New and Emerging Therapies for Parkinson Disease

Joseph Jankovic, MD

Few neurological disorders have been more successful in introducing novel therapies than Parkinson disease (PD). However, despite enormous progress, many challenges remain. Although levodopa is still the most effective drug in the symptomatic treatment of PD, adverse effects, particularly motor fluctuations and dyskinesias, limit its usefulness.1 Furthermore, there is a growing concern about the escalating cost of PD treatment: the cost-benefit aspect of the novel approaches must be balanced against the advantages of long-term experience with established treatments.

NEUROPROTECTIVE THERAPY

Neuroprotective therapies can be defined as those medical or surgical interventions that favorably alter the underlying etiology or pathogenesis and thus delay the onset or slow, or even halt, the progression of the neurodegenerative process. To the extent that such therapies may prevent the neurodegenerative process, it is essential that they are implemented early in the course of the disease.

**Monoamine Oxidase Inhibitors (MAOIs)**

The finding that selegiline prevents Parkinsonism induced by the oxidized form of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) has stimulated interest in an antioxidative therapy to retard the progression of PD and other neurodegenerative diseases.2 Selegiline, the L-isomer of N-propynyl-methamphetamine, acts as a “suicide substrate” for monoamine oxidase (MAO) type B, irreversibly inhibiting this enzyme. While selegiline delays the need for levodopa therapy, the initial benefits of selegiline are not sustained, and the drug does not seem to prevent the development of levodopa-related motor fluctuations and dyskinesias.3 Selegiline does, however, have a levodopa-sparing effect, and it smooths out levodopa-related motor fluctuations, possibly by prolonging dopamine-induced responses in midbrain dopaminergic neurons.4 Although the role of selegiline as a neuroprotective agent has been debated, there is evidence that selegiline may act through mechanisms other than MAO inhibition and have a potent antiapoptotic effect.5

Besides selegiline, there are other MAOIs currently being investigated as potential neuroprotective agents. Rasagiline (TVP-1012), a selective, irreversible MAO type B inhibitor, which is 5 times more potent than selegiline in preventing MPTP-induced parkinsonism, is currently being studied in a multicenter clinical trial. In contrast to selegiline, the major metabolite of rasagiline, 1-(R)-aminodand, is devoid of amphetamine-like properties.6 Although the drug seems to be well tolerated, long-term clinical data are lacking. Experimental studies, however, indicate that rasagiline rescues dying neurons and, in addition to its neuroprotective action, it has a symptomatic, dopaminergic effect.

**Antiexcitatory Drugs**

There is considerable theoretical and experimental support for the use of anti-glutamatergic agents as potential neuroprotective drugs. Since the neuronal activity is increased in the subthalamic nucleus (STN) and in the internal seg-
ment of globus pallidum (GPi) of parkinsonian animals and humans, and since STN provides excitatory (glutamatergic) input to GPi, glutamate inhibition would be expected to improve parkinsonism. Indeed, N-methyl-D-aspartate (NMDA) antagonists prevent the selective toxic effects of the 1-methyl-4-phenylpyridinium ion and therefore may have a neuroprotective effect. Remacemide, an anticonvulsant with anti-NMDA effects, has been shown to enhance the effects of levodopa in parkinsonian rats and monkeys and is currently being evaluated as a potential neuroprotective drug in the treatment of PD and Huntington disease. Certain anticholinergic drugs and amantadine possess NMDA-blocking properties that, in part, may account not only for their symptomatic benefit, but also for their putative favorable effects on the natural course of the disease. Riluzole, a drug approved for the treatment of amyotrophic lateral sclerosis, acts primarily by inhibiting glutamic acid release and noncompetitively blocking NMDA receptors, and as such it may exert anticeitotoxic effects similar to those of NMDA antagonists. Preliminary results indicate that the drug is well tolerated in patients with PD and that it has limited or no symptomatic benefits. Finally, agents that improve energy metabolism, such as coenzyme Q10 and nicotinamide, protect animals against the toxic effects of malonate, a mitochondrial complex II inhibitor, and thus may be valuable neuroprotective agents.

Trophic Factors

One particularly promising therapeutic and potentially neuroprotective approach involves the use of neurotrophic factors, particularly the glial cell line–derived neurotrophic factor (GDNF). This trophic factor has been reported to enhance the survival of midbrain dopaminergic neurons in vitro and to rescue degenerating neurons in vivo. Intraventricular administration of GDNF in experimental monkeys ameliorates parkinsonian findings, reduces levodopa-induced adverse effects, and results in a 20% enlargement of nigral neurons accompanied by increased fiber density. These encouraging observations have led to a multicenter trial in patients with moderately advanced PD currently being conducted in North America. Animal and human studies have provided evidence that GDNF ganglioside treatment improves parkinsonian features, possibly by enhancing dopamine synthesis and release, and this may have a neurotrophic action.

Immunomodulators

The possible role of immunologic mechanisms in PD-related cell death has obvious therapeutic implications. Immunomodulating agents, such as the anti-inflammatory drugs, may exert neuroprotective effects, but these drugs have not been tested in clinical trials. The immunophilin ligands, such as tacrolimus (FK-506), FKB-12, and GPI 1046, combine with receptor proteins called immunophilins, which are abundant in the brain, and cause suppression of the immune system by inhibiting the calcium-activated phosphatase calcineurin. GPI-1046, administered orally, has been found to promote growth of nigrostriatal dopaminergic neurons spared after MPTP-induced damage even more potently than trophic factors. Subsequent studies, however, have not been able to confirm the initial robust effects of GPI-1046. Whether these promising agents provide similar results in humans will not be known until clinical trials are completed.

DOPAMINERGIC THERAPY

Levodopa

Levodopa, the precursor of dopamine, is the most potent drug for controlling PD symptoms, but because of a concern about long-term complications, its use is often delayed until the parkinsonian symptoms are no longer satisfactorily controlled and the patient’s functioning is beginning to be compromised. This approach of delaying the initiation of levodopa therapy is based largely on the following 2 assumptions: (1) levodopa is neurotoxic and (2) levodopa-related complications can be postponed by delaying levodopa therapy. Although these assumptions have been challenged, many parkinsonologists continue to recommend this approach until more data become available to resolve this debate. A large, multicenter study sponsored by the National Institutes of Health evaluating the effects of levodopa on the progression of PD is currently in progress.

The concern about levodopa’s neurotoxic effects is supported by the knowledge that in the process of enzymatic and nonenzymatic oxidation of dopamine, toxic compounds such as quinones, semiquinones, hydrogen peroxide, and other oxylipids are produced. Levodopa’s neurotoxic effects have been demonstrated in some in vitro models, but the results are less compelling in in vivo models. One prospective study found that after 2 years of levodopa therapy, about half of the patients develop “wearing off”; one third, dyskinesias; one tenth, unpredictable on-off response; and many develop motor fluctuations and dyskinesias even during the first year of levodopa therapy. The mechanisms of motor fluctuations and dyskinesias are unknown, but pharmacological studies suggest that the wearing off effect is at least in part related to a shortening of levodopa’s half-life in the striatum as a result of the loss of the striatal dopaminergic terminal. Besides these presynaptic effects, postsynaptic mechanisms also seem to play a role in the development of the wearing off and on-off phenomenon.

Slow-release preparations of carbidopa-levodopa combination drugs (eg, Sinemet CR; DuPont, Wilmington, Del) offer the possibility of “smoothing out” clinical fluctuations by slowly releasing levodopa from a special matrix. Other methods designed to provide continuous dopaminergic stimulation include duodenal infusions of levodopa and oral solutions of levodopa, but these approaches are too cumbersome for most patients. In a double-blind, placebo-controlled study, amantadine reduced the severity of dyskinesia by 60% compared with placebo. This antidykinesic effect may be mediated by amantadine’s inhibition of NMDA receptors. Clozapine, an atypical neuroleptic, may also improve dyskinesias without worsening parkinsonian symptoms.
COMT Inhibitors

Another strategy to prolong levodopa response uses the inhibition of catechol-O-methyl transferase (COMT) by drugs such as tolcapone and entacapone. Although tolcapone has both central and peripheral effects, as compared with entacapone, which inhibits only peripheral COMT, it is not clear whether the 2 drugs have different clinical pharmacological effect. Tolcapone has a longer half-life (2 hours vs 1 hour) and can be administered 3 times per day (eg, 100–400 mg, 3 times per day), whereas entacapone requires more frequent administration (eg, 200 mg, 4–6 times per day), usually taken with each dose of levodopa. Theoretically, the COMT inhibitors have an advantage over slow-release levodopa preparations in that they do not delay the absorption of levodopa and, although they increase the levodopa plasma concentration area under the curve by about 50%, they do not increase the time to reach the peak concentration (Tmax) or the maximal concentration (Cmax) of levodopa. While this pharmacological action of the COMT inhibitors may prolong the on time without markedly increasing dyskinesias, most studies report a higher frequency of levodopa-induced dyskinesias in patients treated with COMT inhibitors.26,27 Both tolcapone and entacapone cause “orange” discoloration of urine; tolcapone may also cause nausea, diarrhea, postural hypotension, and abnormalities in liver enzyme levels requiring periodic monitoring of liver function. When compared with bromocriptine, tolcapone is clinically more effective and better tolerated,28 but further studies are needed to determine the relative roles of COMT inhibitors and dopamine agonists.

Dopamine Agonists

Dopamine agonists exert their pharmacological effect by directly activating dopamine receptors, bypassing the presynaptic synthesis of dopamine. In 1997, 3 new dopamine agonists were added to the armamentarium against PD: cabergoline and 2 nonergoline drugs, pramipexole and ropinirole, joined bromocriptine and pergolide already in use as potent antiparkinsonian drugs. Cabergoline, a potent D2 agonist with a half-life of about 65 hours, however, has not been approved for the treatment of PD in the United States.29 Pramipexole differs from the ergot dopamine agonists such as bromocriptine and pergolide in its preferential affinity for the D3 receptor subtype. The drug has been shown to be a safe and effective drug when used as monotherapy in the early stages of PD20 and in mild to moderate PD.31 Furthermore, pramipexole has been shown to smooth out clinical fluctuations in patients with advanced PD and to exert a levodopa-sparing effect (about 25% reduction in daily levodopa dosage).32 In one study, pramipexole at up to 4.5 mg/d was found to be more effective than bromocriptine at up to 30 mg/d in reducing parkinsonian motor score.33 Since pramipexole is excreted largely unchanged, inhibitors of cytochrome P450 enzymes would not be expected to have an effect on the pharmacokinetics of the drug. In addition to its beneficial effects on the PD motor, and possibly affective, symptoms, pramipexole has been demonstrated to have a possible neuroprotective effect by scavenging hydrogen peroxide and by enhancing neurotrophic activity in mesencephalic dopaminergic cultures.34

In contrast to pramipexole, which has a strong affinity for both the D2 and the D3 receptors, ropinirole is a relatively pure D2 receptor agonist.35 At doses up to 8 mg 3 times per day, ropinirole was associated with a 24% reduction in the total Unified Parkinson's Disease Rating Scale score, as compared with a 3% increase in the score with placebo (P < .001).36 Ropinirole is metabolized by CYP1A2, and therefore ciprofloxacin, estrogens, and other drugs metabolized by the liver may significantly reduce its clearance.

The nonergoline structure of the new agonists pramipexole and ropinirole may have a potential advantage in the adverse effect profile in that they are expected to have a lower risk for such complications as peptic ulcer disease, vasoconstrictive effects, erythrocytosis, and pulmonary and retroperitoneal fibrosis. Similar to the more traditional dopamine agonists, the new dopamine agonists may cause nausea, vomiting, anorexia, malaise, orthostatic hypotension, and psychiatric reactions, and may exacerbate levodopa-induced dyskinesias.

Several other dopamine agonists are currently being tested in clinical trials. Apomorphine is water soluble and thus suitable for intravenous, subcutaneous, intranasal, or sublingual administration.37 In one study, subcutaneous apomorphine therapy (at a mean daily dose of 90.6 mg for an average of 2.7 years) resulted in a 65% reduction in dyskinesias, and the waking time off decreased from 35% to only 10%.38 Furthermore, 9 subjects (47%) were able to discontinue levodopa therapy completely and the others substantially decreased their daily levodopa dosage. A new 5-hydroxy-2-aminotetralin derivative, N-0923, is a highly selective D3 agonist currently undergoing clinical trials. Administration via a transdermal patch bypasses metabolism by the liver and, as a result of sustained delivery, more steady plasma and brain levels can be achieved. Experimental D3 agonists such as ABT-431 and dihydroxydine may have a relative advantage over D3 agonists, in that they are less likely to cause dyskinesias and may even reverse them.39 No selective D1 agonists are currently clinically available, but apomorphine and pergolide activate both D1 and D2 receptors.

To delay or prevent levodopa-induced complications, many parkinsonologists recommend using dopamine agonists as the initial or early form of dopaminergic therapy. When used as monotherapy, dopamine agonists provide only modest improvement in parkinsonian symptoms, but the improvement may be sufficient to delay the introduction of levodopa by several months or years. Furthermore, dopamine agonists when used alone produce fewer clinical fluctuations and dyskinesias than levodopa.40 There is also a growing support for the notion that dopamine agonists have a neuroprotective effect. This is suggested by the following observations: (1) by stimulating dopamine autoreceptors, the dopamine agonists presumably decrease dopamine turnover and thus reduce oxidative stress; (2) dopamine agonists have been demonstrated to scavenge...
hydrogen peroxide, the hydroxyl, superoxide, and nitric oxide radicals and induce up-regulation of the free radical-scavenging enzyme superoxide dismutase and other proteins; (3) certain dopamine agonists enhance growth and survival of cultured dopaminergic neurons; and (4) dopamine agonists exert a levodopa-sparing effect. Furthermore, since levodopa seems to "prime" for the development of dyskinesia, the use of dopamine agonists before levodopa treatment seems to be a prudent practice. 

Some patients treated with levodopa or dopamine agonists develop psychiatric complications, particularly visual hallucinations. These adverse effects respond dramatically to dopamine. This and other atypical neuroleptics offer the advantage over the classic neuroleptics in that they do not exacerbate parkinsonian symptoms.

**NEUROSURGERY**

It is beyond the scope of this article to comprehensively review the advances in the neurosurgical treatment of PD. Only a brief summary will be provided here and the reader is referred to other reviews for additional information about novel surgical interventions.

**Ablative Procedures**

Prior to the advent of levodopa therapy for PD, thalamotomy offered the most effective means of controlling disabling and embarrassing tremor. The renewed interest in surgical treatment of movement disorders has been stimulated in part by improved understanding of the functional anatomy underlying motor control, including the recognition that the STN and GPi nuclei are overactive in experimental and human parkinsonism. Posteroventral pallidotomy improves motor performance in patients with PD, presumably by interrupting inhibitory pallidal projections to the ventrolateral thalamus and partly restoring the normal thalamocortical circuitry. Lesioning (or high-frequency deep brain stimulation [DBS]) of the posteroventral portion of the GPi or the STN may have an advantage over thalamotomy because these procedures seem to improve not only tremor, but also bradykinesia, rigidity, and levodopa-induced dyskinesias. However, the observed improvement in bradykinesia and dyskinesias following pallidotomy (or stimulation) of the GPi or STN cannot be readily explained by the current, obviously oversimplified models of basal ganglia function. For example, it is now well recognized that STN provides powerful excitatory projection not only to GPi, but also to the striatum and globus pallidus externum, and in turn receives input from the cerebral cortex, substantia nigra compacta, and various brainstem and thalamic nuclei. These complex interactions must be taken into account to explain the mechanisms of the various surgical interventions in the treatment of PD.

**Deep Brain Stimulation**

Another promising surgical approach for the treatment of tremors and other parkinsonian symptoms involves DBS with electrodes implanted in the ventral intermediate nucleus of the thalamus, GPi, or STN. Thalamic stimulation seems to be particularly effective in the treatment of parkinsonian and essential tremors. Since bilateral thalamotomy can cause hypophonia, dysarthria, and dysphagia, DBS of the thalamic ventral intermediate nucleus is emerging as a useful alternative in those patients who require bilateral procedures or who had prior unilateral thalamotomy. In contrast to ablative procedures, DBS requires the implantation of hardware that includes (1) a DBS lead with electrodes that are surgically inserted into the desired target and fixed at the skull with a ring and cap, (2) an extension wire that passes from the scalp area under the skin to the chest, and (3) a pulse generator, a pacemaker-like device implanted in the skin of the upper chest that can deliver pulses with a variety of parameters, modes, and polarities and can be activated or deactivated by placing a magnet over the chest area. Despite these relatively complex implantations, DBS has a potential advantage over the traditional ablative procedures because of a lower risk of intracerebral hemorrhage and the ability to select the most appropriate target and customize the stimulation parameters. Globus pallidum and STN DBS have been reported to improve not only PD tremor but, more importantly, to smooth out clinical fluctuations and prolong the on time. Depending on the location of the stimulating electrode, pallidal stimulation has a variable effect on parkinsonian features vs levodopa-induced dyskinesias. Stimulation of the dorsal GPi appears to improve parkinsonian features, whereas stimulation of the posteroventral GPi has beneficial effects on levodopa-induced dyskinesias and worsened gait and bradykinesia. Coupled with a reduction in levodopa dosage, leading to a reduction in levodopa-induced dyskinesias, STN DBS may be more effective than GPi DBS, but the 2 procedures have not been objectively compared. Finally, the possibility that chronic DBS interferes with the STN's excitatory output suggests a potential role for this treatment as a neuroprotective strategy.

**Brain Grafting**

Human and porcine fetal transplants are currently being investigated as potential therapeutic interventions in patients with moderately advanced PD. Further animal and clinical research, however, is necessary before brain grafting becomes an acceptable treatment for PD. Several studies using fluorodopa F 18 positron emission tomographic scans have demonstrated increased uptake following fetal transplantations. The use of immortalized neural progenitor cells in repair and as a source of trophic factors is currently being investigated.

**SUMMARY**

Although a cure is not yet in sight, tremendous strides have been made in the treatment of patients with PD. Levodopa is the most potent antiparkinsonian agent, but its use is associated with the development of motor complications. Furthermore, there is a concern that levodopa primes one for the development of motor complications. Whether levodopa is neurotoxic is debatable; many parkinsonologists prefer delaying the introduction of levodopa and recommend a variety of levodopa-sparing strat-
Parkinson Disease

Nonpharmacological Treatment

Pharmacological Treatment

Neuroprotection

MAOI

COMT

Drug Modification to Improve Efficacy and Reduce Adverse Effects

Surgery

Decision tree in the treatment of Parkinson disease. MAOI indicates monoamine oxidase inhibitor; COMT, catechol-O-methyl transferase; and CR, controlled release.

Dopamine Agonists → Levodopa (CR) → COMT Inhibitors

Combination Therapy

Additional Drugs

Age ≤ 65 y, Cognitively Normal

Age > 65 y

Yes

Cognitively Impaired

No

Anticholinergics

Aramantine

Age ≤ 65 y, Cognitively Normal

Yes

No

Drug Modification to Improve Efficacy and Reduce Adverse Effects

Surgery

The most important principle in the treatment of PD is to tailor the selected therapy to the needs of the individual patient. The recommendation should be based on interpretation of the available basic and clinical information, coupled with clinical experience. This review is intended to provide the background needed to develop the most optimal therapeutic strategy.

Accepted for publication July 13, 1998.

Reprints: Joseph Jankovic, MD, Parkinson’s Disease Center and Movement Disorders Clinic, Baylor College of Medicine, 6530 Fannin St, Suite 1801, Houston, TX 77030.

REFERENCES


