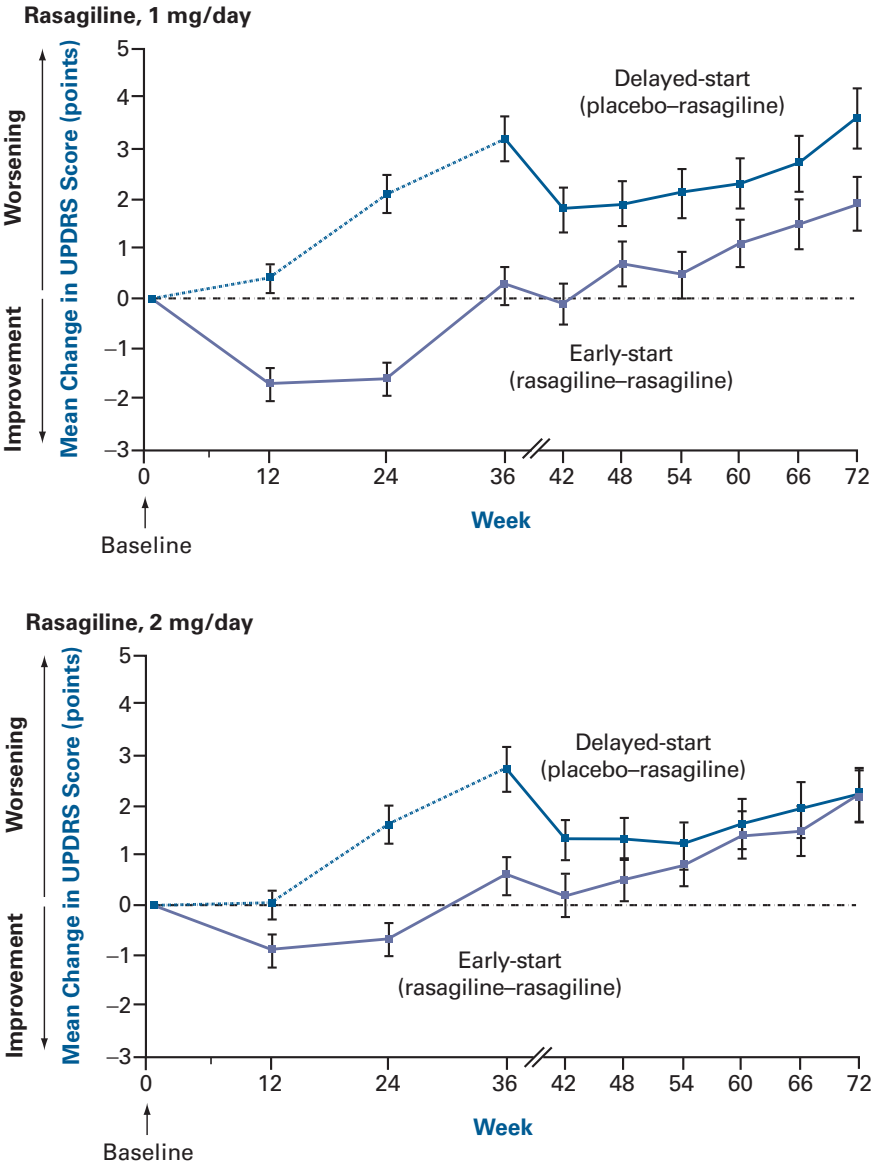
Two double-blind, delayed-start clinical trials of the MAO-B inhibitor rasagiline suggest a possible neuroprotective or disease-modifying effect. In delayed-start studies, one group is assigned to treatment for the entire study (early-start group) and another group is assigned placebo for the first phase of the study and active medication during the second phase of the study (delayed-start group). Both groups receive the same treatment in the second phase of the study and, therefore, should both experience the same symptomatic benefit. Any difference between groups at the end of the study should be due to enduring benefits accruing in the active-treatment group during the initial phase of the study (early-start group), separate from symptomatic improvement.[18]

The initial trial—the TEMPO (TVP-1012 in Early Monotherapy for Parkinson's Disease Outpatients) study—included 404 patients with early PD who received rasagiline 1 or 2 mg/day for 1 year or placebo for the first 6 months followed by rasagiline 2 mg/day for the following 6 months.[19] At 1 year, both early-start treatment groups demonstrated significantly better UPDRS scores than the delayed-start treatment group.[19] An open-label extension of the TEMPO study showed a sustained effect of less worsening in the early-start treatment group over a period of 5.5 years to 6.0 years, even as standard PD therapy was added over time.[20]

A 2009 study—the ADAGIO (Attenuation of Disease Progression with Azilect Given Once-daily) trial—sought to verify the results of TEMPO in a larger patient population with more stringent end points. ADAGIO involved 1176 untreated patients with PD who were given rasagiline 1 or 2 mg/day for 72 weeks or placebo for 36 weeks followed by rasagiline 1 or 2 mg/day for the next 36 weeks.[21] This allowed comparison of early versus delayed start for the 1-mg/day dose and early versus delayed start for the 2-mg/day dose. The outcome for a particular dose would be considered positive for the early-start group only if 3 outcomes were met: (1) superiority to placebo in the rate of change in the UPDRS score between weeks 12 and 36 (ie, less progression in the treated group in the first phase of the study); (2) superiority to delayed-start treatment in the rate of change in score between baseline and week 72 (a difference in change from baseline to the end of the study favoring the early-start group even as both groups were receiving active medication); and (3) noninferiority to delayed-start treatment in the rate of change in the score between weeks 48 and 72 (to demonstrate that the groups were not converging over the second phase of the study).[21]

The rasagiline 1-mg early-start treatment group achieved all 3 outcomes, while the 2-mg group achieved 2 of the end points (the early-start group did not demonstrate significant improvement at week 72 compared with baseline)[21] (**Figure 3**). Thus, the results of the 1-mg/day evaluation are consistent with a disease-modifying effect of rasagiline, while the results of the 2-mg/day evaluation are not. The reason for this discrepancy is not known. It has been

■ **Figure 3.** Change in UPDRS Scores From the ADAGIO Trials[21]



These 2 figures show both treatment groups and describe the results of the second and third primary end points defined in ADAGIO. The dashed lines show the placebo groups.
UPDRS indicates Unified Parkinson's Disease Rating Scale.
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suggested that the 2-mg/day dose provided greater symptomatic benefit and thereby masked the ability to detect a disease-modifying effect.[21] Although the ADAGIO 2-mg/day analysis was negative, the ADAGIO 1-mg/day evaluation, the TEMPO study, and the TEMPO long-term extension are all consistent with a disease-modifying effect of rasagiline. Additional results from the ADAGIO trial are located in the article by Chen[22] in this supplement.

Coenzyme Q10

A small, randomized, double-blind, parallel-group study in 80 patients with early PD examined the effect of 3 doses of coenzyme Q10 (300, 600, and 1200 mg) on UPDRS scores compared with placebo over 16 months.[23] Treatment with coenzyme Q10 trended toward a benefit in slowing symptoms compared with placebo, and with the 1200-mg dose, the difference was significant (P = .04).[23]

These data were promising, but required a larger trial for confirmation.

Storch et al subsequently conducted a somewhat larger (n = 131) 3-month, randomized, double-blind, placebo-controlled trial of coenzyme Q10 in a nanoparticle formulation (100 mg 3 times daily).[24] Patients included in the trial had no motor fluctuations and were on stable antiparkinsonian treatment for at least 4 weeks leading up to the trial. Patients in both groups (coenzyme Q10 or placebo) experienced significant improvements from baseline in UPDRS scores (P <.001 for placebo, P = .007 for coenzyme Q10), but the active-treatment group fared no better than placebo.[24]

The use of coenzyme Q10 in early untreated PD was also assessed in a randomized, double-blind, placebo-controlled futility clinical trial.[25] Coenzyme Q10 was administered as a 600-mg chewable wafer 4 times daily (2400 mg/day). The primary outcome measure was changes in total UPDRS score at 1 year. Although coenzyme Q10 could not be rejected as futile, the mean changes in total UPDRS scores were not significantly greater than the predetermined futility threshold value. Further studies are needed to determine the effect of coenzyme Q10 in early PD; a large phase 3 trial in collaboration with the National Institute of Neurological Disorders and Stroke is currently recruiting participants.[26]

Vitamin E (Tocopherol)

Tocopherol, the biologically active component of vitamin E, is an antioxidant that has been studied for possible disease-modifying properties in PD.[2] The DATATOP (Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism) study was a large clinical trial (n = 800) in which patients with early untreated PD were randomized to receive tocopherol, selegiline (deprenyl), a combination of both, or placebo.[27,28] After a mean follow-up of 14 months, tocopherol was observed to provide no meaningful benefit in the delay of the onset of disability.[27]

Early Symptomatic Treatment of Parkinson's Disease

Levodopa

Although levodopa is the most efficacious medication for PD, its propensity to cause adverse effects, especially dyskinesia, is an important reason to consider delaying its use if alternative treatments are able to adequately control symptoms. This is a particularly important consideration in younger patients who are most prone to developing disabling dyskinesia. Levodopa is associated with a high rate of motor fluctuations and dyskinesia and some risk of nausea and vomiting.[2,29] The Scottish Intercollegiate Guidelines Network (SIGN) states that levodopa can be considered in early PD, but that it should be given at the lowest effective dose and be accompanied by a DDI. Surveillance for dopamine dysregulation syndrome, somnolence and sudden-onset sleep, and impulse control disorders is also advised. The risk of adverse events notwithstanding, levodopa is the most effective medication for treating the signs and symptoms of PD. The effect of levodopa on progression of the underlying disease is uncertain; currently, there are no convincing data supporting neuroprotection or neurotoxicity.

Dopamine Agonists

The American Academy of Neurology (AAN) practice parameters for initiation of treatment in PD, published in 2002, found that while the dopaminergic therapies including levodopa, ropinirole, pramipexole, and cabergoline all improved motor disability and activities of daily living, levodopa was regarded as a generally superior therapy.[30] The AAN guidelines support the use of levodopa for patients requiring an improvement in motor disability and recommend dopamine agonist therapy for reducing the development of motor complications.[30]

A 2008 Cochrane meta-analysis of dopamine agonists for early PD, which included 29 clinical trials and 5247 patients in total, found that compared with levodopa, early treatment with a dopamine agonist was significantly less likely to result in dyskinesia (P <.00001), dystonia (P = .0002), or motor fluctuations (P = .002).[31] Nonmotor adverse effects, however, were more likely to occur with dopamine agonists, including edema (P <.00001), somnolence (P = .007), constipation (P = .01), dizziness (P = .01), hallucinations (P = .01), and nausea (P = .02).[31] Discontinuation of treatment was also more likely with dopamine agonists (P <.00001).[31]

The 2010 SIGN guidelines state that dopamine agonists (either an oral or transdermal formulation) "may be considered" for use in patients with early PD and motor symptoms. The National Collaborating Centre for Chronic Conditions (NCCCC) guidelines for PD management (supported by the United Kingdom's National Health Service) recommend dopamine agonists for symptomatic treatment of early PD. They further recommend titrating to an effective dose and switching to another dopamine agonist, or drug from a different class, should tolerability issues emerge. Ergot dopamine agonists are generally no longer used because of the risk of cardiac valvulopathy.

Nonetheless, the value of early treatment with dopamine agonists remains a matter of debate. Although they clearly delay the onset of dyskinesia, the long-term value of this benefit is unclear.[32,33] In addition, there is an increased awareness of potential side effects including somnolence and sudden-onset sleep, and impulse control disorders including

gambling, shopping, and Internet use.[34,35] The relative risk and benefit for individual patients must be considered.

Monoamine Oxidase Type B Inhibitors

As previously noted, the ADAGIO trial suggests that rasagiline 1 mg/day (but not the 2-mg/day dose) provides a disease-modifying effect in PD.[21] There was also a secondary end point in the ADAGIO trial: change in UPDRS score from baseline to the last measurement in phase 1 (ie, after the first 36 weeks, prior to the delayed-start treatment group switching from placebo to rasagiline).[21] In this case, both rasagiline 1 and 2 mg/day showed significant superiority to placebo in change of UPDRS score (P <.001 for both).[21] These data unambiguously delineate the clinical benefit of rasagiline compared with placebo. In addition, the side-effect profile of rasagiline 1 or 2 mg/day in the ADAGIO trial was not significantly different from placebo.[21] Rasagiline 1 mg/day, but not the 2-mg/day dose, is approved by the FDA for the treatment of PD.

A 2004 Cochrane review examined the efficacy of MAO-B inhibitors in early PD, an analysis that comprised 17 clinical trials (13 involving selegiline, 3 with lazabemide, and 1 with rasagiline) and included 3525 patients.[13] The data showed that MAO-B inhibitors were associated with a reduction in disability in early PD as well as a decreased need for levodopa and fewer motor fluctuations.[13] The impact of these agents on mortality was negligible, while their side-effect profile was relatively mild.

A subsequent Cochrane review, from 2005, included 10 clinical trials (9 with selegiline and 1 with lazabemide) and 2422 patients.[12] Within the rather narrow confines of this analysis, it was concluded that MAO-B inhibitors were associated with significant improvements in impairment and disability based on UPDRS scores, but that these improvements were not clinically significant.[12]

A Cochrane review from 2009 compared MAO-B inhibitors with levodopa and dopamine agonists in early PD, but found only 2 clinical trials (n = 593) worth considering (1 of which was not blinded).[36] MAO-B inhibitors were associated with fewer motor fluctuations compared with levodopa (odds ratio [OR], 0.55; 95% confidence interval [CI], 0.32-0.94) but not dopamine agonists (OR, 1.15; 95% CI, 0.65-2.05).[36] One of the 3 studies, which included 317 patients, found that the time to addition of levodopa was half as long in the MAO-B inhibitor group compared with the dopamine agonist group (15 months vs 30 months, respectively). In the second study, which involved 92 patients, the MAO-B inhibitor group was associated with a marginally longer delay of levodopa than the dopamine agonist group (29.5 vs 26.4 months, respectively).[36] There were fewer adverse event–related withdrawals with MAO-B inhibitors compared with dopamine agonists (OR, 0.11; 95% CI, 0.01-0.99; P = .05). The authors concluded that MAO-B inhibitors were more tolerable than the other drug classes but possessed weaker symptomatic efficacy.[36]

Because of the newness of some of the MAO-B inhibitor data, particularly from the ADAGIO trial, current available clinical guidelines lack consideration of key data that may otherwise influence their recommendations. That said, the AAN guidelines (from 2002) state that selegiline therapy may be considered prior to dopaminergic therapy for mild relief of symptoms.[30] The NCCCC and SIGN guidelines both concur that MAO-B inhibitors may be used for early symptomatic treatment of PD.[2,5]

Other Agents

Anticholinergics

The SIGN guidelines recommend against the use of anticholinergic agents as first-line therapy in PD due to elevated risk for cognitive and neuropsychiatric adverse events.[2] They should usually not be given to patients already exhibiting significant cognitive or neuropsychiatric comorbidities.

Amantadine

A lack of sufficient data regarding amantadine in the treatment of PD makes recommendations untenable, according to both the NCCCC and SIGN guidelines.[2,5]

Beta-Blockers

While there is insufficient evidence to offer recommendations for the use of beta-blockers in PD, the NCCCC guidelines noted that these drugs may be useful and safe in patients with PD suffering from postural tremor.[5]

Conclusion

Early treatment of PD offers the opportunity to forestall clinical progression. MAO-B inhibitors provide mild symptomatic benefit, are very well tolerated, and may provide long-term disease-modifying effects. Dopamine agonists provide moderate symptomatic efficacy and delay the onset of motor complications, but are associated with somnolence and sudden-onset sleep, and impulse control disorders. Levodopa, administered with a DDI, provides the greatest symptomatic benefit but is associated with the development of motor fluctuations and dyskinesias. The optimal selection of medications for each patient very much depends on their anticipated individual risk for side effects and need for symptomatic improvement.

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Authorship Information: Concept and design; analysis and interpretation of data; drafting of the manuscript; and critical revision of the manuscript for important intellectual content.

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REFERENCES

1. We Move. Overview of Parkinson's disease. New York, NY; 2010. http://www.wemove.org/par/par.html.pdf. Accessed February 9, 2010.

2. Scottish Intercollegiate Guidelines Network. Diagnosis and Pharmacological Management of Parkinson's Disease: A National Clinical Guideline. Edinburgh: SIGN; 2010.

3. Grosset DG, Schapira AH. Timing the initiation of treatment in Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 2008;79(6):615.

4. Haycox A, Armand C, Murteira S, Cochran J, François C. Cost effectiveness of rasagiline and pramipexole as treatment strategies in early Parkinson's disease in the UK setting: an economic Markov model evaluation. *Drugs Aging*. 2009;26(9):791-801.

5. National Collaborating Centre for Chronic Conditions. Parkinson's Disease: National Clinical Guideline for Diagnosis and Management in Primary and Secondary Care. London, England: Royal College of Physicians; 2006.

6. Suchowersky O, Gronseth G, Perlmutter J, et al. Practice parameter: neuroprotective strategies and alternative therapies for Parkinson disease (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2006;66(7):976-982.

7. Fahn S, Oakes D, Shoulson I, et al. Levodopa and the progression of Parkinson's disease. *N Engl J Med*. 2004;351(24):2498-2508.

8. Parkinson Study Group. Dopamine transporter brain imaging to assess the effects of pramipexole vs levodopa on Parkinson disease progression. *JAMA*. 2002;287(13):1653-1661.

9. Whone AL, Watts RL, Stoessl AJ, et al. Slower progression of Parkinson's disease with ropinirole versus levodopa: the REAL-PET study. *Ann Neurology*. 2003;54(1):93-101.

10. Lees AJ, Katzenschlager R, Head J, et al. Ten-year follow-up of three different initial treatments in de-novo PD: a randomized trial. *Neurology*. 2001;57(9):1687-1694.

11. Rinne UK, Bracco F, Chouza C, et al. Early treatment of Parkinson's disease with cabergoline delays the onset of motor complications. Results of a double-blind levodopa controlled trial. *Drugs*. 1998;55(suppl 1):23-30.

12. Macleod AD, Counsell CE, Ives N, et al. Monoamine oxidase B inhibitors for early Parkinson's disease. *Cochrane Database Syst Rev*. 2005;(3):CD004898.

13. Ives NJ, Stowe RL, Marro J, et al. Monoamine oxidase type B inhibitors in early Parkinsons's disease: meta analysis of 17 randomised trials involving 3525 patients. *BMJ*. 2004;329(7466):593-596.

14. Pålhagen S, Heinonen EH, Hägglund J, et al; Swedish Parkinson Study Group. Selegiline delays the onset of disability in de novo parkinsonian patients. *Neurology*. 1998;51(2):520-525.

15. Pålhagen S, Heinonen E, Hägglund J, et al; Swedish Parkinson Study Group. Selegiline slows the progression of the symptoms of Parkinson disease. *Neurology*. 2006;66(8):1200-1206.

16. Larsen JP, Boas J, Erdal JE. Does selegiline modify the progression of early Parkinson's disease? Results from a five-year study. The Norwegian-Danish Study Group. *Eur J Neurol*. 1999;6(5):539-547.

17. Przuntek H, Conrad B, Dichgans J, et al. SELEDO: a 5-year long-term trial on the effect of selegiline in early Parkinsonian patients treated with levodopa. *Eur J Neurol*. 1999;6(2):141-150.

18. D'Agostino RB Sr. The delayed-start study design. *N Engl J Med*. 2009;361(13):1304-1306.

19. Parkinson Study Group. A controlled, randomized, delayed-start study of rasagiline in early Parkinson disease. *Arch Neurology*. 2004;61(4):561-566.

20. Hauser RA, Lew MF, Hurtig HI, et al. Long-term outcome of early versus delayed rasagiline treatment in early Parkinson's disease. *Mov Disord*. 2009;24(4):564-573.

21. Olanow CW, Rascol O, Hauser R, et al. A double-blind, delayed-start trial of rasagiline in Parkinson's disease. *N Engl J Med*. 2009;361(13):1268-1278.

22. Chen JJ. Parkinson's disease: health-related quality of life, economic cost, and implications of early treatment. *Am J Manag Care*. 2010;16(4 suppl):S87-S93.

23. Shults CW, Oakes D, Kieburtz K, et al. Effects of coenzyme Q-sub-1-sub-0 in early Parkinson disease: Evidence of slowing of the functional decline. *Arch Neurol*. 2002;59(10):1541-1550.

24. Storch A, Jost WH, Vieregge P, et al. Randomized, double-blind, placebo-controlled trial on symptomatic effects of coenzyme Q10 in Parkinson disease. *Arch Neurol*. 2007;64(7):938-944.

25. NINDS NET-PD Investigators. A randomized clinical trial of coenzyme Q10 and GPI-1485 in early Parkinson disease. *Neurology*. 2007;68(1):20-28.

26. Clinicaltrials.gov. Effects of coenzyme Q10 (CoQ) in parkinson disease (QE3). http://clinicaltrials.gov/ct2/show/NCT00740714?term=qe3&rank=1. Accessed March 10, 2010.

27. Parkinson Study Group. Effects of tocopherol and deprenyl on the progression of disability in early Parkinson's disease. *N Engl J Med*. 1993;328(3):176-183.

28. Shoulson I. Deprenyl and tocopherol antioxidative therapy of parkinsonism (DATATOP). *Acta Neurologica Scandinavica Supplementum*. 1989;80(126):171-175.

29. Hauser RA, McDermott MP, Messing S. Factors associated with the development of motor fluctuations and dyskinesias in Parkinson disease. *Arch Neurol*. 2006;63(12):1756-1760.

30. Miyasaki JM, Martin W, Suchowersky O, Weiner WJ, Lang AE. Practice parameter: initiation of treatment for Parkinson's disease: an evidence-based review: report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2002;58(1):11-17.

31. Stowe RL, Ives NJ, Clarke C, et al. Dopamine agonist therapy in early Parkinson's disease. *Cochrane Database Syst Rev*. 2008;(2):CD006564.

32. Parkinson Study Group CALM Cohort Investigators. Long-term effect of initiating pramipexole vs levodopa in early Parkinson disease. *Arch Neurol*. 2009;66(5):563-570.

33. Hauser RA, Rascol O, Korczyn AD, et al. Ten-year follow-up of Parkinson's disease patients randomized to initial therapy with ropinirole or levodopa. *Mov Disord*. 2007;22(16):2409-2417.

34. Antonini A, Tolosa E, Mizuno Y, Yamamoto M, Poewe WH. A reassessment of risks and benefits of dopamine agonists in Parkinson's disease. *Lancet Neurol*. 2009;8(10):929-937.

35. Weintraub D, Koester J, Potenza MN, et al; DOMINION Study Group. Dopaminergic therapy and impulse control disorders in Parkinson's disease: top line results of a cross-sectional study of over 3,000 patients. Poster presented at: 12th International Congress of Parkinson's Disease and Movement Disorders; June 22-26, 2008; Chicago, IL.

36. Caslake R, Macleod A, Ives N, Stowe R, Counsell C. Monoamine oxidase B inhibitors versus other dopaminergic agents in early Parkinson's disease. *Cochrane Database Syst Rev*. 2009 Oct 7;(4):CD006661.