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Can we achieve neuroprotection with currently available anti-parkinsonian interventions?

C. Warren Olanow, MD, FRCPC

ABSTRACT

A disease-modifying therapy is the most important unmet medical need in the treatment of Parkinson disease (PD). Laboratory studies have identified many promising candidate agents, but none has been proven to be neuroprotective in PD. A major limitation has been the development of an endpoint that accurately reflects the underlying disease state. This dramatically limits the potential for a new drug being approved as a disease-modifying agent in PD. For the present, the best opportunity to provide patients with PD with a disease-modifying effect is with agents that have been approved for their symptomatic effects. This article reviews currently available drugs for PD and considers the evidence that they might have neuroprotective effects in PD.

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The management of patients with Parkinson disease (PD) has become increasingly complex, with a large number of medical and surgical therapies now available to the treating physician.1 Most of these treatments are based on a dopamine replacement strategy, and while they can provide considerable benefit, particularly in the early stages of the disease, patients eventually experience meaningful disability. Chronic treatment is associated with motor complications, neuropsychiatric problems, and impulse control disorders in many patients. Further, new features emerge over time such as falling, freezing, autonomic dysfunction, mood disorders, and dementia which likely reflect degeneration of non-dopaminergic neurons and are not satisfactorily controlled by currently available treatments. Finally, disease progression continues despite current treatment. Accordingly, there is an urgent need for a therapy that can slow, stop, or reverse the progression of the underlying disease process. In the laboratory, there has been an intensive search for new targets and new candidate agents that might block the pathogenic cascade and so modify disease progression.2 However, the development of such a “neuroprotective” drug is likely to be many years into the future and is unlikely to have a significant impact on the lives of patients with PD today who are desperately in need of such a treatment now. This article will review the clinical evidence relating to the possibility that some currently available anti-parkinsonian therapies might have a disease-modifying effect in PD.

Levodopa. Levodopa is the most widely used and most effective anti-parkinsonian agent. However, the introduction of levodopa treatment is frequently delayed because of theoretical concerns about toxicity and the risk of the drug-inducing motor complications when it is administered in standard oral formulations.3 Concerns about neurotoxicity are based on the potential of the oxidative metabolism of levodopa to generate free radicals and other reactive oxygen species. Indeed, high doses of levodopa lead to degeneration of cultured dopamine neurons. However, there is little experimental evidence to suggest that levodopa causes dopamine cell death in vivo. Administration of levodopa to normal or dopamine-lesioned animals does not result in degeneration of dopamine neurons. Further, administration of levodopa to animals treated with buthionine sulfoxamine to reduce levels of glutathione and induce oxidative stress does not cause dopamine cell death. In contrast, it is possible that levodopa might have protective effects. Current evidence indicates that dopamine receptors are linked to trophic receptors (particularly via the epidermal growth factor receptor) and that stimulation leads to activation of the PI-3 Kinase/Akt anti-apoptotic pathway.4

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In the ELLDOPA clinical study, levodopa was tested to determine if early treatment accelerated or protected against the loss of dopamine neurons in comparison to placebo. Drug naïve PD patients were randomized to one of three doses of levodopa (150, 300, or 600 mg per day) or placebo, and treated for 9 months. Thereafter, all treatment interventions were discontinued for up to 2 weeks. A comparison of change in Unified PD Rating Scale (UPDRS) scores between baseline and final visits was the primary endpoint. Patients treated with levodopa had significantly less deterioration in UPDRS scores than those in the placebo group. The mechanism responsible for this observation is not yet known. One possibility is that levodopa has trophic or protective effects. Alternatively, levodopa might have long duration benefits that are not completely eliminated after just 2 weeks of washout, although the magnitude of difference between the placebo and levodopa treatment groups is such that it makes this interpretation difficult to comprehend. Finally, it has been speculated that early treatment with a symptomatic drug might preserve compensatory responses and thus provide long-term benefits independent of any effect on cell survival. As part of this study, 2 beta-carboxymethoxy-3-b-carboxymethoxy-3 beta-(4-idodophenyl)tropane (beta-CIT) single photon emission computerized tomography (SPECT) scans were performed on a subset of patients. Interestingly, levodopa was associated with a faster rate of decline in this biomarker of nigrostriatal function than was placebo. In contrast to the clinical findings, this observation raised the possibility that levodopa might indeed be toxic. It is also possible that this effect could be explained by a pharmacological effect of levodopa on the expression of the dopamine transporter, although this has not been established (see later). For now, it cannot be said with any certainty that levodopa has either protective or toxic effects, and it is generally recommended that levodopa be used based on the needs of the individual patient, and its side-effect profile.

Dopamine agonists. Dopamine agonists are widely used in the early treatment of patients with PD because of their potential to provide symptomatic benefits with a low risk of motor complications. The notion that they might be protective in PD stems from laboratory studies showing their capacity to protect dopamine neurons in both in vitro and in vivo studies. Theoretical mechanisms for a protective effect in PD could include a direct antioxidant effect, permitting lower doses of levodopa to be used thereby reducing the formation of reactive oxygen species, and activation of presynaptic autoreceptors on dopamine neurons leading to reduced dopamine synthesis and metabolism. Most attention, however, has focused on the potential of dopamine agonists to provide antiapoptotic effects, although the responsible mechanism is not known and may differ with different agents. In one set of experiments, a variety of dopamine agonists were shown to be able to protect cultured dopamine neurons by activating the PI-3 Kinase/Akt system. Interestingly, different dopamine agonists had different effects on activating the PI-3 Kinase/Akt system and in providing neuroprotective benefits, despite all showing comparable activation of G proteins. This exciting work indicates that different agonists of the dopamine receptor may activate linked pathways differentially and have different capacities to provide protection in PD. More recently, we have shown that cell death induced by oxidative stress, and protection provided by the dopamine agonist, ropinirole, act through an Akt-mediated activation or inactivation of GSK-3beta, a molecule which appears to be central to cell death and survival in this model. In contrast to these findings, the dopamine agonist, pramipexole, has been shown to provide antiapoptotic effects that do not appear to depend upon dopamine receptor activation.

Two clinical trials have tested dopamine agonists as possible protective agents. The REAL-PET study compared ropinirole with levodopa using striatal fluorodopa uptake on PET as the primary endpoint, whereas the CALM-PD-CIT study compared pramipexole to levodopa using striatal beta-CIT uptake on SPECT as the primary endpoint. Both studies demonstrated that the rate of decline of the imaging biomarker was significantly less with the dopamine agonist than with levodopa. These results are compatible with the agonists being protective or with levodopa being toxic to dopamine neurons. These effects could not be differentiated as there was no placebo group in either study. It has also been suggested, as in the ELLDOPA study, that these results could be explained by dopamine agonists and levodopa having different pharmacological effects on the surrogate biomarker. The INSPECT study tried to test this hypothesis by comparing the effects of levodopa, pramipexole, and placebo on striatal beta-CIT uptake in a 12-week study. They found no evidence of a short-term regulatory effect, although the possibility that this might occur at a later time point could not be excluded. Thus, it remains uncertain if dopamine agonists have disease-modifying effects in PD, although this possibility remains, and has not been excluded. Many physicians routinely use dopamine agonists in early disease because they provide symptomatic benefits with a low risk of motor complications. Recent appreciation that this class of drugs is associated with excessive daytime sleepiness and impulse control disorders has caused some
Physicians to diminish their use of dopamine agonists, but this might change if it were established that they had disease-modifying effects. The PROUD study is currently exploring this potential in a clinical trial using a delayed-start design (see later).

**MAO-B inhibitors.** Selegiline and rasagiline are approved for the treatment of patients with PD and are frequently used in early disease because of their putative neuroprotective effects. Both agents are selective MAO-B inhibitors that are thought to provide symptomatic effects by increasing synaptic dopamine levels. In the laboratory, however, both agents have also been shown to have antiapoptotic effects in both in vitro and in vivo models of PD.\textsuperscript{16–19} Protective benefits with selegiline appear to be primarily related to its metabolite, desmethylselegiline, while these effects are seen with both rasagiline and its metabolite, aminooxidan. Rasagiline also does not generate amphetamine metabolites which are thought to interfere with protective effects. Interestingly these protective effects are not thought to be related to MAO-B inhibition, but rather to the propargylamine ring that is incorporated within the molecular structure of both of these agents.\textsuperscript{17,19} Studies have demonstrated that propargylamine agents provide antiapoptotic effects by binding to glyceraldehyde-3-phosphate dehydrogenase and preventing its translocation to the nucleus where it inhibits the transcriptional upregulation of antiapoptotic proteins such as Bcl-2, SOD-2, and glutathione.\textsuperscript{20–22}

Clinically, selegiline was initially tested for putative neuroprotective effects in the classic DATATOP study.\textsuperscript{23} Here, it was shown to significantly delay the need for levodopa in patients with untreated PD in comparison with placebo. However, the drug was also demonstrated to have symptomatic effects, which confounded interpretation of the study. Thus, it was not possible to determine if the benefits observed in this trial were because the drug slowed the ongoing degeneration of dopamine neurons, or if the symptomatic effects of the drug merely masked ongoing neurodegeneration. The SINDÉPAR study tried to resolve these issues by randomizing patients with untreated PD to selegiline or placebo and comparing the rate of change in UPDRS scores between the untreated baseline and an untreated final visit performed 2 months after withdrawal of study intervention.\textsuperscript{24} Although selegiline treatment was associated with a highly significant reduction in the rate of UPDRS decline, it could not be determined with certainty if this was due to a protective effect or to a long-duration symptomatic benefit with inadequate washout. Thus, here too, the situation was confounded and one could not say with certainty that the drug had a disease-modifying effect. On the other hand, long-term follow-up studies of the DATATOP cohort suggest that patients randomized to selegiline have less freezing,\textsuperscript{25} and two long-term prospective randomized studies performed in Scandinavia suggest that patients initiated on therapy with selegiline have better outcomes.\textsuperscript{26,27} Thus, the possibility that selegiline has neuroprotective effects has not been proven, but neither has it been excluded.

To test if rasagiline has disease-modifying effects, patients in the TEMPO study who were randomized to receive either rasagiline or placebo for 6 months (early treatment phase) underwent a 6-month extension phase in which patients in both treatment groups received rasagiline (delayed-treatment group).\textsuperscript{28,29} At final visit (12 months), patients who had been randomized to receive early treatment with rasagiline were significantly better on UPDRS scores than were those randomized to late rasagiline treatment, even though both groups were receiving the same treatment at this time point. This study suggests that early treatment results in benefits that cannot be equaled with later initiation of the same therapy. These results are consistent with a neuroprotective effect, although they could also be explained by delayed, cumulative, symptomatic effects, or by maintenance of a beneficial compensatory effect which, once lost, cannot be restored.

To further test the possibility that rasagiline has a disease-modifying or neuroprotective effect, the ADAGIO study was performed using the delayed-start design as the primary goal of the study (see figure).\textsuperscript{30} In this study, patients were randomized to receive treatment with rasagiline (1 or 2 mg per day) or placebo for 9 months (phase I). At the end of phase I, patients in all treatment groups received treatment with rasagiline (1 or 2 mg per day) for an additional 9 months without breaking the initial blind (phase II).\textsuperscript{31} The primary analysis of this study involves multiple endpoints: (a) evidence of divergence of the slopes of the change in UPDRS scores during phase I of the study, (b) evidence of a significant difference between the early and delayed treatment groups (rasagiline 1 or 2 mg per day) at the end of phase II of the study, and (c) evidence that there is non-inferiority of slopes of the UPDRS slopes for the early and delayed rasagiline 1 or 2 mg groups during weeks 48–72 in phase II of the study (i.e., the lines are not converging). Change in UPDRS scores between the rasagiline (1 or 2 mg) and placebo groups at the end of phase I of the study is a secondary endpoint. If all of these endpoints are met, this will argue that early treatment with rasagiline has an effect that cannot readily be accounted for by a symptomatic effect and is consistent with the drug having a disease-modifying property as both groups are on the
same drug at the end of the study. This novel trial
design and complex analysis have not been used be-
fore in a regulatory clinical trial and it is not yet
known if positive results will warrant issuing a label
for a disease-modifying effect. Preliminary data pro-
vided at the time of this publication indicate that
positive results with respect to all of these endpoints
was achieved with rasagiline 1 mg per day, but not
with rasagiline 2 mg per day. These data, and their
clinical significance, will be considered in detail in
future publications.

Surgical therapies. Deep brain stimulation has be-
come an accepted form of therapy for the treatment
of patients with advanced PD who suffer motor com-
plications. However, it is theoretically possible that
stimulation or lesions of the subthalamic nucleus
(STN) might have downstream effects that slow dis-
case progression. In the PD state, there is increased
firing of STN neurons, which could be caused by
disinhibition because of reduced dopamine activity
or to excess direct cortical stimulation. It can be hy-
pothesized that increased firing of STN neurons,
which use glutamate as a neurotransmitter, could re-
sult in excitotoxic damage in target structures includ-
ing the substantia nigra pars compacta, globus
pallidus internus, and pedunculopontine nucleus,
and that lesions or stimulation of the STN might have protective effects. Indeed, it has been shown
that STN lesions prevent dopamine neuronal de-
generation following striatal administration of 6-hydroxydopamine in rats. It is not so certain
that this is applicable to patients with PD, as there
was no difference in the rate of decline of off-
medication/off-stimulation UPDRS scores between
patients receiving deep brain stimulation of the STN
and globus pallidus internus. This will be further ex-
plored in ongoing prospective blinded studies where
PD patients have been randomized to stimulation of
these two targets.

Possible neuroprotective effects of current therapeutic
agents for PD: Clinical implications. To date, no agent
has been established to have neuroprotective effects
in PD. Nonetheless, several agents that are routinely
used in PD have been shown to have neuroprotective
benefits in laboratory models and to have benefits in
clinical trials. What does this mean for routine PD
care today? Clearly, if we knew that any one of these
agents did slow down disease progression, we would
favor introducing such therapy at the earliest time
point possible. There are also other indications sug-
gesting that early introduction of symptomatic treat-
ment might have disease-modifying effects and better
long-term outcomes by preserving beneficial compen-
satory responses and avoiding maladaptive compen-
satory effects. However, while there are many
promising agents in the laboratory, establishing that
such agents have protective effects in patients with
PD has not proven to be easy. Obstacles to defining
a neuroprotective therapy include lack of precise
knowledge as to the mechanism responsible for cell
death, lack of relevant animal models, uncertainty as
to dosing, and the lack of a clinical trial methodology
that can unequivocally define a disease-modifying
therapy which is not confounded by symptomatic or
pharmacological effects of the study intervention.

Once these problems have been resolved, it will still
take considerable time to complete all the preclinical
toxicity studies and clinical trials necessary for regis-
tration and approval. Thus, new therapies, as promis-
ing as they might be, are unlikely to be useful for
patients with PD in the clinic today. The advantage
of the therapies discussed above is that, while they are
not proven to be disease-modifying, this possibility
has not been disproven, and they are available now.
Indeed, we have the potential to integrate any
disease-modifying effect that they might have into
our symptomatic treatment approach.
Levodopa is an effective symptomatic therapy, but its initiation is typically delayed because of the risk of motor complications. Dopamine agonists are associated with a very low risk of motor complications, but they are not as efficacious as levodopa and are associated with neuropsychiatric problems, swelling of the limbs, sedation, and impulse control disorders. MAO-B inhibitors have modest anti-parkinsonian effects in early PD and are well tolerated with a very low side-effect profile. A practical approach to a typical PD patient who is not elderly or cognitively impaired, might then be to start treatment at the time of diagnosis with an MAO-B inhibitor, and supplement with a dopamine agonist, and ultimately a levodopa preparation, when enhanced symptomatic effects are required. Introduction of these anti-parkinsonian drugs in this sequential fashion provides benefit from the time of diagnosis, minimizes the risk of adverse effects, and provides patients with the potential to have any disease-modifying effects associated with these therapies.

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