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Managing the patient with newly diagnosed Parkinson disease

■ ABSTRACT

The treatment of early Parkinson disease (PD) is generally symptomatic, although therapy that also offers neuroprotection in early-stage PD would be welcomed. Levodopa remains the most effective agent for relief of PD symptoms, but chronic levodopa therapy is associated with motor fluctuations and dyskinesias, and clinicians may therefore opt to postpone its use. Alternatives to levodopa in early PD include monoamine oxidase (MAO)-B inhibitors, amantadine, and dopamine agonists. MAO-B inhibitors have only mild symptomatic effects. Amantadine is associated with improvement in functional disability and, in a subset of PD patients, a robust symptomatic improvement. Dopamine agonists improve symptoms and may have a neuroprotective effect. Partial dopamine agonists, adenosine A_{2A}-receptor antagonists, and safinamide are symptomatic therapies that are under investigation. Neuroprotective strategies under study include enhancement of mitochondrial function, antiinflammatory mechanisms, calcium channel blockade, and uric acid elevation. Deep brain stimulation may slow cognitive and motor decline when used in early PD. Stem cell therapy and gene therapy are still under investigation.

Parkinson disease (PD) is a slowly progressive neurodegenerative disorder. Early PD, or stage 1 or 2 on the Unified Parkinson's Disease Rating Scale (UPDRS), is characterized by mild symptoms, minimal to mild disability, and lack of postural instability or cognitive decline. The goal of therapy in PD is to help patients retain functional independence for as long as possible. Therapeutic choices in early PD are guided by the effect of symptoms on function and quality of life, consideration of complications associated with long-term levodopa, the likelihood of response fluctuations to levodopa, and the potential for a neuroprotective effect.

■ SYMPTOMATIC THERAPIES IN EARLY PD

Dopaminergic replacement therapy with levodopa is a legitimate choice for the treatment of early PD. Use of carbidopa-levodopa has been shown to slow the progression of PD in a dose-dependent manner as evidenced by a decrease in total score on the UPDRS in patients with early PD who were randomly assigned to receive carbidopa-levodopa compared with those who received a placebo.[1]

Alternatives to levodopa

There are several reasons to choose an alternative to levodopa for the treatment of early PD. The first is to postpone the development of levodopa-induced dyskinesias, which are linked to duration of levodopa treatment and total exposure to levodopa. The second is postponement of the "wearing-off" effect; that is, the reemergence of symptoms that occurs in some patients before their next scheduled dose of levodopa. Such reasoning applies to early PD patients with minimal or no disability and—in particular—to young-onset PD patients who tend to develop vigorous dyskinesias and dramatic wearing-off phenomena. Pharmacologic alternatives to levodopa in early PD include monoamine oxidase (MAO)-B inhibitors, amantadine, and dopamine agonists.

MAO-B inhibitors. Two MAO-B inhibitors are approved by the US Food and Drug Administration for the treatment of PD: rasagiline and selegiline. These agents have a mildly symptomatic effect. In the Attenuation of Disease Progression with Azilect Given Once-daily (ADAGIO) trial, use of rasagiline at doses of 1 and 2 mg/d slowed the rate of worsening of the UPDRS score compared with placebo in patients with untreated PD **(Figure 1)**.[2] Patients were randomly assigned to an early-start group (rasagiline, 1 or 2 mg/d, or placebo for 72 weeks) or a late-start group (placebo for 36 weeks followed by rasagiline, 1 or 2 mg/d, or placebo for 36 weeks). The rate of change in the UPDRS score was
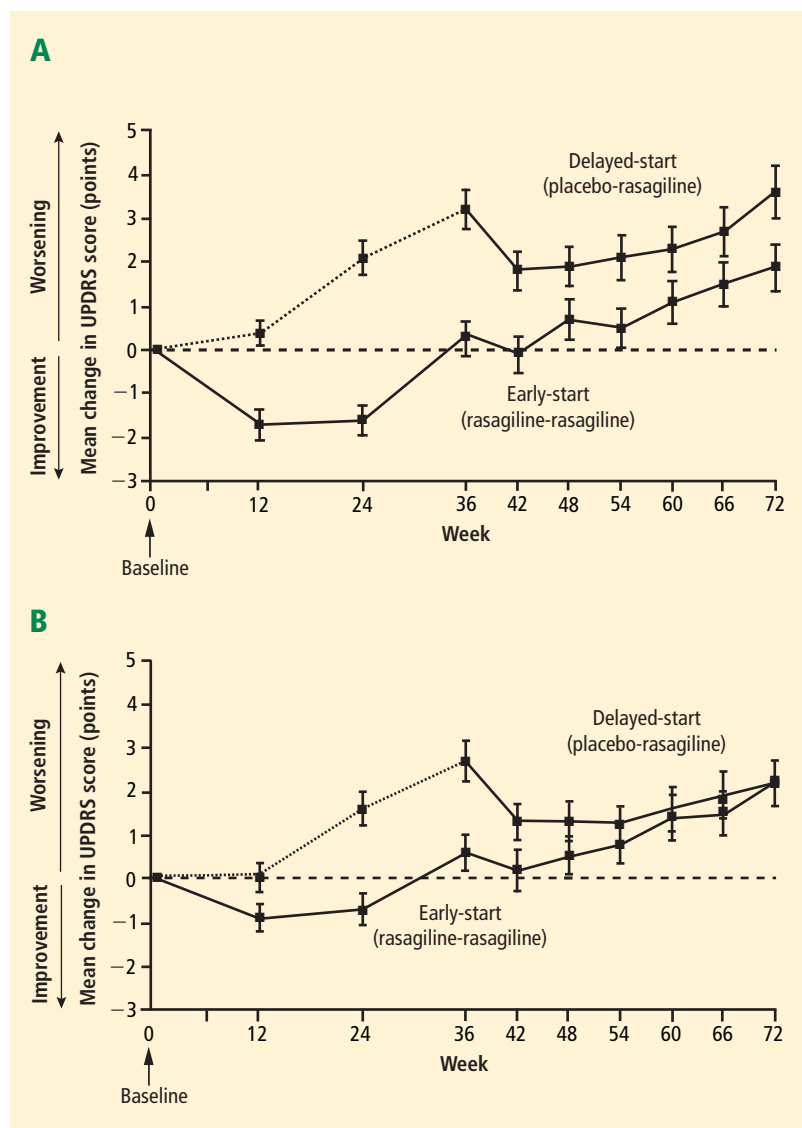
FIGURE 1. Rasagiline at doses of 1 mg/day **(A)** and 2 mg/day **(B)** slowed the rate of worsening of the Unified Parkinson's Disease Rating Scale (UPDRS) score compared with placebo in patients with untreated Parkinson disease.[2]

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Amantadine. In an early study of 54 patients with PD, functional disability scores improved significantly with administration of amantadine 200 to 300 mg/d compared with placebo.[4] A small subset of patients, perhaps 20% or less, who are treated with amantadine experience robust symptom improvement. Side effects of amantadine include hallucinations, edema, livedo reticularis, and anticholinergic effects. A more recently discovered potential side effect is corneal edema.

Dopamine agonists. Pramipexole (immediate-release [IR] and extended-release [ER]), and ropinirole IR and ER are dopamine agonists that have demonstrated disease-modifying effects and efficacy in improving PD symptoms.

Pramipexole ER administered once daily in early PD was shown to be superior to placebo on the mean UPDRS total score.[5] Ropinirole ER produced mean plasma concentrations over 24 hours similar to those achieved with ropinirole IR, and showed noninferiority to ropinirole IR on efficacy measures in patients with de novo PD.[5]

The effective dosage range of pramipexole ER in early PD is 0.375 to 4.5 mg/d. Side effects include hallucinations, edema, excessive diurnal somnolence, and impulse control disorders (ie, pathologic gambling, hypersexuality, excessive craving for sweets). Compared with pramipexole IR, compliance is enhanced with the ER formulation because of ease of administration, but this formulation also is more expensive.

In early PD, the effective dosage range of ropinirole ER is 8 to 12 mg/d.[6] The side effects are the same as with pramipexole ER with the same compliance advantage and cost disadvantage compared with the IR formulation.

Research indicates that dopamine agonists may have a neuroprotective effect. In two large clinical trials in which patients with PD were followed with an imaging marker of dopamine neuronal degeneration (using single-photon emission computed tomography or positron emission tomography), recipients of pramipexole[7] or ropinirole[8] showed slower neuronal deterioration compared with levodopa recipients. A counterargument to the neuroprotective theory is that these differences between the dopamine agonists and levodopa reflect neurotoxicity of levodopa rather than neuroprotection by dopamine agonists. The absence of a placebo comparison in both trials adds to the difficulty

slowed significantly with early treatment with rasagiline at a dosage of 1 mg/d, but not at 2 mg/d. Because the hierarchical primary end points for the ADAGIO trial were met only for the cohort receiving 1 mg of rasagiline early, it remains inconclusive whether rasagiline has a neuroprotective effect.

In a placebo-controlled study of selegiline in de novo early-phase PD, Pålhagen et al showed that selegiline monotherapy delayed the need for levodopa. When used in combination with levodopa, selegiline was able to slow the progression of PD as measured by the change in UPDRS total score.[3]

in drawing a conclusion, as some critics ascribed the differences between groups to downregulation of tracer binding with levodopa.

Nonergoline dopamine agonist. Transdermal rotigotine is a nonergot $D_1/D_2/D_3$ agonist. Higher doses produce higher plasma levels of rotigotine, which remain steady over the 24-hour dosing interval.[9] Transdermal rotigotine has demonstrated effectiveness in early PD in several clinical trials.[10,11] The patch, applied once daily, provides a constant release of medication. Removing the patch immediately interrupts drug administration.

Rotigotine patches must be refrigerated to prevent crystallization, a requirement that has delayed the product's arrival on the market. The patch is reputed to be difficult to peel from its backing and apply. Skin reactions are a side effect, and nonergot side effects are possible. Despite these drawbacks, transdermal rotigotine represents a convenient option for perioperative management of PD and in patients with dysphagia.

Exercise. Exercise has symptomatic and possibly neuroprotective benefits in PD, supporting its use as an additional medical measure. Evidence supports the value of treadmill walking and high-impact exercise in improving stride length, quality of life, and motor response to levodopa.

■ SYMPTOMATIC THERAPIES: THE FUTURE

Partial dopamine agonists

Pardoprunox is a partial dopamine agonist with full 5-HT_{1A}–agonist activity. A partial dopamine agonist acts in two ways: (1) It stimulates dopamine production in brain regions with low dopamine tone, and (2) it has dopamine antagonist activity under circumstances of high dopamine sensitivity, theoretically avoiding overstimulation of dopamine receptors. Because it inhibits excessive dopamine effect, pardoprunox may prevent dyskinesia. In addition, because pardoprunox has serotonin agonist activity, it may also act as an antidepressant.

In a phase 2 study, significantly more patients randomized to pardoprunox had a 30% or greater reduction in UPDRS motor score compared with placebo at end-of-dose titration (35.8% for pardoprunox vs 15.7% for placebo; $P = .0065$) and at end point (50.7% for pardoprunox vs 15.7% for placebo; $P < .0001$).[12]

Adenosine A_{2A}-receptor antagonists

Adenosine A_{2A} receptors are located in the basal ganglia, primarily on gamma aminobutyric acid (GABA)–mediated enkephalin-expressing medium spiny neurons in the striatum. These receptors modulate dopamine transmission by opposing D_2-receptor activity. The D_2 pathway is an indirect pathway that promotes suppression of unnecessary movement.

Two A_{2A}-receptor antagonists have demonstrated efficacy in clinical trials. Vipadenant has been proven effective as monotherapy in phase 2 clinical trials. Preladenant has been shown to improve "off time" as an adjunct to levodopa without increasing dyskinesia.

Safinamide

Safinamide, currently in phase 3 clinical trials, has three mechanisms of action. It is an inhibitor of dopamine reuptake, a reversible inhibitor of MAO-B, and an inhibitor of excessive glutamate release. The addition of safinamide to a stable dose of a single dopamine agonist in patients with early PD resulted in improvement of motor symptoms and cognitive function.[13,14]

■ NEUROPROTECTIVE STRATEGIES UNDER INVESTIGATION

Four neuroprotective strategies are under study: enhanced mitochondrial function, antiinflammatory mechanisms, calcium channel blockade, and uric acid elevation.

Enhanced mitochondrial function

Creatine has generated interest as a disease-modifying agent in response to preclinical data showing that it could enhance mitochondrial function and prevent mitochondrial loss in the brain in models of PD. Creatine is now the subject of a large phase 3 National Institutes of Health–sponsored clinical trial in patients with early-stage PD.[15]

Coenzyme Q10 (CoQ 10) exhibited a trend for neuroprotection at 1,200 mg/d, lowering the total mean UPDRS score compared with placebo in a 16-month study.[16] Current efforts are directed at determining whether 1,200 or 2,400 mg/d of CoQ10 are neuroprotective. A nanoparticulate form of CoQ10, 100 mg three times a day, has been shown to produce plasma levels of CoQ10 equivalent to those produced by 1,200-mg doses of the standard form.[17] CoQ10 is free of symptomatic effects.

Antiinflammatory mechanisms

Parkinson disease may have an important inflammatory component. A meta-analysis of seven studies showed an overall hazard ratio of 0.85 for development of PD in users of nonaspirin nonsteroidal antiinflammatory drugs (NSAIDs), with each of the seven studies demonstrating a hazard ratio less than 1.[18] A similar meta-analysis showed no such association.[19] Further study is warranted.

The antidiabetic agent pioglitazone, shown in mice to prevent dopaminergic nigral cell loss, has been entered into a phase 2 clinical trial to assess its antiinflammatory properties in PD.

Calcium channel blockade

A sustained-release formulation of isradipine, an L-type calcium channel blocker, is being studied in a phase 2
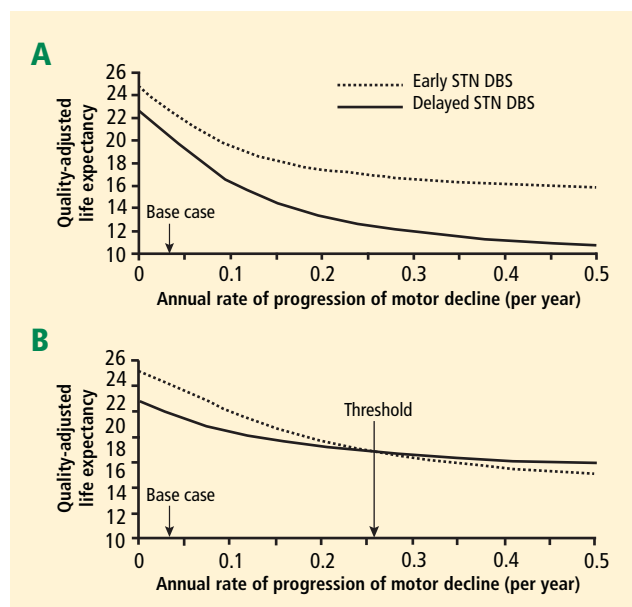
FIGURE 2. In a comparison of early versus late subthalamic nucleus deep brain stimulation (STN DBS), the annual rate of progression of both cognitive **(A)** and motor **(B)** decline was slower when STN DBS was administered earlier in the course of Parkinson disease (PD). Late STN DBS is favored if the annual rate of motor progression is greater than 25%, but this is an unrealistic scenario for PD.[21]

clinical trial for the treatment of early PD; experimental evidence in animals suggests that it may be neuroprotective against PD.

Uric acid elevation

Urate concentration in the cerebrospinal fluid predicts progression of PD, with higher levels associated with slower progression of disease.[20] Urate may delay oxidative destruction of dopaminergic neurons that occurs with progression of PD. Pharmacologic elevation of uric acid is being explored as a treatment option in PD.

■ ELECTRODES, VECTORS, AND STEM CELLS

Deep brain stimulation

Deep brain stimulation (DBS) is currently used as a treatment for advanced PD (patients suffering from levodopa-induced motor complications), but it might also slow the progression of cognitive and motor decline in earlier stages of PD. The annual rate of progression of both cognitive and motor decline was slower when DBS was administered earlier in the course of PD (off time on levodopa of about 2 hours) versus in a later stage of PD (off time on levodopa of about 4 hours) **(Figure 2)**.[21] The strategy is being tested further in clinical trials of early PD.

Stem cell therapy

Stem cells obtained from blastocytes, fibroblasts, bone marrow, or the adult, embryonic, or fetal central nervous system through "molecular alchemy" can form dopaminergic neuroblasts. Given the high cost and potential risks of stem cell therapy, it must be proven superior to DBS to be considered an option for early PD. Several practical problems act as hurdles to successful stem cell therapy. Efficient generation of dopamine-producing neurons and successful grafting are required. Tumor growth is a risk. Involuntary movements have been observed in some patients who received fetal implants. A limitation of stem cell therapy is that it will only affect those aspects of PD that are dependent on dopamine.

Gene therapy

Gene delivery of the growth factor analogue adeno-associated type-2 vector (AAV2)-neurturin has been investigated in patients with advanced PD. When surgically placed inside a neuron, neurturin enhances neuron vitality, enabling it to better fight oxidative stress and other attacks. It fared no better than sham surgery on changes in UPDRS motor score at 12 months in a randomized trial.[22] A few patients enrolled in this trial have been followed for longer than 12 months, at which time the mean change in motor scores appears to favor the group assigned to gene delivery of AAV2-neurturin. A phase 1/2 trial is investigating the safety and efficacy of bilateral intraputaminal and intranigral administration of neurturin.

■ SUMMARY

Levodopa is a legitimate choice for the treatment of early PD. Two MAO-B inhibitors, rasagiline and selegiline, have a symptomatic effect.

Long-acting oral and transdermal dopamine agonists are effective symptomatic therapies, but they also have an interesting array of side effects, making levodopa a reasonable alternative treatment sooner or later despite its dyskinetic effect. Potential neuroprotective effects remain to be identified.

Amantadine is sometimes overlooked as an option for treating early PD, but it has some special side effects including leg edema, livedo reticularis, and corneal edema. Amantadine does not cause orthostatic hypotension and is free of the side effects of excessive diurnal somnolence and impulse control disorders that are prevalent with dopamine agonists.

In the future, partial dopamine agonists and adenosine antagonists may provide us with additional symptomatic therapies. CoQ10, creatine, calcium channel blockers, and inosine, as well as NSAIDs, are being actively studied as potential disease-modifying agents. Further studies are likely to come from the use of NSAIDs.

Early DBS is a new avenue of investigation as a potential disease modifier. Stem cells are still being studied and limitations of sufficient production and potential tumor growth, among others, have delayed the institution of clinical trials. Gene therapy is an interesting additional treatment modality in active research.

■ REFERENCES

1. **Fahn S, Oakes D, Shoulson I, et al.** Levodopa and the progression of Parkinson's disease. N Engl J Med 2004; 351:2498–2508.
2. **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; 361:1268–1278.
3. **Pålhagen S, Heinonen E, Hägglund J, et al.** Selegiline slows the progression of the symptoms of Parkinson disease. Neurology 2006; 66:1200–1206.
4. **Barbeau A, Mars H, Botez MI, Joubert M.** Amantadine-HCl (Symmetrel) in the management of Parkinson's disease: a double-blind cross-over study. Can Med Assoc J 1971; 105:42–46.
5. **Hauser RA, Schapira AH, Rascol O, et al.** Randomized, double-blind, multicenter evaluation of pramipexole extended release once daily in early Parkinson's disease. Mov Disord 2010; 25:2542–2549.
6. **Onofrj M, Bonanni L, De Angelis MV, Anzellotti F, Ciccocioppo F, Thomas A.** Long half-life and prolonged-release dopamine receptor antagonists: a review of ropinirole prolonged-release studies. Parkinsonism Relat Disord 2009; 15(suppl 4):S85–S92.
7. **Parkinson Study Group.** Dopamine transporter brain imaging to assess the effects of pramipexole vs levodopa on Parkinson disease progression. JAMA 2002; 287:1653–1661.
8. **Whone AL, Watts RL, Stoessl AJ, et al.** Slower progression of Parkinson's disease with ropinirole versus levodopa: the REAL-PET study. Ann Neurol 2003; 54:93–101.
9. **Reichmann H.** Transdermal delivery of dopamine receptor agonists. Parkinsonism Relat Disord 2009; 15(suppl 4):S93–S96.
10. **Parkinson Study Group.** A controlled trial of rotigotine monotherapy in early Parkinson's disease. Arch Neurol 2003; 60:1721–1728.
11. **Watts RL, Jankovic J, Waters C et al.** Randomized, blind, controlled trial of transdermal rotigotine in early Parkinson disease. Neurology 2007; 68: 272–276.
12. **Bronzova J, Sampaio C, Hauser RA, et al.** Double-blind study of pardoprunox, a new partial dopamine agonist, in early Parkinson's disease. Mov Disord 2010; 25:738–746.
13. **Stocchi F, Arnold G, Onofrj M, et al; Safinamide Parkinson's Study Group.** Improvement of motor function in early Parkinson disease by safinamide. Neurology 2004; 63:746–748.
14. **Schapira AHV.** Safinamide in the treatment of Parkinson's disease. Expert Opin Pharmacother 2010; 11:2261–2268.
15. **NINDS NET-PD Investigators.** A randomized, double-blind, futility clinical trial of creatine and minocycline in early Parkinson disease. Neurology 2006; 66:664–671.
16. **Shults CW, Oakes D, Kieburtz K; and the Parkinson Study Group.** Effects of coenzyme q10 in early Parkinson disease: evidence of slowing of the functional decline. Arch Neurol 2002; 59:1541–1550.
17. **Storch A, Jost W, Vieregge P, et al.** Randomized, double-blind, placebo-controlled trial on symptomatic effects of coenzyme q(10) in Parkinson disease. Arch Neurol 2007; 64:938–944.
18. **Gagne JJ, Power MC.** Anti-inflammatory drugs and risk of Parkinson disease: a meta-analysis. Neurology 2010; 74:995–1002.
19. **Samii A, Etminan M, Wiens MO, Jafari S.** NSAID use and the risk of Parkinson's disease: systematic review and meta-analysis of observational studies. Drugs Aging 2009; 26:769–779.
20. **Ascherio A, LeWitt PA, Xu K, et al; Parkinson Study Group DATATOP Investigators.** Urate as a predictor of the rate of clinical decline in Parkinson disease. Arch Neurol 2009; 66:1460–1468.
21. **Espay AJ, Vaughan JE, Marras C, Fowler R, Eckman MH.** Early versus delayed bilateral subthalamic deep brain stimulation for Parkinson's disease: a decision analysis. Mov Disord 2010; 25:1456–1463.
22. **Marks WJ Jr, Bartus RT, Siffert J, et al.** Gene delivery of AAV2-neurturin for Parkinson's disease: a double-blind, randomised, controlled trial. Lancet Neur 2010; 9:1164–1172.

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