

Key Clinical Trials in Pharmacological Treatment of Early Parkinson's Disease

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Abstract

Parkinson's disease (PD) is the second most common neurodegenerative disease and affects more than one million people in the US. The management of PD involves treatment of motor and non-motor symptoms of the disease. The armamentarium of treatment options for PD has increased substantially over the last 10 years. This article reviews recent clinical trials investigating efficacy, complications of treatment, and possible neuroprotective agents in patients with early PD.

Keywords

Parkinson's disease, treatment, neuroprotection, levodopa, dopamine agonists, monoamine oxidase B (MAO-B) inhibitors

Disclosure: Binit Shah, MD, has no conflicts of interest to declare. Tanya Simuni, MD, is a current or former consultant and has received honoraria from TEVA, Boehringer Ingelheim, GSK, Novartis, and UCB Pharma.

Received: January 19, 2009 **Accepted:** August 28, 2009 **DOI:** 10.17925/USN.2009.05.01.25

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Parkinson's disease (PD) is the second most common neurodegenerative disease and affects more than one million people in the US.¹ The cause of PD is unknown, but it involves the loss of dopaminergic neurons in the substantia nigra pars compacta of the midbrain. Clinically, PD is characterized by the triad of rigidity, bradykinesia, and rest tremor, and is often associated with postural instability. While motor disability is the hallmark of PD, there is a whole spectrum of non-motor manifestations that can significantly contribute to the disease-related disability.

There are two commonly used scales to measure PD-related disability and severity of the disease. The Hoehn and Yahr Scale is a measure of overall severity of PD, with a score of zero indicating no disease and a score of five indicating end-stage disease.² The Unified Parkinson's Disease Rating Scale (UPDRS) consists of four parts.^{3,4} Part I is a brief evaluation of mentation, behavior, and mood; part II assesses activities of daily living (ADL); part III is objective assessment of motor disability; and part IV is assessment of complications of therapy (i.e. dyskinesia and motor fluctuations).

Recently, there has been a substantial increase in the therapeutic agents approved for the treatment of PD. This article will review key clinical trials of pharmacological agents in the treatment of early PD. The majority of the studies reviewed define early PD as Hoehn and Yahr stage <3. The trials discussed here examine levodopa, monoamine oxidase B (MAO-B) inhibitors, and dopamine agonists. Anticholinergic agents and amantadine are also used for treatment of early PD; however, there have been no recent studies assessing their efficacy.

Levodopa

Levodopa, a dopamine precursor that is converted to dopamine in the nigrostriatal system, remains the most effective agent for the treatment of PD.^{5,6,7} 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 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-naïve patients randomized to receive either placebo or carbidopa-levodopa at doses of 37.5–150, 75–300, and 150–600mg.⁸ Study subjects were treated for 40 weeks and then underwent withdrawal of medication over a subsequent two-week period. The primary outcome measure was change in the UPDRS between baseline and 42 weeks (off medication). The results showed that regardless of levodopa dose, the severity of parkinsonism increased more in the placebo group (7.8 points) than in treatment groups (1.9 points in the 150mg group, 1.9 in the 300mg group, and -1.4 in the 600mg group; $p < 0.001$). The treatment groups showed significantly lower (better) UPDRS ADL and motor scores during the treatment phase as well as after two-week washout (the end-point of the study). Subjects in the 600mg treatment group had a significantly higher incidence of dyskinesia (16.5% compared with 3.3% in the placebo group). However, the incidence of dyskinesia was similar to that seen in the placebo group in the two lower-dose groups of levodopa. The study conclusion

was that levodopa "either slows progression of PD or has a prolonged effect on motor disability" that exceeds the two-week washout period. This benefit has to be weighed against the higher incidence of drug-induced dyskinesia.

Monoamine Oxidase B Inhibitors

Rasagiline

Rasagiline is an irreversible MAO-B antagonist. Compared with selegiline, it does not have amphetamine byproducts of metabolism. Rasagiline is approved for both monotherapy and adjunct therapy (with levodopa) in PD.

The efficacy of rasagiline as monotherapy in early PD was investigated in a number of studies. The TEMPO trial, conducted by the Parkinson Study Group, was a randomized, double-blind, placebo-controlled trial that enrolled 404 patients with early PD not previously exposed to symptomatic therapy other than anticholinergics.^{9,10} Subjects were randomized to receive rasagiline 2mg/day, rasagiline 1mg/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 2mg/day treatment group versus placebo was a 3.6-point benefit, and in the 1mg/day group a 4.2-point benefit (both $p < 0.001$). Rasagiline was well tolerated. Asthenia was the only significantly more prevalent adverse effect seen at a different rate in the placebo (10.9%) and rasagiline (4.5%) groups. Based on the results of this study, rasagiline 1mg was approved for use in early PD.

Due to the chemical structure of rasagiline, physicians should be aware of potential food and drug interactions. While rasagiline is a selective MAO-B antagonist at the approved dose, there is a theoretical risk of 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) and amine-containing medications, including certain cough and cold drugs. While rasagiline can be used with antidepressants that increase brain serotonin level (such as tricyclic antidepressants, selective serotonin re-uptake inhibitors, and serotonin/noradrenergic re-uptake inhibitors), awareness and appropriate patient counseling about possible adverse effects are essential. There are certain restrictions of use of rasagiline with narcotic analgesics, specifically meperidine.

Dopamine Agonists

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

The efficacy of pramipexole and ropinirole as monotherapy in early PD has been demonstrated in a number of well-designed studies.¹¹⁻¹³ Both agents belong to the group of synthetic non-ergot dopamine agonists with affinity to dopamine D₂ family receptors (particularly the D₃ receptor subtype). There are no studies with head-to-head comparison of these two agents, but clinical experience points to comparable

efficacy if used in equivalent doses. Ropinirole requires a longer titration schedule compared with 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, impulse control disorders. For example, in a placebo-controlled study of pramipexole in 335 patients conducted by Shannon et al.,¹⁴ the incidence of these side effects was the following: nausea (39% with pramipexole versus 20.5% with placebo), insomnia (25.6 versus 12.9%), constipation (17.7 versus 6.4%), somnolence (18.3 versus 8.8%), and visual hallucinations (9.7 versus 2.3%). The most common side effects seen in a 241-subject six-month randomized, placebo-controlled study of ropinirole versus placebo in patients with early PD¹² were: nausea (52.6% treatment versus 21.6% placebo), dizziness (36.2 versus 18.4%), somnolence (36.3 versus 4.8%), constipation (10.3 versus 6.4%), and syncope (10.3 versus 1.6%).

Long-acting Preparations of Dopamine Agonists

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

Ropinirole in a 24-hour prolonged-release formulation was recently approved by the US Food and Drug Administration (FDA). The EASE-PD Study¹⁵ evaluated the efficacy of extended-release compared with immediate-release ropinirole in early PD. The study was a randomized, double-blind, non-inferiority cross-over study of 161 patients. Concurrent treatment with selegiline, amantadine, and anticholinergics was allowed. During a 12-week dose-titration period, patients were assigned to either ropinirole immediate- or extended-release, titrated to symptomatic benefit up to a 24mg daily dose, followed by three eight-week maintenance periods. After each period, subjects were switched between the immediate- and extended-release agents in a blinded fashion. There was no significant difference between immediate- and extended-release ropinirole based on change in UPDRS score (-10.4 points for 24-hour ropinirole and -8.9 for immediate-release). The extended-release groups had higher mean daily ropinirole doses (17.9 and 16.8mg/day) than the immediate-release groups (7.5 and 6.9mg/day). This difference in the dosing between the immediate- and extended-release preparations could be due to differing titration schedules rather than reduced potency of the extended-release formulation. The difference could also be explained by better tolerability of ropinirole extended-release when titrated more rapidly than the immediate-release form. 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 controlled-release preparation in equivalent doses directly without re-titration. Ropinirole extended-release is available in a 2-24mg dose range and offers the convenience of once-a-day drug delivery.

Rotigotine

Rotigotine is the first dopamine agonist developed in a transdermal continuous 24-hour delivery preparation. In the US it was approved at doses up to 6mg/24 hours for treatment of early PD. The Parkinson

Study Group conducted a multicenter, double-blind, placebo-controlled trial assessing the efficacy of transdermal rotigotine in early PD.¹⁶ A total of 242 patients were randomized to receive either placebo patches or patches with rotigotine doses of 2, 4, 6, and 8mg/24 hours.¹⁶ The trial consisted of a four-week screening period during which patch-application training and compliance were assessed with a placebo patch. This was followed by a seven-week dose maintenance phase and a one-week dose de-escalation period, and the study concluded with a two-week safety follow-up period. The primary outcome measure was change in the sum of UPDRS parts II and III between baseline and follow-up at 11 weeks. Compared with placebo, the 2mg group experienced a 0.91-point reduction of the UPDRS score, the 4mg group had a 2.78-point reduction, the 6mg group had a 4.83-point reduction, and the 8mg group had a 5.23-point reduction. The effects were significant in the 6 and 8mg treatment groups ($p \leq 0.001$), and a dose-response relationship was demonstrated from the 2 to 8mg dose. Adverse effects noted in the treatment groups over placebo were nausea, dizziness, somnolence, insomnia, vomiting, fatigue, and application-site reaction.

Another six-month efficacy trial of transdermal rotigotine was performed in 2007.¹⁷ In this multicenter, randomized, double-blind, placebo-controlled trial, 277 patients were randomized to receive either placebo or rotigotine patch titrated to symptom control (maximum dose 6mg/day; mean dose 5.7mg/day) and maintained on a stable dose for six months. The rotigotine treatment group showed a mean decrease in UPDRS part II and III scores of 3.98 points ($p < 0.0001$; primary efficacy end-point 1) compared with an increase of 1.31 points in the placebo group. Improvement in the motor component of the UPDRS accounted for the greatest contribution to overall reduction of scores. Additionally, in the rotigotine group 48% of patients were deemed 'responders' (achieving at least 20% improvement in UPDRS scores) compared with 19% for the placebo group. Adverse events in this study were similar to those seen in the Parkinson Study Group trial, with application-site reactions (44% treatment versus 12% placebo), nausea (41 versus 17%), somnolence (33 versus 20%), dizziness (19 versus 13%), and headache (16 versus 9%) more prevalent in the drug treatment group than in the placebo group.

Currently, the commercially available rotigotine patch Neupro[®] has been voluntarily recalled from the US market secondary to 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.

Impact of the Choice of Early Treatment on the Risk for Developing Motor Complications

Treatment of 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, related to the progressive degenerative process with the reduction of the dopamine storage capacity of the nigrostriatal system and pulsatile stimulation of the post-synaptic receptors in which medications play a role. In deciding on pharmacological treatment of early PD, one must consider these motor complications.

A number of studies have been conducted to compare the risk for developing motor complications with the use of levodopa versus dopamine agonists as the initial treatment options. The Parkinson Study Group reported a four-year study in which levodopa and pramipexole were compared with regard to time to onset of motor complications as the primary outcome.¹⁷ Three hundred and one patients were

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randomized to receive either pramipexole 0.5mg three times per day or 25/100mg carbidopa/levodopa three times per day. After dosage escalation of 10 weeks, patients in both groups were allowed additional open-label levodopa as dictated by symptoms. The pramipexole-treated group showed a significantly lower risk of developing dyskinesias (24.5 versus 54%) and wearing off (47 versus 62.7%). Disabling dyskinesia was uncommon in both groups at 48 months. UPDRS score improvement was greater in the levodopa group than the pramipexole group (-3.2 versus 2), despite the fact that both groups were allowed to be supplemented with open-label levodopa as necessary. The levodopa-treated group also showed a significant reduction in the risk for developing freezing (25 versus 37.1%). Somnolence (36 versus 21%) and edema (42 versus 15%) were more common in the pramipexole-treated group.

Rascol et al. reported a five-year study of the incidence of dyskinesia in patients with early PD, comparing levodopa versus ropinirole.¹⁹ Two hundred and sixty-eight patients were randomized to receive either ropinirole or levodopa. Open-label levodopa supplementation was allowed in both groups if symptoms were not adequately controlled with the study medications. At five years there was a significantly lower incidence of dyskinesia in the ropinirole-treated group versus the levodopa group (20 versus 45%) regardless of levodopa supplementation. Ropinirole monotherapy (before levodopa supplementation) was associated with a 5% incidence of dyskinesia. However, the UPDRS mean motor and ADL scores were lower in the levodopa group compared with the ropinirole group, and the difference in the mean motor scores was statistically significant (-0.08 for the ropinirole group versus -4.8 for the levodopa group; $p = 0.008$). Regarding other adverse effects, ropinirole was associated with a higher incidence of hallucinations (17 versus 6%), somnolence (27 versus 19%), and leg edema (14 versus 6%), while depression was seen more prevalently in the levodopa group (23 versus 15%). A similar study was conducted with pergolide.²⁰

All of these studies support the notion that early treatment with dopamine agonists is associated with a lower risk for developing motor complications at least over the span of five years of treatment. When prescribing dopamine agonists, physicians should be aware of certain adverse events more frequently associated with this group

of agents compared with other dopaminergic therapies. These include higher risk for somnolence, confusion, orthostatic hypotension, leg edema, and the more recently reported entity of impulse control disorders (ICDs). For example, a recent cross-sectional study of 3,090 treated PD patients reported an overall prevalence of ICD of 13.6% and a prevalence of ICD of 17.1% in patients treated with a dopamine agonist.^{21,22} The advantage of dopamine agonists in delaying onset of motor complications has to be weighed against the lower efficacy of dopamine agonists compared with levodopa and the higher risk of adverse events.

The Concept of Neuroprotection in Parkinson's Disease

There have been major advances in symptomatic treatment of PD of late. This is particularly true for the motor manifestations of the disease. Despite this progress, there remain no agents proven to slow or arrest the progression of the disease. Moreover, defining neuroprotection and identifying proper metrics by which to measure neuroprotective benefit has been challenging.

The ELLDOPA study discussed earlier investigated the effects of levodopa as a possible neuroprotective agent.⁸ After the washout period, the continued benefit seen in the levodopa-treated cohort over placebo was felt to possibly be evidence of a neuroprotective benefit. However, confounding this is the notion that levodopa may have a prolonged therapeutic effect lasting beyond the two-week washout period used in that study. The study also utilized single photon emission computed tomography (SPECT) imaging labeled with 2beta-carboxymethoxy-3beta (4-iodophenyl) tropane (β -CIT) (DAT) as the surrogate marker of disease progression. Imaging data demonstrated an accelerated loss of dopaminergic transporter uptake in the levodopa groups relative to the placebo group at 40 weeks. It is unclear whether this result reflects a true negative impact of levodopa on the rate of progression of the neurodegenerative process or represents a pharmacokinetic/pharmacodynamic effect of levodopa causing downregulation of dopamine transporter uptake. Additional studies will be necessary to clarify the discrepancy between the clinical and imaging outcomes of the study. Currently, there are no definitive data on the neuroprotective effect of levodopa and no data demonstrating a neurotoxic effect of levodopa. Such information is important to communicate to the patients as the concern of levodopa toxicity frequently becomes the reason for inappropriate delay of initiation of levodopa therapy.

Dopamine agonists have also been demonstrated to have a neuroprotective effect in tissue culture, but no definitive data exist in the clinical trials. The previously discussed Parkinson Study Group study of pramipexole versus levodopa in patients with early PD also used β -CIT imaging (DAT) as a surrogate marker of disease progression in a subset of patients over four years.⁹ β -CIT imaging was performed at 22, 34, and 46 months. The study found that at each of these evaluation periods there was decreased loss of DAT binding in the pramipexole group compared with levodopa ($p=0.004$, 0.009 , and 0.001 at 22, 34, and 36 months, respectively).

A similar study was conducted to compare the impact of ropinirole versus levodopa on the rate of loss of dopaminergic neurons using ¹⁸F-dopa positron emission tomography (PET) imaging in the REAL-PET

study.²³ This prospective, double-blind trial randomized 186 patients with early PD to levodopa versus ropinirole treatment for two years. PET images were obtained at four weeks (baseline) and then at two years. The primary outcome measured was the mean percentage reduction in side-to-side averaged putamen ¹⁸F-dopa uptake. At two years the study found a lower percentage of reduction in the ropinirole group (-14.1%) compared with the levodopa group (-22.9%; $p<0.001$).

These studies, which used different dopamine agonists (pramipexole and ropinirole), different ligands, and different imaging techniques (PET and SPECT), demonstrate consistent results, pointing to a potential neuroprotective effect of dopamine agonists. However, interpretation of these results is limited by the concern of potential pharmacokinetic up- or downregulation of the transporter binding and lack of a placebo arm. To date, there is no proven neuroprotective effect of dopamine agonists in PD.

The potential neuroprotective effect of rasagiline was examined in two studies. The TEMPO study discussed above had a delayed-start extension study in which subjects who were initially randomized to placebo were switched to active therapy after the first 26 weeks of treatment.⁹ The degree of disability was measured by the UPDRS score at 12 months.⁹ Subjects treated with rasagiline from the beginning had a statistically significant reduction of progression of disability compared with those started six months later. The larger ADAGIO study was launched to confirm the disease-modifying benefit of rasagiline.²⁴ This trial also used a delayed-start design similar to the TEMPO study but was larger ($n=1,176$) and had a longer duration (72 weeks). Patients were started on either placebo or rasagiline (1 or 2mg) in the first phase of the trial (36 weeks). In the second phase, all patients were treated with active drug, still blinded to the dosage assignment. This design allows exploration of the potential neuroprotective benefit of a drug that also has a symptomatic effect. If the drug has a purely symptomatic benefit, the impact on disability should be the same at the end of the study independent of the time of initiation of treatment. However, if the drug has a neuroprotective benefit, the difference between the early treatment group versus the delayed treatment group at the end of the study will reflect such effect. The study was completed and presented at the meeting in poster format, but full data are not yet available. The presented data supported a positive impact of early initiation of rasagiline 1mg on delaying progression of motor disability in early PD. Interestingly, the 2mg dose did not reach all primary end-points.²⁵

The PRECEPT trial looked at the potential neuroprotective properties of CEP-1347, a mixed-lineage kinase inhibitor.¹⁰ The rationale for the study is the ability of CEP-1347 to blockade apoptotic pathways implicated in the pathogenesis of PD. In the trial, 806 subjects were randomized equally into four groups to receive CEP-1347 at doses of 10mg twice a day, 25mg twice a day, 50mg twice a day, or matching placebo. The primary clinical end-point was time to development of disability requiring dopaminergic therapy. Secondary end-points examined changes in the UPDRS and β -CIT SPECT DAT imaging. After an average of 21.4 months of follow-up, the pre-specified interim data analysis concluded that it would be futile to continue treatment with CEP-147, and the study was terminated. At the time of study termination, 57% of patients receiving placebo reached

the primary end-point; 65% of the 10mg BID treatment group, 59% of the 25mg BID group, and 64% of the 50mg BID group had reached disability requiring dopaminergic therapy. Mean time to onset of disability was 539 days in the placebo group compared with 365, 457, and 364 in the three treatment groups, respectively ($p=0.0249$). Secondary end-point analysis showed similar patterns.

Coenzyme Q10 (CoQ10), an antioxidant that participates in mitochondrial complex I function, has been investigated as a possible neuroprotective agent in PD. The pathogenesis of PD is not clearly understood; however, there is known mitochondrial dysfunction in nigral cells leading to free radical formation (or decreased scavenging) and toxicity secondary to this. Results of the pilot study of the effects of CoQ10 in early PD were reported in 2002.²⁶ The study randomized 80 newly diagnosed PD patients not exposed to dopaminergic therapy to receive either placebo or CoQ10 at doses of 300, 600, or 1,200mg/day in a multicenter, double-blind trial. The primary end-point of the study was change in the total UPDRS score from baseline to 16-month visit or the time of initiation of symptomatic therapy.

The adjusted mean change in the UPDRS for the placebo group was +11.99 compared with +8.81, +10.82, and +6.69 in the treatment groups receiving 300, 600, and 1,200mg per day, respectively. The difference between the placebo group and the 1,200mg/day group was significant ($p=0.04$). This trial established a positive trend for a possible neuroprotective effect of CoQ10. CoQ10 was investigated in another study that was conducted by the Neuroprotection Exploratory Trials in Parkinson's disease (NET-PD) investigators. The study included two compounds: CoQ10 and a novel compound, GPI-1485.¹⁰ The latter is an immunophilin-ligand compound that binds immunosuppressive drugs such as cyclosporine, FK506, and rapamycin. Immunosuppressive agents bound to this compound can promote nerve growth *in vitro* and *in vivo*. In this trial, 213 patients were randomized to receive either CoQ10 2,400mg/day, GPI-1485 4,000mg, or placebo. This trial was designed as a single-arm futility trial to assess whether further investigation into these compounds would be worthwhile. Futility studies are not powered to assess the efficacy of the compounds but rather to exclude agents that have no chance of succeeding in future investigations. Such a design requires a smaller sample size and allows pilot studies to be conducted more efficiently with fewer subjects. The study used historical placebo control data for comparison (the placebo arm of the previously conducted studies) with a small contemporaneous calibration placebo group. The primary end-point of the study was the change in the total UPDRS score over 12 months or at the time of need

for dopaminergic therapy, whichever was earlier. The mean change in the UPDRS for the CoQ10 group was 7.52 and for the GPI-1485 group it was 7.41. The investigators compared the means with 30% of the historical rate of progression of disability established by the DATAOP study (total 10.65, 30% being 7.65). As such, neither CoQ10 nor GPI-1485 could be rejected as futile using this analysis, and both met the criteria for consideration in further investigation. However, the exploratory analysis using an adjusted futility threshold based on the contemporaneous placebo group demonstrated futility of both agents. A definitive phase III study of CoQ10 is under way now.

The NED-PD group also investigated the potential efficacy of creatine and minocycline in a similar futility trial design.²⁰ In this study, 200 subjects were randomized to either creatine 10g/day or minocycline 200mg/day, with a small calibration placebo group. The primary end-point was identical to that used in the previously described study (namely the change in UPDRS from baseline to the time of need for dopaminergic rescue therapy or 12 months). The mean UPDRS change was 5.6 in the creatine group and 7.09 in the minocycline group. Neither of these results exceeded the pre-determined futility threshold using historical controls, but minocycline was futile using contemporaneous control. Adverse effects noted across the three treatment groups were upper respiratory symptoms (26%), joint pain (19%), and nausea (17%). Creatine was generally well tolerated, although a few patients developed clinically significant elevations in serum creatinine. Minocycline was associated with teeth and skin discoloration. More patients withdrew from the study secondary to intolerability in the minocycline compared with the creatine or placebo groups. Based on the results of that study, the decision was not to pursue further studies of minocycline. A large phase III placebo-controlled five-year study of creatine as a potential disease-modifying agent in early PD is now under way.

Summary

The management of early PD has been enhanced in recent years by the introduction of a number of new agents. While 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. More studies into direct comparison between and within these classes of medications are necessary and are forthcoming. Neuroprotection represents a major unmet need in the management of PD. A number of neuroprotective studies are ongoing and hopefully will lead to the development of disease-modifying treatment of PD. ■

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