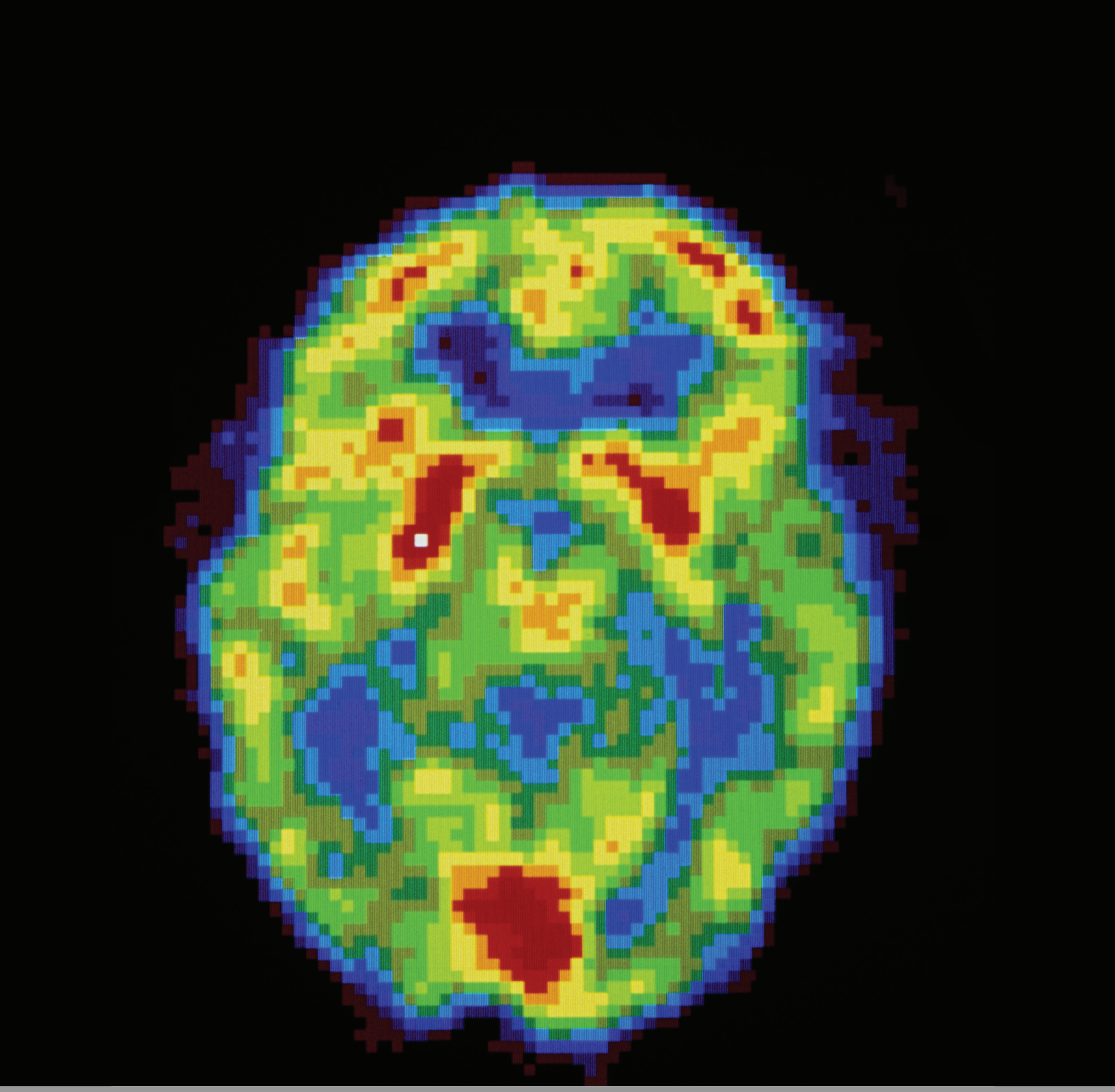

Early Intervention in Parkinson's Disease

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Target Audience
This activity is intended for neurologists and primary care providers, including physicians, nurse practitioners, and physician assistants, nurses, and pharmacists.

Goal
The goal of this activity is to improve the recognition and treatment of early Parkinson's disease and thus enhance health-related quality of life of patients with the disorder.

Learning Objectives
Upon completion of this activity, participants will be able to:

1. Identify early nonmotor complications that may be associated with Parkinson's disease (PD)
2. Describe the potential clinical benefits of early recognition and intervention for nonmotor and motor complications that may be associated with PD
3. Identify and contrast therapeutic strategies (monoamine oxidase inhibitors, safety, tolerability, efficacy profiles) in early-stage PD

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Tanya Simuni, MD

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Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease in the United States, and it affects more than a million people.[1] The cause of PD remains unknown but is attributed to a complex interaction between genetic and environmental factors.[2] Clinically, PD is characterized by a triad of rigidity, bradykinesia, and rest tremor, and is often associated with postural instability. Although motor disability is the hallmark of PD, a broad spectrum of nonmotor manifestations can significantly contribute to disease-related disability (Table 1).

Table 1. Nonmotor Manifestations of Parkinson's Disease

Neuropsychiatric symptoms
Depression, apathy, anhedonia, anxiety
Dementia
Impulse control disorders
Hallucinations, delusions (usually medication induced)
Sleep dysfunction
Disorders of sleep initiation and maintenance
Insomnia, poor sleep efficiency
Primary sleep disorders
Restless legs syndrome, periodic limb movement disorder
Sleep apnea (obstructive and central)
Parasomnias
RBD
Non-REM sleep-related movement disorders
Vivid dreaming
Excessive daytime somnolence
Autonomic dysfunction
Bladder dysfunction
Orthostatic hypotension
Hyperhydrosis
Sexual dysfunction
Gastrointestinal symptoms
Constipation
Hypersalivation
Dysphagia
Sensory symptoms
Pain
Olfactory dysfunction
Visual symptoms (diplopia, vision blurring)
Other symptoms
Fatigue
Weight loss
Weight gain (can be medication induced)

RBD = REM sleep behavior disorder; REM = rapid eye movement

The motor manifestations of the disease are linked to degeneration of dopaminergic neurons in the substantia nigra pars compacta of the midbrain. However, the neuropathologic changes of PD are widespread, affecting multiple nondopaminergic pathways including degeneration of noradrenergic, serotoninergic, and cholinergic neurons. According to the hypothesis of Braak and coworkers,[3] degeneration of these neurons may precede the earliest neuropathologic changes seen in the substantia nigra pars compacta and may explain the wide spectrum of nonmotor symptoms that can be present even early in the course of PD. Traditionally, treatment of PD has been focused on improving motor disability. A change in the score on the Unified Parkinson's Disease Rating Scale (UPDRS) is the most commonly used measure of efficacy in early-stage PD interventional studies.[4] The UPDRS consists of 4 parts: part I is a brief evaluation of mentation, behavior, and mood; part II assesses activities of daily living (ADL); part III is the objective assessment of motor disability; and part IV is the assessment of complications of therapy (ie, dyskinesia and motor fluctuations). The current version of the UPDRS is heavily weighted toward measuring the degree of motor disability. However, multiple studies of disease-related quality of life (QOL) impairment clearly indicate that nonmotor symptoms, specifically depression, are the major variables responsible for the change in QOL.[5,6] A new version of the UPDRS has been recently developed to expand the assessment of nonmotor disability.[7]

Treatment of PD is limited to symptomatic interventions aimed at reduction of disease-related disability. In the absence of curative therapy, our interventions should focus on impact on disease-related QOL and reduction of long-term treatment-related complications. There is a wide armamentarium of agents approved for management of early PD (Table 2). This article will briefly review recent studies on the efficacy and side effect profile of the 3 major classes of agents -- levodopa, dopamine agonists, and monoamine oxidase B inhibitors (MAO-Bs) -- as treatment options for early PD, focusing on the side effect profile of each group of agents. Anticholinergic agents and amantadine are also used for treatment of early PD; however, no recent studies have assessed their efficacy.

Table 2. Classes of Agents Approved for Monotherapy in Early Parkinson's Disease

Class	Agent	Brand Name
MAO-B inhibitor	Rasagiline Selegiline	Azilect®
Levodopa replacement	Carbidopa/levodopa	Sinemet® Sinemet CR® Parcopa®*
Dopamine agonists	Pramipexole Ropinirole Rotigotine†	Mirapex® Mirapex ER® Requip® Requip XL® Neupro®
NMDA antagonist	Amantadine	Symmetrel®

*Orally dissolvable preparation of carbidopa/levodopa
†Currently off the market in the United States
CR = controlled release; ER = extended release; MAO-B = monoamine oxidase B; NMDA = N-methyl-D-aspartate; XL = extended release

The second part of this review will discuss the scope of nonmotor manifestations associated with early PD. Motor disability is the target of most studies; however, clinicians should weigh the impact of the intervention on nonmotor disability against the side effect profile to guide them in selection of a treatment agent. Neuroprotection in PD was reviewed in a recent Medscape publication.[8]

Polling Questions

In your opinion, what is the most significant barrier to early treatment of PD?

- ○ Poor understanding of early nonmotor symptoms of PD
- ○ Lack of effective, well-tolerated medications
- ○ Side effects of existing medications
- ○ Patient resistance to diagnosis and treatment before motor symptoms appear
- ○ Suboptimal adherence to treatment regimens

Which of the following medications is least likely to cause dyskinesia?

- ○ Levodopa
- ○ Ropinerole
- ○ Selegiline
- ○ Rotigotine

Pharmacologic Options for Early PD

Levodopa

Levodopa, a dopamine precursor that is converted to dopamine in the nigrostriatal system, remains the most effective agent for the treatment of PD.[9,10] However, long-term treatment with levodopa has been associated with earlier onset of motor complications (medication wearing off, fluctuations, and dyskinesias), particularly in younger patients. As such, many clinicians choose to limit the use of levodopa in early PD.

The ELLDOPA (Earlier versus Later Levodopa Therapy in Parkinson Disease) study was a 42-week, randomized, double-blind, placebo-controlled trial designed to evaluate the impact of early initiation of levodopa on progression of motor disability in early PD. The study enrolled 361 treatment-naive patients who were randomly assigned to receive either placebo or carbidopa/levodopa at doses of 37.5-150 mg, 75-300 mg, and 150-600 mg.[11] Study subjects were treated for 40 weeks and then underwent withdrawal of medication over a subsequent 2-week period. The primary outcome measure was change in the UPDRS between baseline and 42 weeks (off medication). Results showed that regardless of levodopa dose, the severity of parkinsonism increased more in the placebo group (7.8 points) than in the treatment groups (1.9 points in the 150-mg group, 1.9 in the 300-mg group, and -1.4 in the 600-mg group; $P < .001$). The treatment groups showed significantly lower (better) UPDRS activities of daily living and motor scores during the treatment phase as well as after the 2-week washout (the endpoint of the study). Subjects in the 600-mg treatment group had a significantly higher incidence of dyskinesia (16.5% compared with 3.3% in the placebo group) and medication wearing off (29.7 % vs 13.3% in the placebo group). However, the incidence of dyskinesia and wearing off was similar for patients in the 2 lower-dose levodopa groups and patients receiving placebo. Overall, levodopa was well tolerated. Typical side effects of dopaminergic agents include hypotension, nausea, somnolence, hallucinations, and vivid night dreams. Adverse events reported with the 600-mg daily treatment v placebo included nausea (31.9% vs 13.3%); somnolence, although the incidence was low (5.5% vs 2.2%); abnormal dreaming (5.5% vs 0); and dizziness (15.4% vs 6.7%). The study supports unequivocal high symptomatic benefit and good tolerability of levodopa. That benefit has to be weighed against the higher incidence of drug-induced dyskinesia and medication wearing off with a higher dose of levodopa.

Dopamine Agonists

Dopamine agonists have been used for many years in the treatment of PD. The first-generation dopamine agonists were ergot derivatives (bromocriptine, cabergoline, and pergolide), although their use is limited by safety concerns (particularly valvular heart disease). Newer, non-ergot dopamine agonists are now available, including pramipexole, ropinirole, and rotigotine transdermal patch.

Efficacy of pramipexole and ropinirole as monotherapy in patients with early PD has been demonstrated in a number of well-designed studies.[12-14] Both agents belong to the group of synthetic non-ergot dopamine agonists with affinity to dopamine D2 family receptors (particularly the D3 receptor subtype). These 2 agents have not been compared head to head, but clinical experience points to comparable efficacy if used in equivalent doses. Ropinirole requires a longer titration schedule than pramipexole. Both agents have a similar side effect profile related to common dopaminergic side effects such as nausea, sleepiness, hallucinations, leg edema, and more recently the incidence of impulse control disorders (ICDs). For example, in a placebo-controlled study of pramipexole in 335 patients conducted by Shannon and colleagues,[15] the incidence of these side effects was as follows: nausea (39% with pramipexole vs 20.5% with placebo), insomnia (25.6% vs 12.9%), constipation (17.7% vs 6.4%), somnolence (18.3% vs 8.8%), and visual hallucinations (9.7% vs 2.3%). The most common side effects seen in a 6-month, randomized, placebo-controlled study of ropinirole vs placebo in 241 patients with early PD[13] were nausea (52.6% treatment vs 21.6% placebo), dizziness (36.2% vs 18.4%), somnolence (36.3% vs 4.8%), constipation (10.3% vs 6.4%), and syncope (10.3% vs 1.6%).

Long-Acting Dopamine Agonist Preparations

Dopamine agonists are now available in once-daily long-acting preparations. This approach is particularly promising for patients in whom compliance with the multiple-times-a-day dosing is a concern, and provides steady drug delivery over the course of a day, ideally eliminating fluctuations in serum levels of multiple-dose dopamine agonists.

Ropinirole is now available in a 24-hour prolonged release formulation approved by the US Food and Drug Administration (FDA). The EASE-PD (Efficacy and Safety Evaluation in Parkinson disease) study[16] evaluated the efficacy of extended-release compared with immediate-release ropinirole in patients with early PD. The study demonstrated comparable efficacy of both preparations based on the change in UPDRS score (-10.4 points for the 24-hour ropinirole and - 8.9 points for the immediate-release formulation). Adverse events occurred with about the same frequency in both treatment groups and included nausea, somnolence, dizziness, headache, and constipation. Patients may be switched from the immediate- to the extended-release preparation in equivalent doses directly, without retitration. Ropinirole extended release is available in 2 mg-24 mg doses and offers the convenience of once-a-day drug delivery.

A once-daily pramipexole extended-release preparation was also recently approved by the FDA for management of motor disability in patients with early PD.[17,18] The drug was approved based on the results of a placebo-controlled, 18-week study that evaluated the efficacy of pramipexole extended release vs immediate release in patients with early PD.[19] The efficacy of both preparations of pramipexole was comparable compared with placebo, with no difference in side effect profiles and tolerability between the immediate- and extended-release preparations.[20] Another study evaluated safety of an overnight switch from the immediate- to the extended-release preparation of pramipexole; 95% of patients were able to successfully switch in a 1:1 dosing ratio.[17,20] Pramipexole extended release is available in 0.375-4.5 mg doses. It provides the convenience of once-a-day dosing with an adverse-effects profile that is similar to the immediate-release preparation.

Rotigotine

Rotigotine is the first dopamine agonist available in a transdermal continuous 24-hour delivery preparation. In the United States, rotigotine was approved at dosages up to 6 mg/24 hours for treatment of patients with early PD. The Parkinson Study Group conducted a multicenter, double-blind, placebo-controlled trial assessing the efficacy of transdermal rotigotine in early PD.[21] A total of 242 patients were randomly assigned to receive either placebo patches or patches with rotigotine dosages of 2 mg, 4 mg, 6 mg, and 8 mg/24 hours.[21] Compared with patients receiving placebo, the 2-mg group experienced a 0.91-point reduction of the UPDRS score; the 4-mg group had a 2.78-point reduction; the 6-mg group had a 4.83 point reduction; and the 8-mg group had a 5.23-point reduction. The effects were significant in the 6-mg and 8-mg treatment groups ($P \leq .001$), and a dose-response relationship was demonstrated from the 2 mg to 8 mg doses. Adverse effects noted more often in the treatment vs placebo groups were nausea, dizziness, somnolence, insomnia, vomiting, fatigue, and application site reaction.

Another 6-month trial of transdermal rotigotine demonstrated comparable efficacy (a mean reduction in UPDRS part II and III scores of 3.98 points ($P < .0001$ compared with an increase of 1.31 points in the placebo group).[22] Adverse events in this study were similar to those seen in the Parkinson Study Group trial, with application site reaction (44% treatment vs 12% placebo), nausea (41% vs 17%), somnolence (33% vs 20%), dizziness (19% vs 13%), and headache (16% vs 9%) more prevalent in the drug treatment group than the placebo group.

Currently, the commercially available rotigotine patch has been voluntarily recalled from the US market because of a manufacturing problem in which the drug has crystallized on the patch surface. It is unclear how long the drug will be off the market, although it is anticipated that an alternative manufacturing process will be developed and transdermal rotigotine will return as a treatment option.

Early Treatment and Risk for Motor Complications

Treatment of the motor symptoms of PD is associated with a significant risk for treatment-related motor complications. These include dyskinesia, wearing-off effect, and on-off fluctuations. The mechanism of development of motor complications is multifactorial. It is related to the progressive degenerative process of the disease, with reduction of the dopamine storage capacity of the nigrostriatal system and pulsatile stimulation of the postsynaptic receptors by the medications. When deciding on pharmacologic treatment for early PD, one must consider these motor complications.

A number of studies have been conducted to compare the risk for development of motor complications with the use of levodopa vs dopamine agonists as the initial treatment options. The Parkinson Study Group reported a 4-year study in which levodopa and pramipexole were compared with time to onset of motor complications as the primary outcome.[23] In all, 301 patients were randomly assigned to receive either pramipexole 0.5 mg 3 times daily or 25/100 carbidopa/levodopa 3 times daily. After a 10-week dose escalation, patients in both groups were allowed additional open-label levodopa as dictated by symptoms. The pramipexole-treated group showed a significantly lower risk for dyskinesia (24.5% vs 54% with levodopa) and wearing off (47% vs 62.7%). Disabling dyskinesia was uncommon in both groups at 48 months. UPDRS score improvement was greater in the levodopa group than in the pramipexole group (-3.2 vs -2, respectively) even though both groups were allowed to receive supplemental open-label levodopa as necessary. The levodopa-treated group also showed significant reduction in the risk for freezing (25% vs 37.1% for pramipexole). Somnolence (36% vs 21%) and edema (42% vs 15%) were more common in the pramipexole-treated group.

Rascol and colleagues[24] reported a similarly designed 5-year study comparing the incidence of dyskinesia in 268 patients with early PD who were treated with levodopa or ropinirole. At 5 years, the incidence of dyskinesia was significantly lower in the ropinirole group vs the levodopa group (20% vs 45%), regardless of levodopa supplementation. Ropinirole monotherapy (before levodopa supplementation) was associated with a 5% incidence of dyskinesia. However, levodopa was superior in efficacy to ropinirole (-0.08 UPDRS part III change for the ropinirole group vs -4.8 in the levodopa group; $P = .008$). Ropinirole was associated with a higher incidence of hallucinations (17% vs 6% with levodopa), somnolence (27% vs 19%), and leg edema (14% vs 6%), whereas depression was more prevalent in the levodopa group (23% vs 15%). Similar results were seen in the study of pergolide.[25]

In conclusion, all dopamine agonists provide significant benefit in reducing motor disability in early PD, although the magnitude of benefit is inferior to that of levodopa. All studies support the notion that early treatment with dopamine agonists is associated with a lower risk for the development of motor complications, at least within a 5-year treatment span. However, the incidence of dopaminergic side effects -- specifically somnolence, hallucinations, ICDs (see below), and leg edema -- is higher with dopamine agonists compared with levodopa.

MAO-B Inhibitors

Selegiline

Oral selegiline has been shown to reduce "off" time in patients with advanced PD and is approved at dosages up to 10 mg/day as an adjunctive treatment to levodopa[26]; several clinical trials have shown that selegiline monotherapy also provides mild symptomatic effects in patients with early PD.[9] Selegiline was extensively studied as a potential PD disease-modifying agent; however, the data were inconclusive. In the DATATOP (Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism) study,[27] at 3 months the treatment group saw a 1.5-point improvement in UPDRS total scores vs a 1.6-point worsening in the placebo group ($P < .001$). Of the most common adverse events, dry mouth was the only one that occurred at a significantly greater rate in the selegiline group compared with the placebo group.

Rasagiline

Rasagiline is a newer irreversible MAO-B antagonist. Compared with selegiline, rasagiline does not produce amphetamine byproducts of metabolism. Rasagiline is approved for both monotherapy and adjunct therapy (with levodopa) for PD.

The efficacy of rasagiline as monotherapy in early PD has been investigated in a number of studies. The TEMPO (TVP-1012 in Early Monotherapy for PD Outpatients) trial, conducted by the Parkinson Study Group, was a randomized, double-blind, placebo-controlled trial that enrolled 404 patients with early PD who were not previously exposed to symptomatic therapy other than anticholinergics.[28,29]

Subjects were randomly assigned to receive either rasagiline 2 mg/day, 1 mg/day, or placebo for 26 weeks. The primary efficacy variable was change in the total UPDRS score at 26 weeks. The difference in the total UPDRS score in the 2-mg/day treatment group vs placebo was a 3.6-point benefit with treatment, and in the 1-mg/day group, there was a 4.20-point benefit (both $P < .001$). Rasagiline was well tolerated. Asthenia was the only significantly more prevalent adverse reaction in the placebo (10.9%) vs rasagiline (4.5%) groups. Based on results of the study, a 1-mg dose of rasagiline was approved for use in patients with early PD. The TEMPO study included a delayed-start extension in which subjects who were initially assigned to placebo were switched to active therapy after the first 26 weeks of treatment.[28] The degree of disability was measured by the UPDRS score at 12 months.[28] Subjects treated with rasagiline from the beginning had a statistically significant reduction in progression of disability compared with those who started 6 months later. The subsequent ADAGIO (Attenuation of Disease Progression with Azilect Given Once-daily) study was launched to test the disease-modifying benefit of rasagiline.[30] This trial also used a delayed-start design similar to the TEMPO study but was larger ($N = 1176$) and had a longer duration (72 weeks). Patients were started on either placebo or rasagiline (1 mg or 2 mg) in the first phase of the trial (36 weeks). In the second phase, all patients were treated with active drug but were still blinded to the dosage assignment. Such a design allows investigators to explore the potential disease-modifying benefit of a drug that also has a symptomatic effect. The rasagiline 1 mg/day early-start group reached all 3 primary endpoints consistent with possible disease-modifying effect of the drug. However, the group that received the 2-mg dose did not reach all primary endpoints, and the study was inconclusive regarding the disease-modifying properties of rasagiline. In the absence of any proven options for disease modification in PD, it is reasonable to discuss the available data with patients newly diagnosed with PD and let them make an informed decision regarding the early use of rasagiline.

Rasagiline has a beneficial side effects profile; the occurrence of adverse events was not significantly different between treatment and placebo groups in the ADAGIO study.[30] Specifically, the risk for nausea, somnolence, hypotension, and hallucinations, which are common dopaminergic side effects, was not increased in the rasagiline group. However, based on the chemical structure of rasagiline, clinicians should be aware of potential food and drug interactions. Although rasagiline is a selective MAO-B antagonist at the approved dose, there is a theoretic risk for loss of selectivity and inhibition of other brain amines, leading to hypertensive crisis, hyperpyrexia, serotonin syndrome, and other serious complications. Therefore, caution must be exercised when combining this class of medications with tyramine-containing foods (such as aged cheeses and red wines), although no dietary restrictions are necessary. The same precaution applies to the amine-containing medications, including certain cough and cold drugs. Although rasagiline can be used with antidepressants that increase brain serotonin level (such as tricyclic antidepressants, selective serotonin reuptake inhibitors, and serotonin/noradrenergic reuptake inhibitors), awareness and appropriate patient counseling about possible adverse effects is essential. There are certain restrictions on the use of rasagiline with narcotic analgesics, specifically meperidine.

Question

You are preparing to discuss treatment options with a newly diagnosed 51-year-old patient with early nonmotor symptoms of PD and no disability. She plays viola in the local symphony orchestra and loves socializing with friends. She takes no prescription medications, just vitamin and mineral supplements. Which of the following is the most accurate information to include in your discussion of treatment options?

- ○ Levodopa is highly effective; nonmotor (eg, cognitive, autonomic) side effects are more significant than motor complications with long-term treatment
- ○ Dopamine agonists are effective but the risk for motor complications is higher than with other dopaminergic medications, and thus it should be saved for latest-stage treatment
- ○ The MAO-B inhibitors are effective and well tolerated in early PD, but the patient and the clinician must be aware of the potential for drug and food interactions
- ○ At this early stage, because of side effects associated with all the medications in the long term, she may want to delay treatment until she begins to experience motor symptoms

Impact of Medication Side Effect Profile on Choice of Treatment

Clinicians should be aware of certain adverse events more frequently associated with specific groups of dopaminergic therapies. Dopamine agonists overall have a higher risk of somnolence, confusion, orthostatic hypotension, leg edema, and a more recently reported entity of ICDs(see below). These side effects can also occur with levodopa, but at a lower rate than seen with dopamine agonists. On the other hand levodopa is associated with a higher risk of delayed motor complications, as discussed.
The advantage of dopamine agonists in delaying the onset of motor complications has to be weighed against the lower efficacy and the higher risk of complications with dopamine agonists compared with levodopa.

Rasagiline has a benign side effect profile but lower potency and certain potential drug interactions that warrant consideration. The ultimate decision about the choice of treatment should be weighed with regard to risk vs benefit for the individual patient (Table 3).

Table 3. Categoric Comparison Between Classes of Agents Used in Early Parkinson's Disease

Class of Agents	Efficacy	Risk for Long-term Motor Complications (Dyskinesia, Fluctuations)	Risk for Nonmotor Side Effects (Somnolence, ICD, Cognitive AEs)	Potential Drug Interactions
Carbidopa/Levodopa	+++	+++	++	+
Dopamine agonists	++	+	+++	+
MAO-B inhibitors	+	None/+ *	None/+	++

*No long-term studies have been performed
AEs = adverse events; ICD = impulse control disorders; MAO-B = monoamine oxidase-B

Question

Nonmotor symptoms of Parkinson's disease can appear throughout the course of the disease, and even before the hallmark motor symptoms. Which of the following statements correctly characterizes the implications of certain nonmotor symptoms of PD?

- ○ The prevalence of depression in patients with PD is estimated at 40% but is less likely to impair quality of life than tremors and bradykinesia
- ○ Because anosmia frequently precedes motor symptoms in early PD, a smell test may become an easy, inexpensive screening method for PD in the very early stages of the disease
- ○ Cognitive dysfunction, such as dementia and executive dysfunction, is typically related to dopaminergic treatment rather than to the disease itself
- ○ Although sleep disorders are common in patients with PD, excessive daytime sleepiness occurs only rarely

Treatment of Nonmotor Symptoms of PD

The majority of clinical trials in patients with early PD were designed to assess the efficacy of novel therapeutic agents for motor disability. Traditionally, nonmotor symptoms were attributed to more advanced stages of PD; however, we now know that many nonmotor symptoms (eg, anosmia, depression, sleep dysfunction) can manifest early in the course of the disease and can even precede the onset of motor symptoms. The high prevalence, associated disability, and often early occurrence of nonmotor symptoms in PD not only warrant the development of therapeutic agents aimed specifically at their treatment but also necessitate the re-evaluation of existing PD agents for potential benefits in alleviating nonmotor symptoms.[31]

Depression

Depression remains the major factor contributing to impairments in QOL of patients with PD.[5] Depression can occur early in the course of the disease and can even precede the onset of motor disability. Early recognition and treatment of depression is essential for effective disease management. The current estimated prevalence of depression in PD is 40%, although the prevalence in early stages of the disease has not been well established.[32] Compared with depressive disorders in non-PD populations, depression in PD is often characterized by less guilt and lower suicide ideation but higher rates of anxiety, pessimism, and irrationality.[33]

Similar to elderly patients in general, patients with PD more commonly have less severe forms of depression (ie, minor depression and dysthymia rather than major depression). Other symptoms frequently seen in the spectrum of PD-related mood dysfunction include anhedonia (ie, loss of pleasure), apathy (ie, loss of interest or motivation), and anxiety.

Despite the high prevalence of depression in PD, there is a paucity of well-designed, controlled clinical trials to systematically evaluate the efficacy of standard antidepressants or dopaminergic therapy for mood dysfunction in this population, and no studies focusing on mood disorders in early PD have been performed. Practice parameters on the treatment of depression in PD identified only 6 well-controlled studies, some of which were not sufficiently powered to detect efficacy of the tested agent.[34] The authors of the practice parameters concluded that there is insufficient evidence to either support or refute the efficacy of most antidepressants for the treatment of depression in PD. A recent study demonstrated efficacy of the tricyclic antidepressant nortriptyline for the treatment of PD-related depression.[35] Dopamine agonists may be effective for mood control in PD, as well.[36] Additional data are necessary and a number of studies are ongoing; however, in clinical practice, selective serotonin reuptake inhibitors remain the most commonly used antidepressants for the treatment of depression in patients with PD.[37]

Cognitive Dysfunction

Compared with depression, which can be seen early in the course of PD, dementia is a manifestation of advanced disease; however, signs of cognitive dysfunction can be seen even in the early stages of PD. In a study that compared 115 consecutive newly diagnosed patients with PD with 70 healthy controls, 24% of those newly diagnosed with PD vs 4% of the controls had abnormal performance on at least 3 neuropsychological tests, with impairment predominately in the domains of executive function and psychomotor speed.[38]

The profile of cognitive impairment in PD is frequently labeled as "dysexecutive syndrome" and is characterized by impaired visuospatial abilities, attention, memory retrieval, and executive function, with relative preservation of encoding memory, praxis, and language compared with the mild cognitive impairment that precedes Alzheimer's disease.[39,40]

Recommendations for the diagnostic evaluation of dementia in patients with PD were recently published by the Movement Disorders Society task force.[41] No guidelines have been proposed for the diagnosis and there are no data on the treatment of mild cognitive impairment in early PD. A number of studies have investigated the role of cholinesterase inhibitors in the treatment of PD dementia[42]; however, there are no data on the efficacy of these agents or of the N-methyl-D-aspartate receptor antagonist memantine in patients with mild cognitive impairment in early PD.

Sleep Dysfunction

Disorders of sleep and wakefulness are ubiquitous in PD, with an estimated prevalence of 98%.[43] Sleep dysfunction can occur early in the course of PD, and PD-associated sleep dysfunction spans the spectrum of sleep pathology. The etiology is multifactorial and includes PD pathology affecting the reticular activating system, which according to Braak and colleagues,[3] is involved early in the course of the disease process. PD-related motor dysfunction that directly affects sleep quality and side effects of complex PD pharmacologic therapy also play a role.

Some of the specific problems that contribute to sleep fragmentation and poor sleep efficiency in patients with PD include parasomnias, specifically rapid eye movement (REM) behavior disorder (RBD), which is present in about 15%-33 % of patients,[44] restless legs syndrome, and obstructive sleep apnea.[45] RBD is of particular significance in early PD as it can precede the onset of motor disability by a number of years and is considered a potential premotor sign of PD.[46] Excessive daytime sleepiness (EDS) occurs in up to 50% of patients with PD.[47] Interestingly, a prospective survey of 3078 elderly men in the Honolulu-Asia Aging Study demonstrated that pre-existing EDS was one of the risk factors for development of PD.[48] Risk factors for EDS in PD include advanced age, presence of cognitive dysfunction, and cumulative dose of dopaminergic therapy.[49] Surprisingly, EDS does not correlate with the quality of nocturnal sleep. All patients treated with dopaminergic agents should be counseled, and appropriate measures should be taken if episodes occur. Assessment for EDS and sudden onset of sleep is especially important in patients with PD who drive.

Treatment of sleep dysfunction in PD should focus on an accurate diagnosis of the specific problem.[31] PD medications should be reviewed and simplified if possible, and sleep studies should be ordered if other causes of sleep dysfunction are suspected. RBD can be effectively managed with clonazepam,[44] although placebo-controlled studies are lacking, and nocturnal confusion can occur with bedtime benzodiazepine use in the geriatric population. Melatonin was reported to be effective in 1 small study at dose ranges of 3 mg-12 mg and is generally well tolerated.[50] Restless legs syndrome is readily responsive to dopamine agonists.[51,52]

Use of hypnotics should be limited to cases that do not respond to behavioral modifications and other measures, as there are no efficacy data for specific hypnotic agents in PD. Clinicians also should be vigilant about the treatment of depression and psychosis, as these are possible contributing factors to sleep dysfunction in patients with PD. Treatment of EDS is challenging because the majority of dopaminergic agents can cause EDS; reducing or changing dopamine agonists should be attempted in these cases.[53] Modafinil has shown mixed results for PD-related EDS,[53] with some studies showing mild improvement[54] and others showing no improvement.[55]

ICDs

In recent years, a growing number of published reports have described ICDs in patients with PD.[56] ICDs are defined as failure to resist an impulse or temptation to perform an act that is harmful to the patient or others. The most common clinical manifestations of ICDs in patients with PD are compulsive gambling, sexual behavior, buying, and eating. A recently completed cross-sectional study of 3090 treated patients with PD reported an overall prevalence of ICD of 13.6% and a prevalence of ICD of 17.1% in patients treated with a dopamine agonist.[57] The frequency of each ICD for the entire population was: compulsive buying (5.7%), problem or pathological gambling (5.0%), binge-eating disorder (4.3%), and compulsive sexual behavior (3.5%); more than one third of patients with an ICD had more than 1 disorder. ICDs were more common in patients receiving dopamine agonists than in those not receiving dopamine agonists (17.1% vs 6.9%, respectively, $P < .001$). There was no difference in ICD frequency between different dopamine agonists. From the results of this study and others, the strongest risk factor for ICD development appears to be treatment with dopamine agonists, with additional risk factors being a history of related behaviors or substance abuse, younger age, and male sex.[56-59] Additional data are necessary, but all patients who are to be treated with dopamine agonists should be counseled in advance about the potential risk for the development of 1 or more ICDs. Although no controlled treatment research has been conducted, management options for patients with an ICD include discontinuation of the dopamine agonist, using a lower dosage, switching to a different dopamine agonist, or adding a psychiatric medication (eg, a selective serotonin reuptake inhibitor).[60]

Autonomic Dysfunction

Autonomic dysfunction (ADS) is an intrinsic part of PD symptomatology. The spectrum of ADS in patients with PD is broad and includes orthostatic hypotension, bladder and bowel dysfunction, erectile dysfunction, and hyperhydrosis. ADS has been thought to be a manifestation of advanced PD, but ADS symptoms can be present early in the course of the disease and can have a major impact on QOL.[61,62] The etiology of ADS in PD is believed to be related to the spread of Lewy body pathology to the autonomic centers, augmented by the potential negative impact of dopaminergic medications on at least some of the symptoms (eg, orthostatic hypotension and constipation). Studies have reported efficacy of domperidone, a peripheral dopamine receptor blocking agent, and pyridostigmine, a peripheral cholinesterase inhibitor, for the management of orthostatic hypotension in PD.[63,64] Although data on the prevalence of ADS in PD have increased, literature on disease-specific treatment options is scarce.[31] Clinicians should use a standard symptomatic treatment approach to manage ADS as in other disorders but with an awareness of potential PD-specific side effects (eg, confusion with the use of drugs for neurogenic bladder dysfunction).

Anosmia and Other Sensory Manifestations of PD

Loss of smell has long been reported to be an early sign of PD, present in 70%-100% of patients with PD.[65] As the loss of smell frequently can precede the onset of motor symptoms, recent research has focused on the role of smell-testing in the early identification of PD.[65] If proven to be sensitive and specific, a smell test would be an easy-to-administer, inexpensive screening tool that would be useful for identifying populations at risk for PD and for enrollment in neuroprotection clinical trials. Anosmia does not improve with dopaminergic therapy and thus cannot be used as a measure of efficacy for dopaminergic agents.

Pain is another common manifestation of PD.[65,66] The pattern and distribution of pain varies, but a subset of patients experiencing pain is responsive to dopaminergic therapy.[65,66] The nature of pain in PD is likely multifactorial, and more data on the mechanisms of pain and potential disease-specific treatment interventions are necessary.

Summary

The management of early PD has been enhanced in recent years by the introduction of a number of new agents. Although levodopa remains the "gold standard" of treatment, concern regarding the risk for motor complications warrants careful consideration of alternative options. MAO-B inhibitors and dopamine agonists have a role as both monotherapy and adjunct treatment in early PD.

Decisions regarding the choice of treatment for an individual patient should be based on careful consideration of the scope of disability, including nonmotor manifestations, efficacy, and the potential side effect profile of a particular agent, as well as on short- and long-term treatment goals. More studies on the treatment of nonmotor manifestations of PD are needed and are forthcoming.

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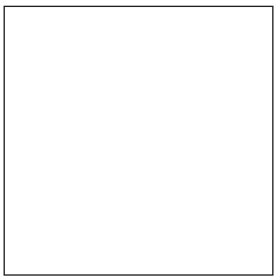

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