Parkinson Disease in Primary Practice: Keys to Diagnosis and Management

H. James Brownlee, MD
University of South Florida College of Medicine

Dopamine Agonists in Parkinson Disease: Special Focus on Pramipexole

Theresa A. Zesiewicz, MD, FAAN
University of South Florida College of Medicine

Supported by Boehringer Ingelheim Pharmaceuticals
ABSTRACT: More than 1 million Americans older than 60 years have Parkinson disease (PD). Diagnosis is clinical and based on the history and physical findings. The 4 cardinal motor symptoms are bradykinesia, resting tremor, muscle rigidity, and a gait disorder. The stereotypic PD tremor is a “pill-rolling” movement of the fingers and thumb with the arm at rest in the lap. However, no single clinical feature is sensitive or specific enough to distinguish PD from other diseases with parkinsonian features. Levodopa effectively treats the motor features of PD; however, the drug can cause a variety of adverse effects and is associated with end-of-dose bradykinesia and the “on-off” phenomenon. Coadministration of levodopa with a COMT inhibitor has the potential to deliver levodopa to the brain in a predictable, stable fashion, thereby decreasing fluctuations in levodopa concentrations. The dopamine agonists pramipexole and ropinirole are approved for use as monotherapy in early PD. Their initiation in early disease as monotherapy is believed to reduce motor fluctuations in later years. MAO-B inhibitors help to conserve endogenous dopamine. Amantadine has an antiparkinsonian effect in patients with early disease. A number of organizations provide support and medical information for patients with PD and for their families, caregivers, and clinicians.

One of the most common human neurodegenerative disorders, second only to Alzheimer disease, Parkinson disease (PD) proves to be a diagnostic and therapeutic challenge in medical practice. Significant advances have been made in defining its pathogenesis and pathology and, in turn, in the development of therapeutic interventions designed to maximize control of symptoms while minimizing long-term disability and treatment-related complications.

Diagnostic criteria are primarily clinical and conventional imaging studies are not often helpful. The best reference standard is, unfortunately, neuropathological (depletion of brain stem pigmented neurons and proliferation of Lewy bodies). But because symptomatic treatment is available, accurate differential diagnosis of PD is crucial.

This article is designed to provide primary clinicians with clinical criteria to better distinguish PD from other conditions with parkinsonian features and to present an evidence-based review of PD treatment.

DIAGNOSIS

Of the estimated 1 million Americans 60 years and older who have PD, perhaps 20% do not demonstrate a core feature of the condition—ie, resting tremor. Most patients with PD do not even begin to show the characteristic shuffling gait, freezing, and falls for years until the loss of most dopaminergic neurons. Thus, diagnosis of PD in its early stages, when parkinsonian features are mild, is based almost entirely on careful history taking and physical examination.

Motor Signs and Symptoms

The 4 cardinal motor symptoms of parkinsonism are bradykinesia, resting tremor, muscle rigidity, and

H. JAMES BROWNLEE, MD
University of South Florida College of Medicine
gait disorder. PD is the most common cause of parkinsonism, but there are other causes as well, which complicates making the diagnosis. In PD, the signs usually occur asymmetrically. Thus the common presentations of PD are often a stiff, or weak limb, tremor, asymmetric slowness, shuffling (infrequent in early PD), and reduced arm swing. In early PD, patients may complain of difficulty getting out of cars, rising from deep chairs, and rolling over in bed.

Essential tremor (ET) is the entity most commonly confused with early PD, despite the fact that it is an action tremor rather than the rest tremor of PD. Briefly, a postural tremor occurs when a limb is positioned against gravity, whereas the parkinsonian rest tremor occurs when a limb is fully supported against gravity and the muscles are not voluntarily activated. The stereotypical PD tremor is a "pill-rolling" movement of the fingers and thumb, with the arm at rest in the lap. However, although a rest tremor is more specific for PD, some PD patients can have solely an action tremor—especially early in the course. To distinguish PD from ET in these patients, it is important to look for the other signs of PD, especially bradykinesia and rigidity. Patients with ET should not have bradykinesia or rigidity. Up to 20% of patients with PD have no tremor throughout the course of the disease.

Although rest tremor is strongly suggestive of PD, it has been reported (in patients whose disease was diagnosed at autopsy) to occur with other neurodegenerative conditions, including multiple-system atrophy, progressive supranuclear palsy, and dementia with Lewy bodies. These parkinsonism-plus syndromes have a worse prognosis than idiopathic PD, respond poorly to antiparkinsonian medication, and carry other features not associated with PD. These include prominent early bowel or bladder incontinence, prominent orthostatic hypotension, early falls, early dementia, and eye movement abnormalities. Drug-induced parkinsonism, the result of medications that can block dopamine receptor function in the brain, is not unusual and is usually reversible, so it is a crucial consideration in taking patient histories. This secondary parkinsonism may persist for months after the drugs that caused it are discontinued.

Given these differential considerations and the absence of any standard test or marker for PD, diagnosis relies on history and physical examination, including simple tests of reflexes and movements. At least 1 attempt to develop a clinical diagnostic

**Table – Drugs that can block dopamine function in the brain**

<table>
<thead>
<tr>
<th>Generic</th>
<th>Trade name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxapine</td>
<td>Ascendin</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>Thorazine</td>
</tr>
<tr>
<td>Danzapine</td>
<td>Zyprexa</td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>Perimil, Profloxin</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>Haldol</td>
</tr>
<tr>
<td>Loxapine</td>
<td>Loxitane, Daxolin</td>
</tr>
<tr>
<td>Mesoridazine</td>
<td>Serentil</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>Reglan</td>
</tr>
<tr>
<td>Molindone</td>
<td>Moban</td>
</tr>
<tr>
<td>Perphenazine</td>
<td>Trilafon or Triavil</td>
</tr>
<tr>
<td>Prochlorperazine</td>
<td>Compazine, Combid</td>
</tr>
<tr>
<td>Promazine</td>
<td>Sparine</td>
</tr>
<tr>
<td>Promethazine</td>
<td>Phenergan</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Risperdal</td>
</tr>
<tr>
<td>Thiethylperazine</td>
<td>Torecan</td>
</tr>
<tr>
<td>Thoridazine</td>
<td>Mellaril</td>
</tr>
<tr>
<td>Thiothixene</td>
<td>Navane</td>
</tr>
<tr>
<td>Trifluoperazine</td>
<td>Stelazine</td>
</tr>
</tbody>
</table>

* Several other disorders have certain features that are similar to those of PD, and are sometimes mistaken for PD. These include essential tremor, in which tremor is the only symptom; progressive supranuclear palsy, characterized by inability to look downward and falls early in disease; multiple system atrophy, characterized by early and prominent autonomic symptoms, vascular parkinsonism, caused by multiple small strokes; and poisoning by carbon monoxide, manganese, or certain pesticides.

classification was based on a comprehensive review of the literature regarding the sensitivity and specificity of the characteristic clinical features of PD.7

The investigators came to 3 major conclusions:

• No individual clinical feature has sufficient sensitivity and specificity to serve as the sole basis for distinguishing PD from other diseases with parkinsonian features.

• Despite this, some features are more useful than others.

• The opportunity for diagnostic confusion is greatest early in the clinical course when some of the more distinctive clinical features may not yet have developed.

According to one clinicopathological study, the features that best predict the pathological changes of idiopathic PD are resting tremor, asymmetry with one side more affected than the other, and a good response to levodopa.9 However, the use of levodopa to differentiate PD from other parkinsonian conditions is not absolute. Patients with very mild features of PD may not show great benefit from levodopa, and response to the drug is not specific.7 Some patients with parkinsonism-plus conditions may show a modest, early response to levodopa. Moreover, animal studies suggest that even a single dose of levodopa may prime the basal ganglia for the subsequent development of abnormal movements (dyskinesia).10

Although the clinical assessment of PD is based on one well-characterized pathophysiological feature—the degeneration of dopamine neurons—the factors responsible for the initiation and inexorable progression of cell loss remain elusive.11,12 Thus, the development of imaging biomarkers that target specific sites in the brain represents a significant advance in the diagnosis and treatment of PD. Imaging may serve to improve the accuracy, timeliness, and reliability of diagnosis; monitor progression of disease; and evaluate neuroprotective or so-called disease-modifying treatments designed to retard disease progression.

From the clinician’s perspective, the real potential for aiding the diagnosis lies in12:

• Ensuring accurate and early identification of PD.

• Promoting appropriate treatment for both early- and late-stage PD.

• Avoiding unnecessary tests with a definitive diagnostic test.

• Providing general physicians and general neurologists with a tool for ruling in PD.

• Ensuring appropriate referral to experts.

In conclusion, the current role of imaging is to rule out other masqueraders of PD (eg, diffuse vascular disease or normal pressure hydrocephalus). Although promising, imaging does not now exist for the clinician to “rule in” PD. The diagnosis is still made in the office.

Non-Motor Signs and Symptoms

Depression and anxiety; cognitive impairment; sleep disturbances; reduced sense of smell (anosmia); and disturbances of autonomic function, such as orthostatic hypotension, constipation, excessive sweating, and pain, may appear long before motor symptoms.13–15 Most cognitive abnormalities—including difficulties with complex tasks, long-term planning, and memorizing new information—are common and mostly mild to moderate in severity. It is unknown whether such symptoms form a continuum with the dementias that affect some patients in late-stage PD. Psychotic symptoms affect 6% to 40% of patients with PD.16

Pharmacotherapy for these non-motor symptoms complicates anti-parkinsonian drug therapy, which, in turn, contributes to their onset. Thus, the management of non-motor symptoms is best coordinated by a neurologist in consultation with a psychiatrist and the patient’s primary clinician.

TREATMENT

The goal of treatment should be to obtain optimal reduction of PD symptoms with minimal risk of long-term complications.16,17 The goal of treatment should be to obtain optimal reduction of PD symptoms with minimal risk of long-term complications.16,17

The goal of treatment should be to obtain optimal reduction of PD symptoms with minimal risk of long-term complications.16,17
term adverse effects. Therapy can be divided into treatments for early stage disease and for advanced stage disease.

**Levodopa**

Levodopa—the biochemical precursor of the deficient neurotransmitter dopamine—is the drug most commonly used in PD, primarily because, unlike dopamine, it can cross the blood-brain barrier (Figure). Levodopa improves bradykinesia and rigidity and remains the gold standard against which other drugs are judged. Levodopa has its own pharmacological drawback, however. In the liver or the intestinal mucosa, about 70% of the oral dose becomes the substrate of a peripheral decarboxylase, thus creating a pool of dopamine in the periphery where it can cause a number of adverse effects, including nausea, vomiting, anorexia, hypotension, and psychiatric disturbances. To reduce these peripheral side effects, levodopa is given in combination with carbidopa (Sinemet), a peripheral decarboxylase inhibitor that improves the delivery of levodopa to the brain.

Levodopa remains effective throughout the course of PD, but its effects are modified as a consequence of disease progression and the eventual loss of the dopaminergic cells required to metabolize the drug and to store and release dopamine. The drug is also associated with motor complications, which include “wearing off,” defined as end-of-dose bradykinesia; and the “on-off” phenomenon, characterized by abrupt, transient fluctuations in clinical state, resulting in alternating periods of marked akinesia or greater mobility accompanied by iatrogenic dyskinesia.

According to the American Academy of Neurology’s (AAN) latest evidence-based review of initiation of PD therapy, the incidence of motor complications ranges from 30% to 80% after 5 to 7 years of levodopa use. The common occurrence of the wearing-off phenomenon with immediate-release levodopa led to the development of sustained-release levodopa. However, a prospective, randomized, double-blind, 5-year study that compared both formulations found no difference in the rate of motor complications, al-

---

**Figure** – In this illustration, levodopa passes through the blood-brain barrier to be metabolized to dopamine in dopaminergic neurons. Dopa-decarboxylase (DDC) and COMT (catechol-O-methyltransferase) inhibitors prevent the peripheral metabolism of extrinsic levodopa, thus allowing it to reach the brain. In the periphery, DDC prevents the peripheral decarboxylation of levodopa, and COMT inhibitors convert levodopa to 3-OMD. Dopamine agonists bind directly to postsynaptic dopamine receptors, mimicking the action of dopamine. Monoamine oxidase-B (MAO-B) metabolizes dopamine in glial cells located close to dopaminergic neurons. Selegiline increases dopamine availability by inhibiting MAO-B activity in glial cells. Finally, the balance between the neurotransmitter acetylcholine (ACh) and dopamine is important for controlled movement. In Parkinson disease, the levels of ACh signaling are increased relative to dopamine signaling. Anticholinergics reduce ACh signaling, thereby helping restore the relative signaling balance of dopamine and ACh in the striatum.
though it must be recognized that this study had important methodological limitations.20

Dopamine Agonists

Dopamine receptor agonists were introduced as adjuncts to levodopa therapy to help control the motor fluctuations that occur in PD. Unlike levodopa, however, their initiation in early disease as monotherapy is believed to reduce motor fluctuations in later years. In fact, dopamine agonist treatment of patients requiring dopaminergic therapy results in fewer motor complications than levodopa therapy after 2.5 years of follow-up.21 Levodopa is more effective in treating motor features of PD; however, thus, both agents may be used alone to initiate therapy; the choice depends on the relative impact of diminished motor disability versus the lessening of motor complications.

First-generation dopamine agonists, such as bromocriptine (Parlodel) and pergolide (Permax) stimulate postsynaptic dopamine receptors and are well established as add-on therapy to levodopa. Permax was withdrawn from the US market because of associated cardiac valve injury. Two newer dopamine agonists, pramipexole (Mirapex) and ropinirole (Requip) are approved for use as monotherapy in early PD, although it is not FDA-approved for this use, and as an adjunct to levodopa therapy to alleviate tremor or levodopa-associated wearing-off. A newer MAO-B inhibitor, rasagiline (Azilect), is 5 to 10 times more potent than selegiline and is not broken down to amphetamine deriva-
tives.22 Rasagiline is similarly useful as monotherapy and in combination with levodopa.

Orally disintegrating tablets of selegiline (Zelapar), which dissolve seconds after placement on the tongue, are once-daily adjunctive therapy for patients whose response to levodopa is deteriorating. There is no evidence from controlled studies that the tablets have any beneficial effect in the absence of concurrent levodopa therapy.

Amantadine

Another option for the treatment of early disease is amantadine (Symmetrel), an antiviral agent found to have an antiparkinsonian effect as well. Amantadine’s mechanism of action remains to be defined, but it is thought to cause release of dopamine, delay its neuronal reuptake, and antagonize another neurotransmitter, glutamate. It appears to be most effective in patients with akinesia or rigidity rather than tremor. It appears to act synergistically with levodopa as well. Amantadine can also be effective in combination with levodopa or anticholinergics to reduce the dyskinesias that occur in later disease, perhaps through antagonist activity at certain glutamate receptors.23 In patients with renal dysfunction, it should be used only at low dosages or not at all. Adverse effects include hallucinations, dry mouth, insomnia, orthostatic hypotension, and nausea.

Anticholinergic Agents

The mainstay of PD therapy until the introduction of levodopa in the late 1960s, anticholinergic agents effectively reduce tremor but provide minimal benefit for rigidity and bradykinesia. The most commonly used anticholinergics include trihexyphenidyl (Artane) and benztropine (Cogentin). Use of these agents is limited by such effects as confusion, hallucinations, blurred vision, dry mouth, urinary retention, constipation, and tachycardia.

COMT Inhibitors

Dopamine and its precursor, levodopa, are both metabolized by the enzyme catechol-O-methyltransferase (COMT) in the liver, GI tract, and other organs. By preventing this breakdown, COMT inhibitors, like the decarboxylase inhibitor carbido-

Ma

www.Consultantlive.com SEPTEMBER 2008 (SUPPLEMENT) CONSULTANT 55
Entacapone is less potent than tolcapone, does not cross the blood-brain barrier, and has a very short half-life, such that it should be given every 2 to 4 weeks for the first 6 months of therapy, then continued periodically at intervals deemed clinically relevant. Patients’ written informed consent is still required before tolcapone is prescribed.

Surgery

The major indications for surgery are a diagnosis of idiopathic PD, a therapeutic response to levodopa, significant intractable symptoms, drug-induced dyskinesias, and wearing off. The benefits from surgery are unlikely to exceed the benefits of antiparkinsonian medication. The decision for surgery should be made by a team that includes a neurologist, neurosurgeon, psychiatrist, and primary clinician.

Surgery for PD includes pallidotomy, thalamotomy, and deep brain stimulation (DBS). DBS has essentially replaced the older ablative surgical improvements. During DBS, electrodes are implanted in the brain to deliver continuous stimulation via a programmable stimulator implanted in the patient’s chest wall. DBS is a therapeutic option to treat the symptoms of PD, including dyskinesias and tremors. However, it is important to note that surgery is not suitable for everyone and should only be considered after other treatments have been tried and have proven ineffective.

Neuroprotective Therapy

Recent studies have drawn attention to and raised considerable controversy regarding the potential for MAO-B inhibitors selegiline and rasagiline, coenzyme Q10, and the dopamine agonist pramipexole to provide neuroprotective benefits in PD. The question is: do the clinical and imaging end points used in these trials in fact measure disease progression? Unfortunately, the clinical end points used to date are readily confounded by any symptomatic effect of the study intervention. To circumvent this problem, surrogate neuroimaging markers have been used, and 2 recent trials have reported that patients randomly selected to receive treatment with a dopamine agonist had a reduced rate of decline in these measures of nigrostriatal function compared with levodopa. Neither study included a placebo control, which prevented the ability to differentiate whether these results could be from a protective effect of dopamine agonists or a toxic effect of levodopa. The combination of in vitro and in vivo laboratory evidence demonstrating a neuroprotective effect of the agents combined with imaging studies has stimulated further research.

Thus, there is no clear answer regarding neuroprotection for patients with early PD. The decision to introduce a putative neuroprotective agent remains a matter of the treating physician’s judgment.
proves dyskinesia. Thalamic DBS is primarily effective against tremor. A third area, the subthalamic nucleus (STN), has become the target of choice for DBS for most patients with advanced PD who are surgical candidates. A recent study that examined the long-term efficacy of bilateral STN DBS reported that patients’ scores for motor function while off medication at 5 years improved by 54% and those for activities of daily living, by 49%.20 However, DBS is expensive and car-
ries the risk of adverse events, including brain bleed.

Transplantation

Transplantation surgery with fetal mesencephalic cells has not been shown to provide significant improvement in the motor compi-
lcations of PD and it has been associ-
ed with “L-dopa-independent” dyskinesia.20 Transplantation of an alternative tissue, human retinal pig-
ment epithelial cells, is now being studied.21

Chronic, controlled infusion of glial cell line-derived neurotrophic factor (GDNF) has been associated with structural and functional recovery in monkeys with advanced parkinsonian symptoms.22 An open-label, phase I safety trial, in which GDNF was deliv-
ered into the dorsal putamen of 5 pa-
ients with PD resulted in significantly reduced UPDRS-III scores in the off-
state and of L-dopa-induced dyskine-
rias in the on-state.23 A subsequent phase 2, double-blind, placebo-con-
trolled study involving 34 patients with advanced PD failed to show clinical improvement, however.24

COMMUNITY RESOURCES

A number of organizations pro-
vide support and medical informa-
tion, both live and online, for patients with PD as well as caregivers, health care professionals, and physicians. The major currently active organiza-
tions as well as 2 helpful independent

Internet sites are listed in the Sidebar (page S6).

REFERENCES:

3. Grondin R, Chen-Shimony Y, Magalhaes M, et al. Clinical-pathological study of 35 cases of multiple sys-
5. Louis ED, Goldman ML, Powers JM, Fahn S. Par-
6. Louis ED, Klatka LA, Ly Y, Fahn S. Comparison of extraPyramidal abnormalities in 31 pathologically con-
7. Grill DJ, Oliver E, Gilman S. Diagnostic crite-
9. Hughes AJ, Jinn-Simony Y, Daniel SE, Lees AJ. What features improve the accuracy of clinical diag-
11. Sebby J, Jennings D, Tabano R, Marek K. Neu-
12. Sebby J, Jennings D, Tabano R, Marek K. The role of neuroimaging in the early diagnosis and eval-
13. Chandhuri KR, Yates L, Martinez-Martín F. The non-motor symptom complex of Parkinson’s disease: a comprehensive assessment is essential. Cure Neu-
14. Kristen DW, Moore DJ, Hayes M, et al. Identifying the pattern of olfactory deficits in Parkinson dis-
19. Stacy M. Pharmacotherapy for advanced Par-
kinson’s disease: an evidence-based review: report of the Quality Standards Subcommittee of the Ameri-
care, Inc; 2006;3360-3365.
26. Schapira AH, Olson CW. Neuroprotection in Parkinson disease: mysteries, myths, and misconcep-
29. Watts RL, Raisier CD, Stover NP, et al. Stereo-
tactric intraoperative implantation of human retinal pig-
ment epithelial (BRPE) cells attached to gelatin mi-
icrocarriers: a potential new cell therapy for Parkin-
trolled GDNF infusion promotes structural and func-
32. Nutt JG, Burchiel KJ, Cornelis CL, et al. Ran-
ABSTRACT: Dopamine receptor agonists have played an important role in anti-parkinsonian therapy since the first ergoline derivative was introduced in 1974. The non-ergoline dopamine agonists, developed later to provide the benefits of the ergolines with fewer side effects, are currently used as both monotherapy and as adjunctive therapy to treat symptoms of Parkinson disease (PD), to postpone the onset of levodopa therapy, to delay the development and minimize the severity of levodopa’s complications, and to reduce the dosage of levodopa. When the effects of dopamine agonists wane and levodopa is added, patients who receive combined dopaminergic treatment still exhibit less severe motor complications than those who started antiparkinsonian therapy with levodopa. In addition to abating the core symptoms of PD (eg, akinesia and rigidity) and delaying the onset of motor complications, the dopamine agonist pramipexole has been shown to ameliorate tremor and depressive symptoms in clinical practice.

The second most common age-related neurodegenerative disorder (after Alzheimer disease), Parkinson disease (PD) affects more than 1 million Americans. Treatments for PD have been primarily based on correcting the characteristic nigrostriatal dopamine deficiency. A number of pharmacological approaches have been introduced over the years, including agents that reduce the peripheral decarboxylation of levodopa to dopamine (carbidopa), that prolong levodopa’s 90-minute half-life (controlled-release carbidopa/levodopa), that increase the amount of levodopa crossing the blood-brain barrier (catechol-O-methyltransferase [COMT] inhibitors), that slow dopamine’s metabolic breakdown (monoamine oxidase type B [MAO-B] inhibitors), and that directly stimulate dopamine receptors in the normal striatum (dopamine receptor agonists).

Levodopa has remained the mainstay of antiparkinsonian drug therapy since its introduction in the 1960s. Unfortunately, early treatment with levodopa has been shown to lead to disabling motor fluctuations and dyskinesias; this prompted the development of alternative medications to treat PD, including dopamine agonists. The dopamine agonists represent a rational and effective alternative to levodopa for the treatment of early PD—especially in patients younger than 80 years and in older patients whose overall health is good. When disease progression finally requires the addition of levodopa, patients who are receiving combination levodopa/dopamine agonist therapy have fewer motor complications than those receiving levodopa monotherapy.

While levodopa remains the gold standard for PD therapy, dopamine agonists are being used increasingly as first-line therapy for patients with PD and have become an integral part of the disease’s treatment. The initial use of dopamine agonists to forestall the onset of motor fluctuations and lessen their severity remains controversial for...
some movement disorder specialists, however.

In this article, I focus on the use of dopamine agonists in early and advanced PD, with an emphasis on pramipexole.

PATHOPHYSIOLOGY OF PARKINSON DISEASE

PD is caused by a massive loss of dopaminergic neurons in the substantia nigra, resulting in drastic depletion of dopamine levels in the striatum, to which these neurons project. The loss of dopamine creates an imbalance between excitatory and inhibitory effects in the basal ganglia, resulting in hypokinetic motor behavior (Figure 1). Although the dopaminergic nigrostriatal tract seems to be the most important site of change, a number of other selected but heterogeneous populations of neurons are involved in the progressive cell death characteristic of PD. Neurodegeneration also occurs in selected aminergic brain stem nuclei, both catecholaminergic and serotonergic; in the cholinergic nucleus basalis of Meynert; in the hypothalamus; in the small cortical neurons, particularly those in the cingulate gyrus and entorhinal cortex, as well as in the olfactory bulb and sympathetic ganglia; and in the parasympathetic neurons in the gut. These widespread degenerative changes are believed to result in the nonmotor, cognitive, and behavioral changes that are characteristic of PD.

For example, degeneration of olfactory-bulb neurons is believed to cause anosmia. Degeneration of neurons in the spinal cord and sympathetic and parasympathetic ganglia and the central amygdaloid nucleus is associated with autonomic dysfunction. In addition, degeneration in the brain stem serotonergic and noradrenergic nuclei may contribute to behavioral dysfunction, including depression.

TREATMENT OF PD: AN OVERVIEW

Levodopa continues to be the most effective agent for the symptomatic treatment of the motor effects of PD. No other drug matches its ability to suppress parkinsonian symptoms, especially in patients with advanced disease. But over time, initial benefits begin to wane; each dose is effective for progressively shorter periods and levodopa-induced side effects, such as unpredictable on-off fluctuations and the abnormal involuntary movements of dyskinesias, become increasingly prominent.

Although the pathogenesis of levodopa-related on-off fluctuations remains poorly understood, the degree of nigrostriatal degeneration and the half-life of the dopaminergic agonist used to treat parkinsonian symptoms have been shown to correlate with their development. The loss of striatal neurons and terminals means that activation of striatal dopamine receptors becomes increasingly dependent on the peripheral availability of the exogenously administered dopaminergic agonist. Moreover, considerable evidence now indicates that abnormal, intermittent, or pulsatile activation of brain dopamine receptors leads to the development of motor complications in PD through induction of plastic changes in striatal neurons and altered neuron firing patterns (Figure 2).

Thus, it has been proposed that fluctuations in plasma levels of orally administered short-acting levodopa (half-life of 30 to 90 minutes) are not adequately buffered because of the lost dopamine terminals, causing receptors to be exposed to alternating high and low levels of activation and, in turn, to perturbations of an already abnormal basal ganglia network. Both animal and human studies have led to the concept that continuous delivery of a dopaminergic drug will prevent this pulsatile stimulation and avoid motor complications.

In patients with early PD, several prospective, double-blind, controlled trials have shown initiation of therapy with a long-acting dopamine agonist to be associated with a lower risk of motor complications compared with initiation with levodopa (Figure 3). A prospective, controlled 4-year study of 40 patients with advanced PD and severe levodopa-related motor complications showed continuous infusion of levodopa or a dopamine agonist to provide long-lasting and dramatic improvement in established motor complications. However, infusions are cumbersome and may be associated with side effects at the site of administration; patients with early disease are likely to resist this treatment approach. Continuous levodopa delivery by intraintestinal infusion has been shown to reduce established dyskinesia in patients with advanced disease, but the procedure requires surgery and frequent repositioning or replacement of the catheter. On the basis of these factors, it is logical to start treatment in appropriate patients with a long-acting dopamine agonist and to add levodopa when their symptoms can no longer be satisfactorily controlled with that agent. Factors such as the cognitive state of the patient and financial resources should be taken into account when deciding on initial therapy for PD. Dopamine agonists fall into 2 major classes: first-generation ergot derivatives (eg, bromocriptine, pergolide [no longer marketed in the United States]) and the second-generation non-ergolines (eg, pramipexole, ropinirole). A transdermal dopamine agonist, rotigotine, was recently removed from the market (see below).

All stimulate dopamine receptors directly, but the second-generation agents are not associated with retro-
Figure 1 – Illustrated here is a simplified proposed functional model of the basal ganglia in patients with parkinsonism. In the striatum, the GABAergic output neurons projecting directly to the internal segment of the globus pallidus (GPi) and the pars reticulata of the substantia nigra (SNr) contain a predominance of D_1 dopamine receptors. The neurons projecting to the external segment of the globus pallidus (GPe) and subthalamic nucleus (STN) carry predominantly D_2 receptors. Dopamine has different effects on these receptors and, in turn, on the subpopulations of striatal output neurons, exciting those expressing D_1 receptors (green arrows, the direct striatopallidal pathway) and inhibiting those with D_2 receptors (red arrows, the indirect pathway).

The width of the arrows indicates degree of overall functional change in the activity of each pathway (changes in neural firing rates) compared with the normal state. The size and outlining of each box indicate the activity of the brain region compared with normal. Dashed lines and arrows indicate the dysfunctional nigrostriatal dopamine system in Parkinson disease.

(Adapted from Lang AE, Lozano AM. N Engl J Med. 1998.)

Dysfunctional motor control in parkinsonism

D_2 receptors

D_1 receptors

VA/VL thalamic nuclei

Cortex

GABA

Enkephalin

Dopamine

GABA

Substance P

GABA

Glutamate

Glutamate

GABA

Glutamate
peritoneal and pulmonary fibrosis and cardiac valve dysfunction, which have been reported with ergot-derived agents. The first- and second-generation agonists also show different pharmacological properties because they tend to act on different subsets of receptors. For example, the older, ergoline agents bind with high affinity to D₂ family receptors but also show affinity of varying degrees for D₁, adrenergic, and 5HT receptors. On the other hand, the non-ergolines bind only to D₂ and D₃ receptors with high affinity; pramipexole is more potent at D₃ binding.

When used as an adjunct to levodopa, dopamine agonists reduce both motor disability and on-off fluctuations in patients with advanced PD. According to more recent prospective, double-blind, multicenter trials, the rate of motor complications associated with levodopa therapy is significantly reduced in patients who were randomized initially to pergolide, cabergoline, ropinirole, or pramipexole.

All dopamine agonists are associated with CNS side effects in varying degrees, which may include insomnia, somnolence, and visual hallucinations (neuropsychiatric adverse effects). Dopamine agonists can also cause GI side effects, including nausea and vomiting. Moreover, although dopamine agonists delay the introduction of levodopa, they neither prevent nor delay the development of motor complications once levodopa is initiated. The time to the development of motor complications is about the same whether the drug is used to initiate therapy or is added to supplement the waning agonist response.

**ERGOT DOPAMINE AGONISTS**

**Bromocriptine.** This dopamine agonist directly stimulates both pre- and postsynaptic receptors, with a high affinity to D₂ receptors (it is also

---

**Figure 2** – Illustrated here is the pharmacological response to a levodopa challenge in patients with mild (A), moderate (B), and severe (C) PD. In the early stage, response is slow in onset, has small magnitude, and a long duration. In the intermediate stage, the severity of motor dysfunction in the off state has increased and the response is of greater magnitude and shorter duration. Dyskinesias may be elicited at this stage. In the late stage, motor response is abrupt and has a very large magnitude, but the duration is short and the threshold for dyskinesia is reduced.

(From Olanow CW, Obeso JA, eds. In: *Dopamine Agonists in Early Parkinson’s Disease*. 1997*)
In a 42-month study of levodopa monotherapy versus levodopa plus bromocriptine (as partial substitution for more than 30% of levodopa) in de novo patients with early PD, the severity and extent of motor dysfunction was significantly less in those receiving combination therapy. However, the usefulness of bromocriptine has been tempered by a lengthy titration schedule (weeks to months) and by reports of retroperitoneal fibrosis in patients receiving long-term therapy at high dosages. The introduction of non-ergoline agents with more rapid titration schedules and greater tolerability has also superseded bromocriptine in the treatment of levodopa-induced dyskinesia and on-off phenomena.

Pergolide. A strong D₂ and a weak D₃ receptor agonist, pergolide is effective in reducing motor complications as both monotherapy and adjunctive therapy to levodopa.

Four earlier reports of retroperitoneal, pericardial, or pleural fibrosis and valvular insufficiency in patients treated with high-dose pergolide were followed in 2003 by one report of pergolide-associated valvular heart disease. A year later, echocardiographic evidence of valvular insufficiency was reported in 10 patients who were receiving high-dose pergolide. At least 4 more studies have described the association of pergolide with valvular heart disease. In 2007 the US FDA announced that the manufacturers of pergolide were voluntarily withdrawing it from the market.

Non-Ergot Dopamine Agonists

ROPINIROLE

A highly selective non-ergoline D₂ agonist, ropinirole is effective as early monotherapy and as an adjunct to levodopa. A study of ropinirole as monotherapy in patients with early-stage PD demonstrated a 24% improvement in motor function at 6 months in the monotherapy group compared with a 3% worsening in the placebo group (P < .001).

The safety and efficacy of ropinirole and of levodopa were compared in a 5-year double-blind, randomized, multicenter study of patients with early PD who required dopaminergic therapy. The primary outcome measure was the occurrence of dyskinesia. A total of 268 de novo patients were randomized to receive either levodopa (89 patients) or ropinirole (179 patients). Patients could receive supplementary levodopa in an open-label fashion if symptoms were inadequately controlled. At 5 years, the cumulative incidence of dyskinesia, regardless of levodopa supplementation, was 20% in the ropinirole group and 45% in the levodopa group. The investigators concluded that early PD can be managed successfully for up to 5 years with a reduced risk of dyskinesia by initiat-
ing treatment with ropinirole alone and supplementing it with levodopa if necessary.

The 2-year, double-blind Requip As Early Therapy Versus L-dopa—Positron Emission Tomography (REAL-PET) study compared the rates of loss of dopamine-terminal function in 162 de novo patients randomized with either levodopa or ropinirole, with levodopa supplementation if necessary.12 The primary outcome measure was reduction in putaminal (18)F-dopa uptake between baseline and 2-year PET scans. A significantly slower reduction in (18)F-dopa uptake in the putamen was seen over the 2 years with ropinirole (−13.4%) than with levodopa (−20.3%). However, direct pharmacological effects of the study medications or compensatory mechanisms induced by them cannot be excluded as alternative explanations for these results. Of note, levodopa supplementation was allowed in both groups. Although dyskinesia developed in 3% of patients taking ropinirole compared with 27% of those taking levodopa, patients who received levodopa showed significantly greater motor improvement.

Ropinirole is also effective as an add-on therapy to levodopa. In one study, 27.7% of ropinirole-treated patients had at least a 20% reduction in levodopa dose as well as a 20% reduction in off time, compared with 11% in the placebo group.13

Rotigotine. This dopamine agonist was developed for administration via a silicone-based transdermal patch.40 This agent was recently removed from the market, however, because of crystal formation on the patches that diminished the amount of available drug. For this reason, this agent will not be discussed further here.

Pramipexole. This non-ergot synthetic amino-benzathiazol derivative binds to D_{3} receptors with 7-fold greater affinity than it does to either D_{1} or D_{2} receptors.25 Its terminal half-life is about 8 hours in young healthy volunteers and about 12 hours in elderly volunteers.51 In all clinical studies, dosage was initiated at a subtherapeutic level to avoid intolerable adverse effects and orthostatic hypotension. Pramipexole should be titrated gradually with doses increased every 5 to 7 days to achieve a maximum therapeutic effect, balanced against the principal side effects of dyskinesia, hallucinations, somnolence, and dry mouth. Starting with 0.125 mg tid, a suggested ascending dosage schedule increases to an individualized effective and well-tolerated maintenance dose. Inhibitors of cytochrome P-450 enzymes would not be expected to affect the elimination of pramipexole because it is not appreciably metabolized by these enzymes in vivo or in vitro. Pramipexole is effective as both monotherapy and in combination with levodopa in the treatment of PD.

An early 24-week multicenter, randomized, double-blind study of pramipexole’s safety and efficacy that included 335 patients with early PD concluded that the drug was safe and significantly improved motor function and activities of daily living, compared with placebo.24 In the assessment of adverse events, nausea, insomnia, constipation, somnolence, and visual hallucinations occurred more frequently in the pramipexole group than in placebo recipients.

The Comparison of the Agonist Pramipexole With Levodopa on the Motor Complications in Early PD (CALM-PD) trial was the first controlled study to compare long-term outcomes with dopaminergic therapy.55 This randomized, multicenter, parallel-group, double-blind clinical trial involved 301 patients who required antiparkinsonian therapy to treat emerging disability. Subjects were randomized to active pramipexole or levodopa monotherapy; starting at week 11, addition of open-label supplemental levodopa was allowed in both treatment groups. The primary outcome measure was the time to the first occurrence of any of 3 dopaminergic complications: wearing off, dyskinesias, or on-off motor fluctuations.

Patients treated initially with pramipexole had significantly less developmental of wearing off, dyskinesias, or on-off motor fluctuations (28%) compared with those taking levodopa (51%) (hazard ratio, 0.45; 95% confidence interval [CI], 0.30 to 0.66; P < .001). However, there was a greater mean improvement in total UPDRS score from baseline to 23.5 months in the levodopa group compared with the pramipexole group (pramipexole, 4.5 [12.7]; levodopa, 9.2 [10.8]; P < .001). Somnolence, peripheral edema, and hallucinations were more common in pramipexole than in levodopa-treated patients (32.4% vs 17.3%; P = .003). At the end of the study, patients treated with levodopa had greater improvement in UPDRS motor scores than those treated with pramipexole (pramipexole 3.4 [8.6]; levodopa 7.3 [8.6]; P < .001). Nevertheless, mean changes in quality-of-life scores did not differ between the treatment groups.

The question of whether pramipexole could actually slow disease progression was examined in the CALM-PD-CIT substudy, in which 82 patients with early PD underwent dopamine transporter imaging at baseline and at 22, 34, and 46 months as an index of remaining dopamine neurons.56 Single photon emission CT (SPECT) showed that the mean percentage loss in striatal uptake from baseline was significantly reduced in the pramipexole group compared with the levodopa group (Figure 4). However, direct pharmacological effects of the medications or compensatory mechanisms induced...
by them cannot be excluded as possible alternative explanations for the difference.

One double-blind, placebo-controlled study compared the efficacy, safety, and tolerability of pramipexole with placebo in 291 patients with advanced PD who were treated with levodopa and who were experiencing motor fluctuations.28 There was improved motor function in pramipexole-treated patients during “on” and “off” periods compared with those patients treated with placebo, as well as decreased time spent in “off” periods and a reduction in the severity of “off” periods. The use of pramipexole also permitted a reduction in levodopa dosage. Adverse effects were similar to those usually attendant on dopamine agonists.

Another double-blind, placebo-controlled study in 354 patients with PD who had marked rest tremor during the on period.29 Subjects represented a subgroup of patients recruited by one center to participate in a placebo-controlled, randomized, double-blind, multicenter European phase 3 trial of pramipexole’s efficacy and safety. Eleven patients received pramipexole; 5 received placebo.

The first effects were seen with a pramipexole dose of 0.75 mg/d, with a reduction of tremor item on the UPDRS (part III rest tremor parameters, during on periods) of 25% and of rigidity and akinesia of 22%. With the highest dose, 4.5 mg/d, tremor score was improved by 61% over baseline and the sum of rigidity and akinesia items was improved by 63%. The 5 patients who received placebo did not show any improvement of motor function except at dose levels of 3.57 and 4.5 mg/d. At 3.57 mg/d UPDRS scores were 136% of baseline for tremor and 139% for rigidity and akinesia. Correspondingly, placebo patients’ UPDRS scores did not change significantly after washout from the study’s double-blind phase.

Another double-blind, randomized, placebo-controlled study compared the tremorlytic properties of pramipexole with those of placebo as add-on medication in 84 patients with PD who had marked drug-resistant tremor.59 Patients were taking optimized antiparkinsonian medication at the time of study entry, and they were randomized to either pramipexole (n = 44) or placebo (n = 40) as adjunct medication. The primary end point of the study was the change in tremor score (the sum of tremor-related items 16, 20, and 21 on the UPDRS in the “on” state).

Pramipexole significantly reduced tremor compared with placebo, with a 34.7% reduction in tremor scores \((P < .0001)\). The visit-by-visit analysis of the change in tremor score showed that the improvement under pramipexole increased in a dose-dependent manner during the

Figure 4 – The rate of decline in striatal uptake from baseline, measured by single photon emission CT (SPECT), was significantly reduced in the pramipexole compared with the levodopa group.

(Adapted from Parkinson Study Group. JAMA. 2002.56)
ascending dose interval and seemed to remain stable between the beginning and end of the maintenance period (Figure 5). The mean daily dose of pramipexole during the maintenance phase of the study was 4.1 mg (SD, 0.9). Long-term electromyographic recordings were performed as an objective measure of tremor; significant improvement was noted in pramipexole-treated patients. There were also improvements in investigators’ and patients’ assessments of tremor. Patients who were treated with pramipexole had more fatigue, insomnia, nausea, abdominal pain, and headache than patients who were treated with placebo.

Apomorphine. This potent non-ergot dopamine agonist exerts strong activity at both the D₁ and D₂ dopamine receptors of the striatum, thus mimicking the action of dopamine more closely than any other available agent. The efficacy of apomorphine is identical to that of levodopa and substantially greater than that of any other orally administered dopamine agonist. Because of extensive first-pass hepatic metabolism when taken orally, apomorphine can be administered only parenterally, resulting in a half-life of about 40 minutes, with clinical effects that last about an hour. Given the relatively brief clinical response to its short half-life, apomorphine will not have an additive effect when used with longer-acting oral drugs. Furthermore, because the drug does not accumulate in the brain, dyskinesias do not typically increase later in the day when it is initiated during off periods; this is in contrast to the accentuation of dyskinesias associated with levodopa when used as-needed for off states.

Because one of the most common side effects of apomorphine is nausea and vomiting, all patients should be pretreated for at least 3 days with an antiemetic (domperidone in Europe; trimethobenzamide, 250 to 300 mg tid, in the United States) before the first injection.

The pivotal trial for the approval of subcutaneous apomorphine injectable in the United States assessed its efficacy in patients with advanced PD who had at least 2 hours of off time daily despite optimized oral antiparkinsonian medications. Of 29 patients recruited, 20 were randomized to receive titrated doses of subcutaneous apomorphine (2 to 10 mg) and 9 were to receive placebo during an inpatient and 1-month outpatient phase. The average levodopa equivalent dose of apomorphine was 5.4 ± 0.5 mg, and mean placebo dose was 1 mL. Phase 1 consisted of an inpatient assessment of PD symptom reversal with apomorphine after withholding antiparkinsonian medications overnight; phase 2, a 4-week outpatient treatment trial, assessed drug effectiveness in terms of reversal of spontaneous off episodes and total time off.

Mean inpatient UPDRS motor scores were reduced by 23.9 (62%) and 0.1 (1%) points by apomorphine treatment and placebo, respectively (P < .001). Twenty-five subjects (17 active and 8 placebo) completed phase 2 and were allowed to administer up to 5 doses of apomorphine daily. The active group self-administered 2.5 doses per day; the placebo group, 2.3 doses per day. The active group reported a 95% rate of off-state events arrested compared with 23% in those taking placebo. The apomorphine group reported a median of 2 hours less off time per day, whereas the placebo group reported no change. A significantly greater frequency of yawning and drowsiness was reported with apomorphine. Nausea occurred in 35% of apomorphine patients compared with 11% of
placebo patients, but the difference was not significant. No other significant changes were seen in symptoms, physical findings, ECGs, or blood test results.

Following antiemetic treatment, the initial dose of apomorphine should always be given under nurse or physician supervision because of the possibility of acute orthostatic hypotension. The patients should be in an off state, and baseline blood pressure should be measured in both the standing and supine positions. A test dose of 2 mg should be given with repeated measurement of orthostatic blood pressures at 20, 40, and 60 minutes. The 2-mg dose for reversal of spontaneous off states can be prescribed for patients who respond with motor improvement and without an acute adverse event. Those who do not respond to the 2-mg test dose but have no acute adverse reaction may be given an additional test dose of 4 mg (2 hours after the initial test), and if the response is positive, they may be discharged with a 3 mg prescription.

Most patients respond to doses of 3 to 6 mg; the average frequency of dosing in the apomorphine development program was 3 times daily. Experience with dosing frequencies greater than 5 times per day or total daily doses exceeding 20 mg is limited.

OTHER DOPAMINE RECEPTOR AGONISTS

A number of ergot and non-ergot dopamine agonists are available in Europe but are either not available or not indicated for PD in the United States. These agents include the ergotamine derivatives cabergoline, dihydrotergocryptine, lisuride, and the non-ergoline piribedil.

SIDE EFFECTS OF DOPAMINE AGONISTS

Ergoline dopamine agonists may cause retroperitoneal and pleuropulmonary fibrosis, albeit very rarely. In addition, they may give rise to Raynaud syndrome and erythromelalgia. The ergoline derivatives in high doses have also been associated with valvular heart disease, most recently in a study that found echocardiographic changes with cabergoline and pergolide, the latter now withdrawn from the market. The non-ergolines pramipexole and, to a lesser degree, ropinirole have been associated with sudden sleep attacks or at least somnolence. According to a large European survey, the non-ergolines have a slightly higher tendency towards somnolence than the ergolines. The propensity for levodopa and the dopamine agonists to cause psychosis or neuropsychiatric symptoms in patients with PD, including hallucinations and compulsive symptoms such as pathological gambling or stereotyped behaviors (termed punding), has been reported.

Sleepiness and sleep attacks. Patients with PD are known to have disordered sleep architecture, including vivid dreaming, nocturnal vocalization, excessive daytime sleepiness, and altered sleep-wake cycles, as well as movement disorders specific to sleep. Virtually all dopaminergic antiparkinsonian medications may contribute to sleep problems, but somnolence, excessive daytime sleepiness, and sleep attacks appear to be more common in patients with PD who are treated with dopamine agonists than in those treated with other agents. Somnolence caused by dopamine agonists may be dose related and occurs most frequently during the dose-escalation phase of therapy. Sleep attacks, described as sudden, irresistible, overwhelming sleepiness without awareness of falling asleep, may be triggered by down-regulation of dopaminergic input to the reticular activating system, possibly by the action of the agents on presynaptic receptors. Sleep attacks can occur with all dopaminergic drugs, including alpha-1 blockers, bromocriptine, cabergoline, lisuride, pergolide, pramipexole, and ropinirole, with no significant difference between ergot and non-ergot agents.

Psychosis. This is defined as a disturbance of perception and thought and commonly includes hallucinations, delusions, paranoid beliefs, agitation, and delirium. Psychotic symptoms are common in patients with PD and dementia but are also observed as a drug-induced phenomenon in patients without obvious cognitive dysfunction. Early drug-induced psychosis has been observed in up to 10% of patients treated with dopamine agonists and has been associated with an increased risk of the development of dementia later on. Visual hallucinations are the most common clinical manifestations and have been observed in about 30% of patients over the course of PD. Up to 16% of patients exposed to dopamine agonists or combinations of dopamine agonists with levodopa have been observed to develop symptoms of drug-induced psychosis.

In an animal study of the relative propensity of clinically available dopaminergic drugs (levodopa, pergolide, ropinirole, and pramipexole) to induce neuropsychiatric symptoms, levodopa-treated 1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine (MPTP)-lesioned marmoset models of psychosis-like behavior in parkinsonism were administered doses of study agents that produced an equivalent full reversal of parkinsonism. All drugs significantly reversed peak-dose parkinsonian disability and induced peak-dose psychosis-like behaviors (agitation, stereotypies, and hallucinatory-like and obsessive-compulsive behaviors). These findings suggest that the nature of the dopaminergic agent employed may not be a major factor in determining the degree of the comparative neuropsychiatric effects.
Impulse control and dopamine dysregulation disorders. A number of reports in the literature suggest that impulse control disorders (ICDs) and dopamine dysregulation disorders, including pathological gambling, pathological hypersexuality, punding, binge eating, compulsive shopping, and compulsive dopaminergic medication use, may occur in patients with PD and are possibly associated with dopaminergic stimulation. In a survey of patients with PD, ICD during the course of PD was seen in 6.0% of patients, while 4.0% of patients had an active ICD. Another study found the lifetime prevalence of these impulse-control behaviors was 6.1% and increased to 13.7% in patients receiving dopamine agonists.

The precise pathophysiology of ICDs is unknown, but appears to involve alterations in specific neurotransmitter systems, brain regions, and neural circuits. Dopamine function is important in the mediation of reward and reinforcement behavior. For example, the prefrontal cortex, ventral striatum, and amygdala mediate aspects of impulsivity.

Several explanations for an association between ICDs in PD and treatment with dopamine agonists have been proposed, which include:

- The loss of dopamine influences dopaminergic cortical-subcortical circuits, leading to cognitive and emotional impairment that can predispose to the development of psychiatric disorders, including ICDs.
- Patients who have PD may display executive function deficits linked to degeneration in the frontal-striatal tracts secondary to cell loss within the SN.
- In addition to activating D1 and D2 receptors in the dorsal striatum that are associated primarily with their motor effects, agonists also bind to the D3 receptors, which are localized to limbic areas and may mediate psychiatric manifestations of dopamine receptor stimulation.

Gambling. In a prospective screening study (using a modified South Oaks Gambling Scale) of 297 patients with PD who attended a tertiary clinic, lifetime prevalence of pathological gambling was 3.5% and prevalence while taking any dopamine agonist was 7.2% (The DSM-defined pathological gambling prevalence in the patients’ area was 1%). Pathological gambling was associated with earlier onset of PD and with dopamine agonists but not with agonist subtype or doses. The D1/D2 (pergolide) and the D2/D3 (ropinirole and pramipexole) agonists were equally implicated. As a point of comparison, a recent general-population survey in California found the overall lifetime prevalence of problem or pathological gambling was 3.7%; the rate was higher among people who were disabled or unemployed.

Hypersexuality. This condition has not been associated with any specific agonist, and it has been reported in patients receiving levodopa monotherapy as well. Among 297 patients who completed systematic screenings and met rigorous diagnostic criteria for hypersexuality, 2.4% of 297 patients found that punding was associated with severity of dyskinesias but not with dopamine agonist use. A review of compulsive and punding behaviors associated with dopaminergic treatment in PD places punding in obsessive-compulsive spectrum disorders, noting that OCD is conceptualized as a disorder of corticostriatothalamo-cortical circuitry.

INITIATING TREATMENT WITH PRAMIPEXOLE

In all clinical studies, dopamine agonists were initiated at a subtherapeutic level to avoid side effects, particularly orthostatic hypotension. Thus, in patients with normal renal function, pramipexole is initiated at a starting dose of 0.125 mg tid (0.375 mg/d) for 1 week, 0.25 mg tid for the second week, and 0.50 mg tid for the third week, with further incremental dose adjustments of 0.25 mg per week based on patient response, up to 1.50 mg tid (Table). Pramipexole in monotherapy, Pramipexole has demonstrated efficacy and is well tolerated over a dosage range of 1.5 to 4.5 mg/d, with
or without levodopa at approximately 800 mg/d. A fixed-dose study using 1.5, 3, 4.5, and 6 mg/d showed no significant therapeutic benefit beyond that achieved at 1.5 mg/d. However, the frequency of some dose-related adverse events (postural hypotension, nausea, constipation, somnolence, and amnesia) was 2-fold greater than that of placebo at pramipexole dosages greater than 3 mg/d.

Pramipexole in combination therapy. When pramipexole is used in combination with levodopa, reduction of the levodopa dosage should be considered. A controlled study of patients with advanced PD found that the dosage of levodopa was reduced by an average of 27%. In this trial, the dosage of levodopa was reduced by an average of 27%. In this trial, pramipexole was initiated by incremental titration over a 7-week period.

SWITCHING DOPAMINE RECEPTOR AGONISTS

Switching dopamine agonists may be necessary because of tolerance issues, potential for fibrotic adverse events, control of non-motor symptoms of PD, such as hallucinations and depression; or because the efficacy of an agonist wanes. Soon after the non-ergoline dopamine agonists were introduced, one of the first studies to look at how best to switch from an ergot to a new non-ergot agent, pramipexole, involved 16 patients receiving stable regimens of carbidopa/levodopa and bromocriptine or pergolide. An end-equivalency pramipexole dose was calculated using a daily milligram conversion of 1:1 for pergolide and of 10:1 for bromocriptine. Patients were randomized to 2 titration schedules: the slow schedule (8 patients), following the early package insert, which could take up to 8 weeks to reach an equivalent dose; or rapid titration, with patients receiving the full converted dose the day after stopping the former agonist, with subsequent weekly adjustments. Both groups showed equivalent and statistically significant improvement after the switch to pramipexole.

The mean time to reach a UPDRS score superior to baseline without increased adverse effects was significantly shorter for the rapid-titration group. Moreover, with slow titration, 2 patients experienced enhanced UPDRS part II scores, 2 patients experienced enhanced UPDRS part III scores, 2 patients experienced enhanced UPDRS part IV scores were reported. The investigators concluded that switching from the 2 ergot dopamine agonists or 1 non-ergot dopamine agonist to pramipexole on an overnight schedule was safe, and that the observed clinical improvement may be related to a placebo effect, to the use of low doses of dopamine agonists, or to a direct effect of pramipexole.

<table>
<thead>
<tr>
<th>Week</th>
<th>Dosage (tid)</th>
<th>Total daily dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.125</td>
<td>0.375</td>
</tr>
<tr>
<td>2</td>
<td>0.25</td>
<td>0.75</td>
</tr>
<tr>
<td>3</td>
<td>0.5</td>
<td>1.50</td>
</tr>
<tr>
<td>4</td>
<td>0.75</td>
<td>2.25</td>
</tr>
<tr>
<td>5</td>
<td>1.0</td>
<td>3.0</td>
</tr>
<tr>
<td>6</td>
<td>1.25</td>
<td>3.75</td>
</tr>
<tr>
<td>7</td>
<td>1.5</td>
<td>4.50</td>
</tr>
</tbody>
</table>

REFERENCES:
10. Rascol O, Broks D, Kurtsay AD, et al. A five-year study of the incidence of dyskinesia in patients with early Parkinson’s disease who were treated with...
term duodenal infusion of levodopa for motor fluctuations in patients with Parkinson’s disease.


Dopamine Agonists in Parkinson Disease: Special Focus on Frapamoline


