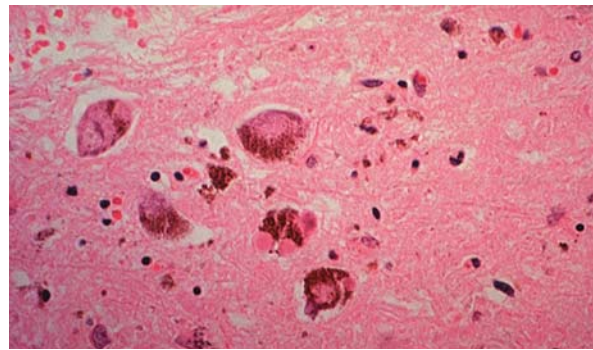
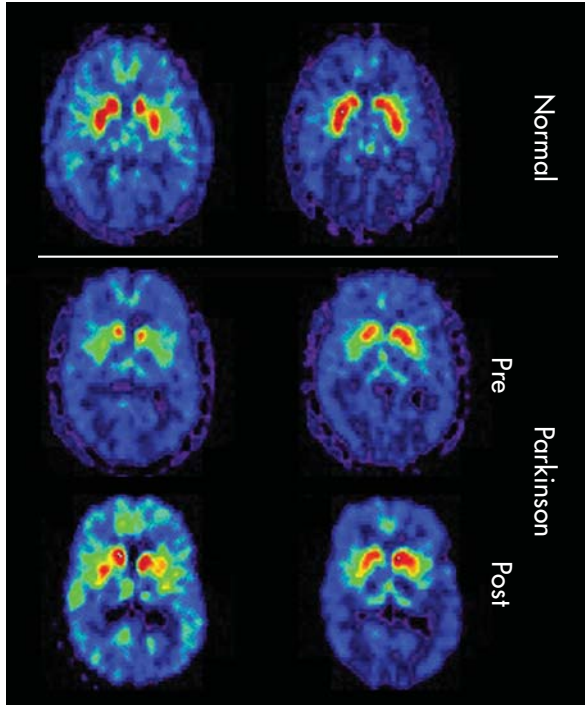


# Consultant®

[www.ConsultantLive.com](http://www.ConsultantLive.com)

A CLIGGOTT PUBLICATION



## 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

---

CONSULTANT (ISSN 0010-7069) is published 14 times a year by the Cliggott Publishing Group, a division of CMPMedica. It is distributed to over 250,000 physicians, MD and DO, in office- and hospital-based general practice, family practice, internal medicine, and cardiology; physician assistants; and nurse practitioners. Subscription rates: \$10 per copy; \$115 a year in the U.S.; \$125 a year (U.S. funds only) for Canada and overseas countries (foreign delivery not guaranteed); \$45 a year for students. Visa and MasterCard are accepted. CMP Healthcare Media LLC will honor claims for missing issues only within three months of the issue dates. Back issues are available for \$10 per copy (\$15, foreign) plus postage and handling. Reprints are available from PARS International at [CMPMedicaReprints@parsintl.com](mailto:CMPMedicaReprints@parsintl.com) or 212-221-9595, ext. 426. Periodicals postage paid at Darien, CT 06820-4027 and additional mailing offices. Copyright © 2008 by CMP Healthcare Media LLC, 330 Boston Post Road, Box 4027, Darien, CT 06820-4027, (203) 662-6400. Printed in U.S.A. All rights reserved. No part of this publication may be reproduced or transmitted in any form, by any means, without written permission. CONSULTANT, *What's Your Diagnosis?*, and *What's The "Take Home"?* are registered trademarks of CMP Healthcare Media LLC. Postmaster: If undelivered, send form 3579 to CONSULTANT, 330 Boston Post Road, Box 4027, Darien, CT 06820-4027.

The opinions expressed herein are those of the authors and do not necessarily represent those of CONSULTANT, Curry Rockefeller Group, or Boehringer Ingelheim Pharmaceuticals. Any procedures or other courses of diagnosis or treatment discussed or suggested by authors should not be used by clinicians without evaluation of their patients' conditions and possible contraindications or dangers in use, review of any applicable manufacturer's prescribing information, and comparison with the recommendations of other authorities.

# Parkinson Disease in Primary Practice: Keys to Diagnosis and Management

Dr Brownlee is chairman and professor in the department of family medicine at the University of South Florida College of Medicine in Tampa.

**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 patho-

genesis 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

## Parkinson Disease in Primary Practice:

Keys to Diagnosis  
and Management

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.<sup>1</sup> 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.<sup>2</sup> 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,<sup>3</sup> progressive supranuclear palsy,<sup>4</sup> and dementia with Lewy bodies.<sup>5,6</sup> These parkinsonism-plus syndromes have a worse prognosis than idiopathic PD, respond poorly to antiparkinsonian medication, and carry other features not associated with PD.<sup>7</sup> 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 (**Table**). This secondary parkinsonism may persist for months after the drugs that caused it are discontinued.<sup>8</sup>

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<sup>a</sup>**

Generic	Trade name
Amoxapine	Ascendin
Chlorpromazine	Thorazine
Danzapine	Zyprexa
Fluphenazine	Permitil, Prolixin
Haloperidol	Haldol
Loxapine	Loxitane, Daxolin
Mesoridazine	Serentil
Metoclopramide	Reglan
Molindone	Moban
Perphenazine	Trilafon or Triavil
Prochlorperazine	Compazine, Combid
Promazine	Sparine
Promethazine	Phenergan
Risperidone	Risperdal
Thiethylperazine	Torecan
Thioridazine	Mellaril
Thiothixene	Navane
Trifluoperazine	Stelazine

<sup>a</sup> 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.

Modified from WeMove (Worldwide Education and Awareness for Movement Disorders).  
[http://www.wemove.org/par/par\\_dia.html](http://www.wemove.org/par/par_dia.html). Accessed August 4, 2008.

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

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.<sup>9</sup> 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.<sup>7</sup> 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).<sup>10</sup>

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.<sup>11,12</sup> 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 in<sup>12</sup>:

- 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, and may contribute as much to the burden of PD.<sup>13</sup> Cognitive impairment generally does not appear until later in the disease's course.

Selective olfactory deficits, independent of disease severity and duration, occur in 70% to 90% of patients with PD.<sup>14</sup> The ability to detect some odors remains unchanged, with identification of others significantly impaired.<sup>14</sup> The olfactory deficit in PD appears stable and is not an inherited trait; this suggests the possibility that olfactory tests may be designed specif-

ically to assist in the early specific, even preclinical, diagnosis of PD.

Changes in mood, cognition, and behavior commonly accompany the later stages of PD and may be the direct result of the disease or of its pharmacotherapy. On questioning 163 consecutive patients attending a PD clinic, investigators found that problems with balance, sleep disturbance, memory failure or confusion-episodic, and dribbling were rated the most disabling symptoms, ahead of such cardinal motor features as bradykinesia and tremor.<sup>15</sup>

Depression, which may occur at any stage of PD, affects as many as 50% of patients.<sup>16</sup> Often unrecognized, depression seems to be an intrinsic part of the illness rather than merely a perhaps understandable reaction to it, and can account for not only sleep disruption but for otherwise unexplained somatic symptoms.

Anxiety may accompany depression or progressive cognitive impairment or may be a consequence of undertreatment of motor symptoms.<sup>16</sup> 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.<sup>16</sup>

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-

## Parkinson Disease in Primary Practice:

Keys to Diagnosis  
and Management

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).<sup>17-19</sup> 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.<sup>20</sup> 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-

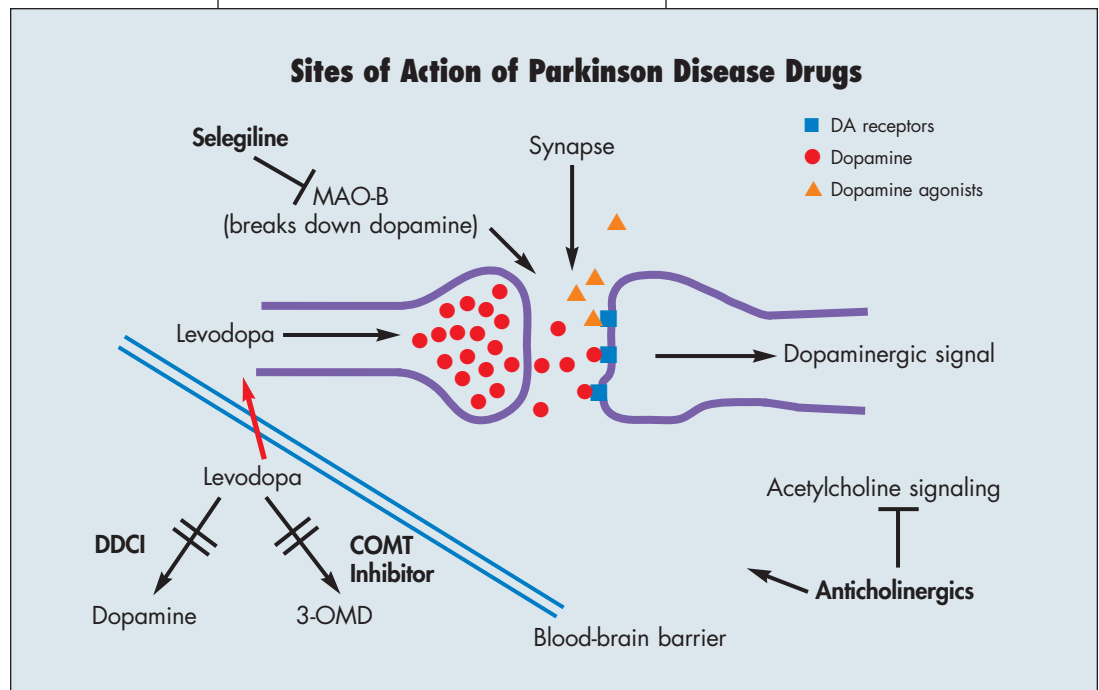


Figure – In this illustration, levodopa passes through the blood-brain barrier to be metabolized to dopamine in dopaminergic neurons. Dopa-decarboxylase (DDC) and COMT (catechol-O-methyltransferase) inhibitors prevent the peripheral metabolism of extrinsic levodopa, thus allowing it to reach the brain. (In the periphery, DDCI prevents the peripheral decarboxylation of levodopa, and COMT inhibitors convert levodopa to 3-O-methyldopa [3-OMD]). Dopamine agonists bind directly to post-synaptic 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.<sup>20</sup>

### **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.<sup>20</sup> 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 early in the disease. Adverse effects, including nausea, dizziness, somnolence, hallucinations, and cognitive effects, tend to occur most commonly during the first few weeks after initiation. Therefore, dopamine agonists should be started at a low dose and gradually titrated to therapeutic levels. Use caution when prescribing dopamine agonists to elderly patients or those who have already experienced hallucinations, confusion, or cognitive impairment. The incidence of adverse effects is higher when a dopamine agonist is taken

with levodopa than when it is given as monotherapy.

A dopamine agonist patch, rotigotine (Neupro),<sup>21</sup> was recently withdrawn from the market after it was found that crystal formation on the patches diminished the amount of available drug.

### **MAO-B Inhibitors**

Monoamine oxidase-B (MAO-B) inhibitors help conserve endogenous dopamine by inhibiting monoamine oxidase enzyme type B, one of the major enzymes responsible for metabolizing dopamine. Selegiline (Eldepryl), the first MAO-B inhibitor to be introduced, has been used 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 derivatives.<sup>22</sup> 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.<sup>23</sup> 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 bztropine (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 carbidopa, enhance the amount of levodopa that reaches the brain, thereby allowing more of the drug to be converted to dopamine.

Administration of levodopa with a COMT inhibitor has the potential to deliver levodopa to the brain in a predictable and stable fashion, thereby decreasing the fluctuations in levodopa concentrations seen when that agent is administered alone and which are believed to be associated with the development of motor complications. There is no evidence to

## Parkinson Disease in Primary Practice:

Keys to Diagnosis  
and Management

### Parkinson Disease Resources

**National Parkinson Foundation, Inc.**  
1501 NW 9th Ave/Bob Hope Road  
Miami, FL 33136-1494  
Telephone: 305-243-6666  
Toll-free: 800-327-4545  
<http://www.parkinson.org>

#### **American Parkinson Disease Association**

135 Parkinson Ave  
Staten Island, NY 10305  
Telephone: 718-981-8001  
Toll-free: 800-223-2732  
<http://www.apdaparkinson.org>

#### **The Michael J. Fox Foundation for Parkinson's Research**

Grand Central Station  
PO Box 4777  
New York, NY 10163  
Toll-free: 800-708-7644  
<http://www.michaeljfox.org>

**Parkinson's Action Network**  
1025 Vermont Ave NW, Suite 1120  
Washington, DC 20005  
Telephone: 202-638-4101  
Toll-free: 800-850-4726  
<http://www.parkinsonsaction.org>

**The Parkinson's Web**  
<http://pdweb.mgh.harvard.edu>

#### **Awakenings, the Internet Focus on Parkinson's Disease**

<http://www.parkinsonsdisease.com>

suggest that the COMT inhibitors are effective as monotherapy.

The 2 available COMT inhibitors are tolcapone (Tasmar) and entacapone (Comtan). The first to be released, tolcapone is a very potent inhibitor of the enzyme COMT with high lipid solubility, which permits it to cross the blood-brain barrier well. Its addition to levodopa/carbidopa resulted in a 25% reduction in levodopa dosage and a reduction in off-time.<sup>24</sup> Reports of hepatocellular injury and acute fulminant liver failure with the use of tolcapone resulted in a restricted license and an FDA warning that the drug be used only when other effective treatments have failed.<sup>25</sup>

Recently, however, the FDA has approved less restrictive labeling that provides for an overall reduction in the required frequency of liver monitoring. For example, blood tests of hepatic function are now required 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.

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 with each dose of levodopa. It is the most widely used COMT inhibitor and when combined with levodopa increases "on" time and reduces "off" time.<sup>26</sup> A new formulation of levodopa, carbidopa, and entacapone (Stalevo) has been found to be well tolerated by patients and to provide clinical improvements similar to those obtained with the separate agents.<sup>27</sup> Ongoing studies are examining whether initiation of therapy with the combination agent will result in a lower dyskinesia rate.<sup>1</sup>

### Neuroprotective Therapy

Recent studies have drawn attention to and raised considerable controversy regarding the potential for the MAO-B inhibitors selegiline and rasagiline, coenzyme Q<sub>10</sub>, and the dopamine agonists pramipexole and ropinirole to provide neuroprotective benefits in PD.<sup>28</sup> 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.

### 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 im-

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%.<sup>29</sup> However, DBS is expensive and carries 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 complications of PD and it has been associated with "L-dopa-independent" dyskinesia.<sup>30</sup> Transplantation of an alternative tissue, human retinal pigment epithelial cells, is now being studied.<sup>31</sup>

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.<sup>32</sup> An open-label, phase 1 safety trial, in which GDNF was delivered into the dorsal putamen of 5 patients with PD resulted in significantly reduced UPDRS-III scores in the off-state and of L-dopa-induced dyskinesias in the on-state.<sup>33</sup> A subsequent phase 2, double-blind, placebo-controlled study involving 34 patients with advanced PD failed to show clinical improvement, however.<sup>34</sup>

### COMMUNITY RESOURCES

A number of organizations provide support and medical information, both live and online, for patients with PD as well as caregivers, health care professionals, and physicians. The major currently active organizations as well as 2 helpful independent

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

### REFERENCES:

1. Nutt JG, Wooten GF. Clinical practice. Diagnosis and initial management of Parkinson's disease. *N Engl J Med.* 2005;353:1021-1027.
2. Charles PD, Esper GJ, Davis TL, et al. Classification of tremor and update on treatment. *Am Fam Physician.* 1999;59:1565-1572.
3. Wenning GK, Ben-Shlomo Y, Magalhães M, et al. Clinicopathological study of 35 cases of multiple system atrophy. *J Neurol Neurosurg Psychiatry.* 1995;58:160-166.
4. Collins SJ, Ahlskog JE, Parisi JE, Maraganore DM. Progressive supranuclear palsy: neuropathologically based diagnostic clinical criteria. *J Neurol Neurosurg Psychiatry.* 1995;58:167-173.
5. Louis ED, Goldman JE, Powers JM, Fahn S. Parkinsonian features of eight pathologically diagnosed cases of diffuse Lewy body disease. *Mov Disord.* 1995;10:188-194.
6. Louis ED, Klatka LA, Liu Y, Fahn S. Comparison of extrapyramidal features in 31 pathologically confirmed cases of diffuse Lewy body disease and 34 pathologically confirmed cases of Parkinson's disease. *Neurology.* 1997;48:376-380.
7. Gelb DJ, Oliver E, Gilman S. Diagnostic criteria for Parkinson disease. *Arch Neurol.* 1999;56:33-39.
8. Rao G, Fisch L, Srinivasan S, et al. Does this patient have Parkinson disease? *JAMA.* 2003;289:347-353.
9. Hughes AJ, Ben-Shlomo Y, Daniel SE, Lees AJ. What features improve the accuracy of clinical diagnosis in Parkinson's disease: a clinicopathologic study. *Neurology.* 1992;42:1142-1146.
10. Jenner P. Factors influencing the onset and persistence of dyskinesia in MPTP-treated primates. *Ann Neurol.* 2000;47(4, suppl 1):S90-S104.
11. Seibyl J, Jennings D, Tabamo R, Marek K. Neuroimaging trials of Parkinson's disease progression. *J Neurol.* 2004;251(suppl 7):vII9-vII13.
12. Seibyl J, Jennings D, Tabamo R, Marek K. The role of neuroimaging in the early diagnosis and evaluation of Parkinson's disease. *Minerva Med.* 2005;96:353-364.
13. Chaudhuri KR, Yates L, Martinez-Martin P. The non-motor symptom complex of Parkinson's disease: a comprehensive assessment is essential. *Curr Neurol Neurosci Rep.* 2005;5:275-283.
14. Double KL, Rowe DB, Hayes M, et al. Identifying the pattern of olfactory deficits in Parkinson disease using the brief smell identification test. *Arch Neurol.* 2003;60:545-549.
15. Gulati W, Forbes A, Stegie F, et al. A clinical observational study of the pattern and occurrence of non-motor symptoms in Parkinson's disease ranging from early to advanced disease. *Mov Disord.* 2004;19(suppl 9):S406.
16. Kasper DL, Braunwald E, Fauci AS, et al, eds. *Harrison's Principles of Internal Medicine.* 16th ed. New York: McGraw Hill; 2004.
17. Deleu D, Northway MG, Hanssens Y. Clinical pharmacokinetic and pharmacodynamic properties of drugs used in the treatment of Parkinson's disease. *Clin Pharmacokinet.* 2002;41:261-309.
18. Olanow CW, Obeso JA. Pulsatile stimulation of dopamine receptors and levodopa-induced motor complications in Parkinson's disease; implications for the early use of COMT inhibitors. *Neurology.* 2000;55(11, suppl 4):S72-S81.
19. Stacy M. Pharmacotherapy for advanced Parkinson's disease. *Pharmacotherapy.* 2000;20(1, pt 2):8S-16S.

20. Miyasaki JM, Martin W, Suchowersky O, et al. Practice parameter: initiation of treatment for Parkinson's disease: an evidence-based review: report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology.* 2002;58:11-17.
21. Rascol O. Transdermal delivery of dopaminergic agents. *Neurology.* 2005;65(2, suppl 1):S1-S2.
22. Blandini F. Neuroprotection by rasagiline: a new therapeutic approach to Parkinson's disease? *CNS Drug Rev.* 2005;11:183-194.
23. Young R. Update on Parkinson's disease. *Am Fam Physician.* 1999;59:2155-2170.
24. Martinez-Martin P, O'Brien CF. Extending levodopa action: COMT inhibition. *Neurology.* 1998;50(6, suppl 6):S27-S32, S44-S48.
25. Tasmir (tolcapone) tablets. In: *Physicians' Desk Reference.* 60th ed. Montvale, NJ: Thomson Healthcare, Inc; 2006:3360-3365.
26. Schapira AH. Present and future drug treatment for Parkinson's disease. *J Neurol Neurosurg Psychiatry.* 2005;76:1472-1478.
27. Brooks DJ, Agid Y, Eggert K, et al; TC-INT Study Group. Treatment of end-of-dose wearing-off in Parkinson's disease. Stalevo (levodopa/carbidopa/entacapone) and levodopa/DDCI given in combination with Comtess/Comtan (entacapone) provide equivalent improvements in symptom control superior to that of traditional levodopa/DDCI treatment. *Eur Neurol.* 2005;53:197-202.
28. Schapira AH, Olanow CW. Neuroprotection in Parkinson disease: mysteries, myths, and misconceptions. *JAMA.* 2004;291:358-364.
29. Krack P, Batir A, Van Blercom N, et al. Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease. *N Engl J Med.* 2003;349:1925-1934.
30. Metman LV, O'Leary ST. Role of surgery in the treatment of motor complications. *Mov Disord.* 2003;20(suppl 11):S45-S56.
31. Watts RL, Raiser CD, Stover NP, et al. Stereotaxic intrastriatal implantation of human retinal pigment epithelial (hRPE) cells attached to gelatin microcarriers: a potential new cell therapy for Parkinson's disease. *J Neural Transm Suppl.* 2003;65:215-227.
32. Grondin R, Zhang Z, Yi A, et al. Chronic, controlled GDNF infusion promotes structural and functional recovery in advanced parkinsonian monkeys. *Brain.* 2002;125:2191-2201.
33. Gill SS, Patel NK, Hottel GR, et al. Direct brain infusion of glial cell line-derived neurotrophic factor in Parkinson disease. *Nat Med.* 2003;9:589-595.
34. Nutt JG, Burchiel KJ, Comella CL, et al. Randomized, double-blind trial of glial cell line-derived neurotrophic factor (GDNF) in PD. *Neurology.* 2003;60:69-73.

# Dopamine Agonists in Parkinson Disease: Special Focus on Pramipexole

Dr Zesiewicz is professor of neurology, director of clinical research at the Parkinson Research Foundation, and director of the Ataxia Research Center at the University of South Florida College of Medicine in Tampa. She is also director of the Parkinson's Disease Center at James A. Haley Veterans' Hospital in Tampa.

**ABSTRACT: Dopamine receptor agonists have played an important role in antiparkinsonian 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.<sup>1</sup> The loss of dopamine creates an imbalance between excitatory and inhibitory effects in the basal ganglia, resulting in hypokinetic motor behavior (**Figure 1**).<sup>2</sup>

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.<sup>3</sup> 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 non-motor, cognitive, and behavioral changes that are characteristic of PD.

For example, degeneration of olfactory-bulb neurons is believed to cause anosmia.<sup>3</sup> 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 con-

tribute 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 dyskinesia, 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 agent used to treat parkinsonian symptoms have been shown to correlate with their development.<sup>4</sup> 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 agent.<sup>4,5</sup> 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**).<sup>6,9</sup>

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.<sup>6,9</sup>

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**).<sup>10-13</sup> 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.<sup>14</sup> 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.<sup>6</sup> Continuous levodopa delivery by intractestinal 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.<sup>15-21</sup> 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.<sup>22,23</sup> 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).<sup>24</sup> 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-

## Dopamine Agonists in Parkinson Disease:

Special Focus on Pramipexole

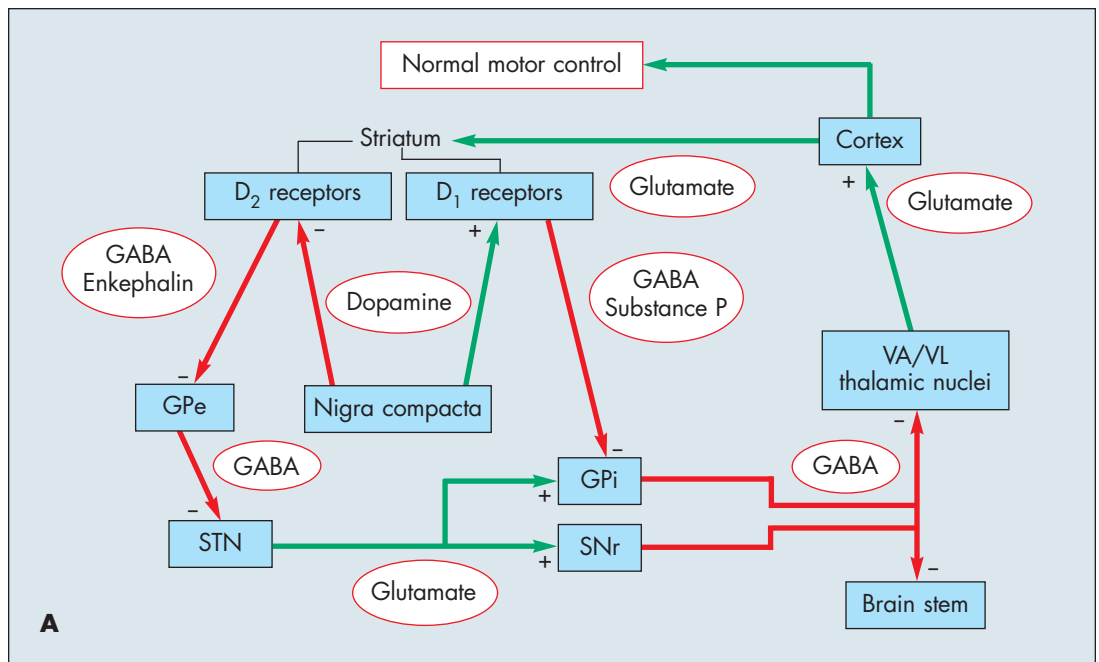
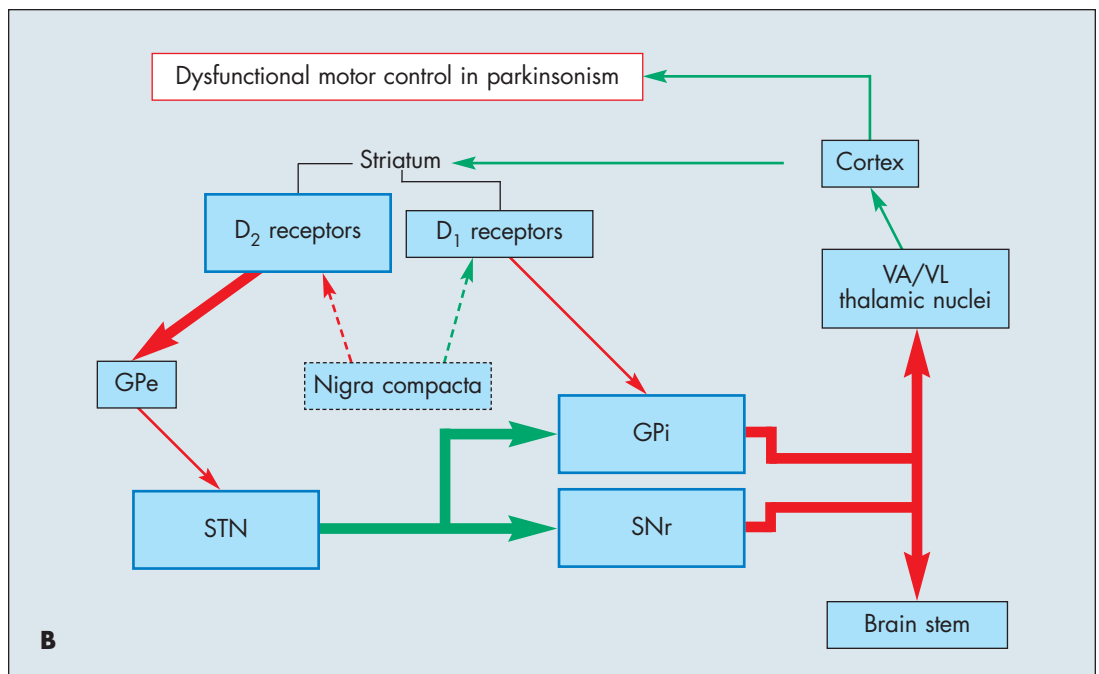


Figure 1 – Illustrated here is a simplified proposed functional model of the basal ganglia in patients with parkinsonism. In the striatum, the GABAergic output neurons projecting directly to the internal segment of the globus pallidus (GPI) and the pars reticulata of the substantia nigra (SNr) contain a predominance of D<sub>1</sub> dopamine receptors. The neurons projecting to the external segment of the globus pallidus (GPe) and subthalamic nucleus (STN) carry predominantly D<sub>2</sub> receptors. Dopamine has different effects on these receptors and, in turn, on the subpopulations of striatal output neurons, exciting those expressing D<sub>1</sub> receptors (green arrows, the direct striatopallidal pathway) and inhibiting those with D<sub>2</sub> 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.<sup>2</sup>)



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  $D_2$  family receptors but also show affinity of varying degrees for  $D_1$ , adrenergic, and 5HT receptors. On the other hand, the non-ergolines bind only to  $D_2$  and  $D_3$  receptors with high affinity; pramipexole is more potent at  $D_3$  binding.

When used as an adjunct to levodopa, dopamine agonists reduce both motor disability and on-off fluctuations in patients with advanced PD.<sup>25-29</sup> 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,<sup>30</sup> cabergoline,<sup>31,32</sup> ropinirole,<sup>10,33</sup> or pramipexole.<sup>11</sup>

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.<sup>10,23</sup>

## ERGOT DOPAMINE AGONISTS

**Bromocriptine.** This dopamine agonist directly stimulates both pre- and postsynaptic receptors, with a high affinity to  $D_2$  receptors (it is also

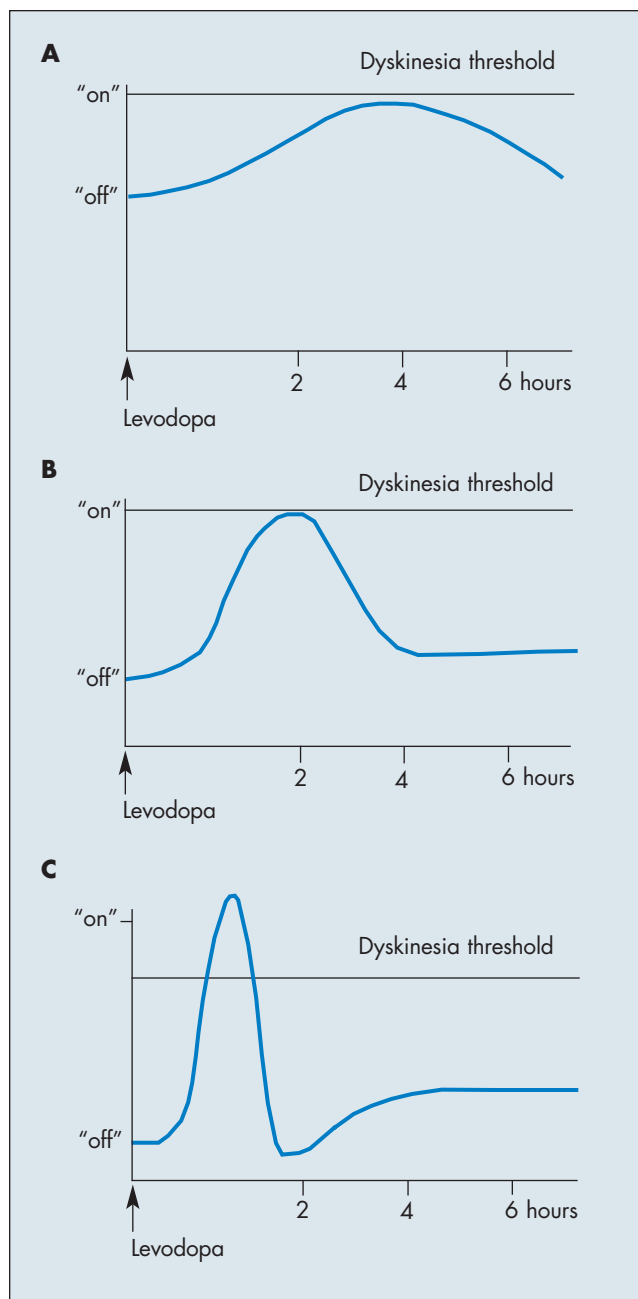


Figure 2 – Illustrated here is the pharmacological response to a levodopa challenge in patients with mild (A), moderate (B), and severe (C) PD. In the early stage, response is slow in onset, has small magnitude, and a long duration. In the intermediate stage, the severity of motor dysfunction in the 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.<sup>6</sup>)

## Dopamine Agonists in Parkinson Disease:

Special Focus on Pramipexole

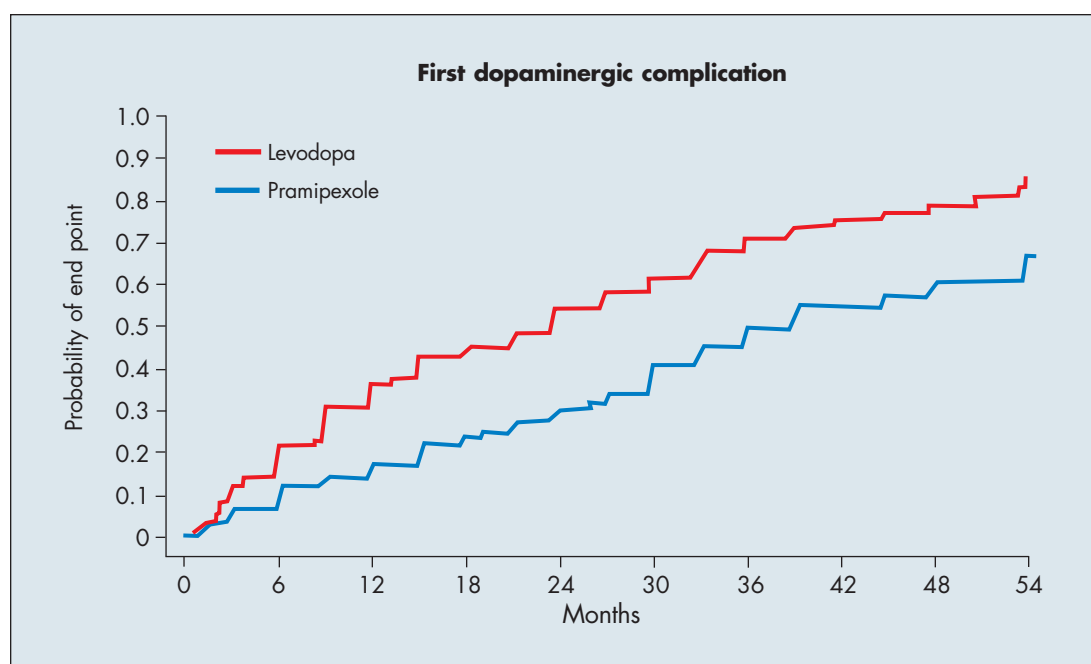


Figure 3 – Time to first dopaminergic complications<sup>a</sup> for initial therapy with either levodopa or the dopamine agonist pramipexole.

<sup>a</sup> Wearing-off, dyskinesias, on-off fluctuations. Levodopa supplementation was allowed for both groups after 10 weeks.

(From Holloway RG et al. *Arch Neurol.* 2004.<sup>11</sup>)

a partial antagonist of D<sub>1</sub> receptors). 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.<sup>34</sup> However, the usefulness of bromocriptine has been tempered by a lengthy titration schedule (weeks to months)<sup>35</sup> and by reports of retroperitoneal fibrosis in patients receiving long-term therapy at high dosages.<sup>36</sup> 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 D<sub>2</sub> and a weak D<sub>1</sub> receptor agonist, pergolide is effective in reducing motor complications as both monotherapy<sup>30</sup> and adjunctive therapy to levodopa.<sup>27,30</sup>

Four earlier reports of retroperitoneal, pericardial, or pleural fibrosis and valvular insufficiency in patients treated with high-dose pergolide<sup>37-40</sup> were followed in 2003 by one report of pergolide-associated valvular heart disease.<sup>41</sup> A year later, echocardiographic evidence of valvular insufficiency was reported in 10 patients who were receiving high-dose pergolide.<sup>42</sup> At least 4 more studies have described the association of pergolide with valvular heart disease.<sup>43-46</sup> 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 D<sub>2</sub> 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 ( $P < .001$ ).<sup>47</sup>

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.<sup>10</sup> 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.<sup>12</sup> The primary outcome measure was reduction in putamen (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.<sup>48</sup>

**Rotigotine.** This dopamine agonist was developed for administration via a silicone-based transdermal patch.<sup>49-51</sup> 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-benzothiazol derivative binds to D<sub>3</sub> receptors with 7-fold

greater affinity than it does to either D<sub>2</sub> or D<sub>4</sub> receptors.<sup>52</sup> Its terminal half-life is about 8 hours in young healthy volunteers and about 12 hours in elderly volunteers.<sup>53</sup> 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.<sup>54</sup> 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.<sup>55</sup> 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 pramipex-

ole 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 development 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.<sup>56</sup> 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

## Dopamine Agonists in Parkinson Disease:

Special Focus on  
Pramipexole

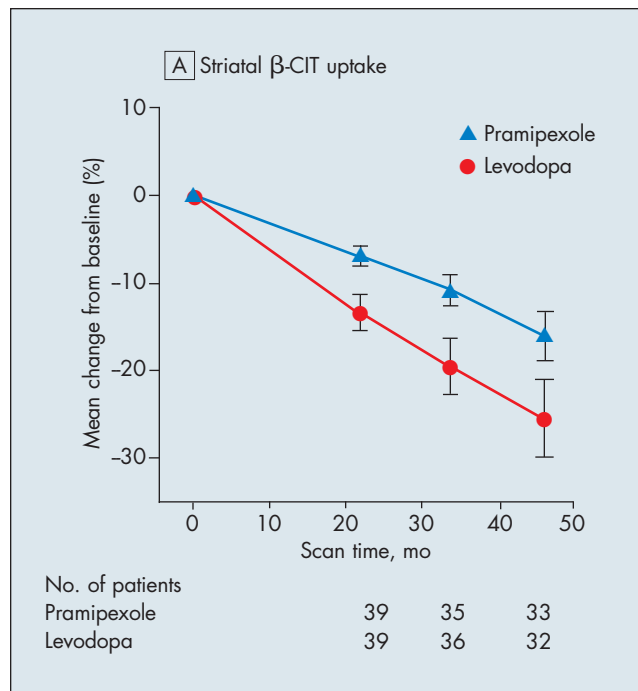


Figure 4 – The rate of decline in striatal uptake from baseline, measured by single photon emission CT (SPECT), was significantly reduced in the pramipexole compared with the levodopa group.

(Adapted from Parkinson Study Group. *JAMA*. 2002.<sup>56</sup>)

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.<sup>28</sup> 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 motor fluctuations and who were taking levodopa found that

pramipexole treatment improved UPDRS parts II and III (activities of daily living and motor examination) scores by 30% and reduced off times by roughly 2.5 hours per day.<sup>57</sup> There were significant differences between treatment groups at a relatively low daily dose of pramipexole (0.75 mg/d). An open-label extension phase of this study provided data for up to 57 months and confirmed the long-term safety and efficacy of pramipexole. Post hoc analysis of these findings further showed that in the subgroup of patients with a UPDRS I score of greater than 0 at inclusion, decreases in this score with pramipexole were mainly caused by significant improvements in motivation/initiative and depression.

In addition to its efficacy in treating rigidity and akinesia, pramipexole reduced parkinsonian tremor in 16 patients with advanced PD and marked rest tremor during the on

period.<sup>58</sup> 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 35% 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 65%. 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 tremolytic properties of pramipexole with those of placebo as add-on medication in 84 patients with PD who had marked drug-resistant tremor.<sup>59</sup> 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

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 D<sub>1</sub> and D<sub>2</sub> dopamine receptors of the striatum, thus mimicking the action of dopamine more closely than any other available agent.<sup>60</sup> 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. When given by intermittent subcutaneous injection, the most common route, in doses ranging from 2 to 10 mg, apomorphine produces adequate blood and cerebrospinal levels within 7.5 to 10 minutes, resulting in robust antiparkinsonian effects.<sup>60,61</sup> Thus, apomorphine is well suited for the purpose of "rescue," the rapid termination of levodopa-induced fluctuations, including tremor, bradykinesia, and limb rigidity.<sup>62</sup>

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.<sup>60</sup>

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.<sup>63</sup> 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

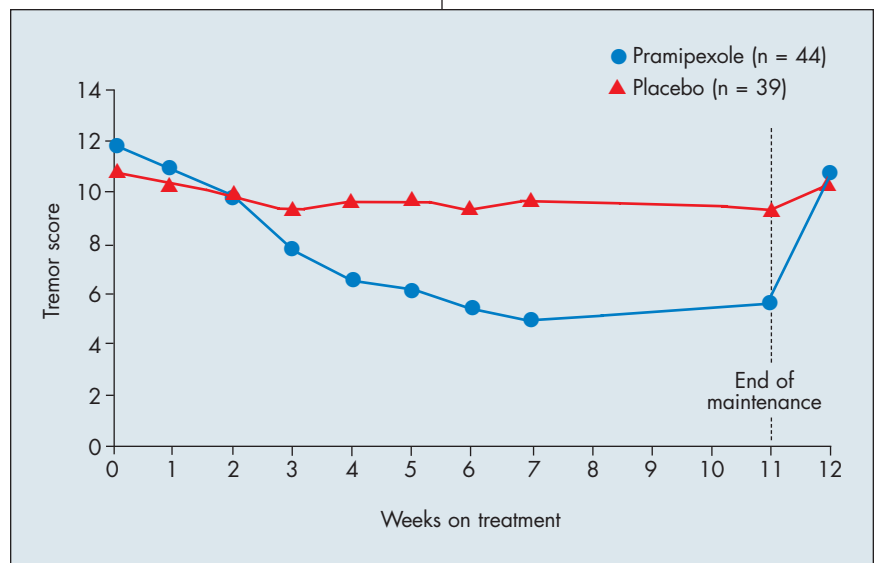


Figure 5 – Shown here is the development of mean tremor score (sum of UPDRS items 16, 10, and 21) per week with pramipexole and placebo from baseline, through weeks 1 to 7 (ascending dose interval), weeks 7 to 11 (maintenance period), to weeks 11 and 12 (dose reduction). (Adapted from Pogarell O et al. *J Neurol Neurosurg Psychiatry*.2002.<sup>59</sup>)

## Dopamine Agonists in Parkinson Disease:

Special Focus on  
Pramipexole

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.<sup>60</sup> 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.<sup>60</sup> 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 ergoline derivatives cabergoline,<sup>64-71</sup> dihydroergocryptine,<sup>72,73</sup> and lisuride,<sup>74-82</sup> and the non-ergoline piribedil.<sup>83-89</sup>

### SIDE EFFECTS OF DOPAMINE AGONISTS

Ergoline dopamine agonists may cause retroperitoneal and pleuropulmonary fibrosis, albeit very rarely.<sup>82</sup>

In addition, they may give rise to Raynaud syndrome and erythromelalgia.<sup>90</sup> 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,<sup>91</sup> 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.<sup>92,93</sup> According to a large European survey, the non-ergolines have a slightly higher tendency towards somnolence than the ergolines.<sup>94</sup> The propensity for levodopa and the dopamine agonists to cause psychosis or neuropsychiatric symptoms in patients with PD, including hallucinations<sup>95</sup> and compulsive symptoms such as pathological gambling or stereotyped behaviors (termed *punding*), has been reported.<sup>96,97</sup>

**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-awake 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.<sup>93</sup> 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.<sup>90</sup> Sleep attacks can occur with all

dopaminergic drugs, including alpha-dihydroergocryptine, bromocriptine, cabergoline, lisuride, pergolide, pramipexole, and ropinirole, with no significant difference between ergot and non-ergot agents.<sup>87,93</sup>

**Psychosis.** This is defined as a disturbance of perception and thought and commonly includes hallucinations, delusions, paranoid beliefs, agitation, and delirium.<sup>96</sup> 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.<sup>10,98,99</sup> Early drug-induced psychosis has been observed in up to 16% of patients treated with dopamine agonists and has been associated with an increased risk of the development of dementia later on.<sup>96</sup> Visual hallucinations are the most common clinical manifestations and have been observed in about 30% of patients over the course of PD.<sup>100,101</sup> 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.<sup>96</sup>

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.<sup>102</sup> 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 neuropsychi-

atric adverse events of antiparkinsonian therapies, although no similar study in humans exists.

**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,<sup>103</sup> pathological hypersexuality,<sup>104</sup> punding,<sup>105</sup> binge eating,<sup>106</sup> compulsive shopping,<sup>107</sup> and compulsive dopaminergic medication use,<sup>108</sup> 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 6.6% of patients, while 4.0% of patients had an active ICD.<sup>109</sup> Another study found the lifetime prevalence of these impulse-control behaviors was 6.1% and increased to 13.7% in patients receiving dopamine agonists.<sup>110</sup>

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.<sup>111</sup> 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.<sup>109</sup>

- Patients who have PD may display executive function deficits<sup>112</sup> linked to degeneration in the frontal-striatal tracts secondary to cell loss within the SN<sub>c</sub>.<sup>113</sup>

- In addition to activating D<sub>1</sub> and D<sub>2</sub> receptors in the dorsal striatum that are associated primarily with their

motor effects, agonists also bind to the D<sub>3</sub> receptors,<sup>114</sup> which are localized to limbic areas and may mediate psychiatric manifestations of dopamine receptor stimulation.<sup>115</sup>

**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%.<sup>103</sup> (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 D<sub>1</sub>/D<sub>2</sub> (pergolide) and the D<sub>2</sub>/D<sub>3</sub> (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.<sup>116</sup>

**Hypersexuality.** This condition has not been associated with any specific agonist, and it has been reported in patients receiving levodopa monotherapy as well.<sup>104,110</sup> Among 297 patients who completed systematic screenings and met rigorous definitional criteria, 7 reported behaviors consistent with diagnostic criteria for hypersexuality.<sup>110</sup> In 2 patients, hypersexuality occurred either while receiving levodopa monotherapy or before the initiation of adjunctive agonist therapy. The lifetime prevalence of pathological hypersexuality was found to be 2.4% and that of compulsive shopping to be 0.7%. Six of 7 patients had comorbid depression, but whether it was secondary to the behavior, the result of similar pathophysiological substrates, or as mediator of the behavior is unknown. Timing of the depression in relation to

the onset of the hypersexuality was not clearly established.

**Punding.** This refers to engaging in complex, prolonged, purposeless, and stereotyped behavior.<sup>105</sup> A questionnaire survey found that Punding Scale scores were higher among 141 patients with PD than among 103 controls (11.88 vs 10.21, respectively;  $P < .001$ ). Of 14 clinical, demographic, and medication factors investigated as predictors of punding, daily use of dopamine-receptor agonists was 1 of 9 independent predictors of a higher score. The largest independent predictors, however, were age at onset of PD, score on the Barratt Impulsivity Scale, and Parkinson's Disease Questionnaire-39 score. The authors note that dopamine-agonist use was higher in patients with an earlier onset of PD.<sup>105</sup> Another study of 45 patients found that punding was associated with severity of dyskinesias but not with dopamine agonist use.<sup>117</sup> 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.<sup>118</sup>

## INITIATING TREATMENT WITH PRAMIPEXOLE

In all clinical studies, dopamine agonists were initiated at a subtherapeutic level to avoid side effects, particularly orthostatic hypertension. 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 tid per week based on patient response, up to 1.50 mg tid (Table).<sup>119</sup>

**Pramipexole in monotherapy.** Pramipexole has demonstrated efficacy and is well tolerated over a dosage range of 1.5 to 4.5 mg/d, with

## Dopamine Agonists in Parkinson Disease:

Special Focus on Pramipexole

or without levodopa at approximately 800 mg/d.<sup>119</sup> 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%.<sup>28</sup> 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 tolerability 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.<sup>120,121</sup> 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.<sup>120</sup> 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 parkinsonian side effects (falls with fractures) requiring hospitalization.

In a later open-label trial, 217 patients with advanced PD who were not optimally controlled by levodopa and a stable dose of bromocriptine (58 patients), pergolide (125), or ropinirole (34) were converted over-

night to pramipexole.<sup>121</sup> The switch was made according to the following dose equivalency scheme: 1 mg of pramipexole = 1 mg of pergolide = 10 mg of bromocriptine = 4 mg of ropinirole. Clinical assessments were performed just before conversion and after 2, 6, and 12 weeks of treatment, when an optimal dose of pramipexole was achieved.

Mean levodopa dose was slightly reduced in all groups, and UPDRS activities of daily living, motor examination, and complications of therapy (parts II, III, and IV) scores were reduced by 26% to 30% in all patients. No serious or unexpected side effects 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. ■

### REFERENCES:

1. Cardoso SM, Moreira PI, Agostinho P, et al. Neurodegenerative pathways in Parkinson's disease: therapeutic strategies. *Curr Drug Targets—CNS Neurol Disord.* 2005;4:405-419.
2. Lang AE, Lozano AM. Parkinson's disease: second of two parts. *N Engl J Med.* 1998;339:1130-1143.
3. Lang AE, Lozano AM. Parkinson's disease: first of two parts. *N Engl J Med.* 1998;339:1045-1053.
4. Stocchi F, Olanow CW. Continuous dopaminergic stimulation in early and advanced Parkinson's disease. *Neurology.* 2004;62(suppl 1):S56-S63.
5. Olanow CW, Obeso JA, Stocchi F. Continuous dopamine-receptor treatment of Parkinson's disease: scientific rationale and clinical implications. *Lancet Neurol.* 2000;5:677-687.
6. Olanow CW, Obeso JA, eds. Beyond the decade of the brain. In: *Dopamine Agonists in Early Parkinson's Disease.* Vol 2. Kent, UK: Wells Medical; 1997: 11-35.
7. Calon F, Grondin R, Morissette M, et al. Molecular basis of levodopa-induced dyskinesias. *Ann Neurol.* 2000;47(suppl 1):S70-S78.
8. Filon M, Tremblay L, Bedard PJ. Effects of dopamine agonists on the spontaneous activity of globus pallidus neurons in monkeys with MPTP-induced parkinsonism. *Brain Res.* 1991;547:152-161.
9. Olanow CW, Obeso JA. Pulsatile stimulation of dopamine receptors and levodopa-induced motor complications in Parkinson's disease: implications for early use of COMT inhibitors. *Neurology.* 2000;55(suppl 4):S72-S77.
10. Rascol O, Brooks DJ, Korczyn AD, et al. A five-year study of the incidence of dyskinesia in patients with early Parkinson's disease who were treated with

**Table – Ascending dosage schedule for pramipexole**

Week	Dosage (tid)	Total daily dose (mg)
1	0.125	0.375
2	0.25	0.75
3	0.5	1.50
4	0.75	2.25
5	1.0	3.0
6	1.25	3.75
7	1.5	4.50

ropinirole or levodopa. *N Engl J Med.* 2000;342:1484-1491.

**11.** Holloway RG, Shoulson I, Fahn S. Pramipexole vs levodopa as initial treatment for PD: a 4-year randomized controlled trial. *Arch Neurol.* 2004;61:1044-1053.

**12.** Whone AL, Watts RL, Stoessel AJ, et al. Slower progression of Parkinson's disease with ropinirole versus levodopa: the REAL-PET study. *Ann Neurol.* 2002;54:93-101.

**13.** Parkinson Study Group. Dopamine transporter brain imaging to assess the effects of pramipexole vs levodopa on PD progression. *JAMA.* 2002;287:1653-1661.

**14.** Nutt JG, Obeso JA, Stocchi F. Continuous dopamine-receptor stimulation in advanced Parkinson's disease. *Trends Neurosci.* 2000;23(suppl):S109-S115.

**15.** Sage JI, Trooskin S, Sonsalla PK, et al. Long-term duodenal infusion of levodopa for motor fluctuations in parkinsonism. *Ann Neurol.* 1998;24:87-89.

**16.** Ruggieri S, Stocchi F, Carta A, et al. Jejunal delivery of levodopa methyl ester. *Lancet.* 1989;8653:45-46.

**17.** Kurlan R, Rubin AJ, Miller C, et al. Duodenal delivery of levodopa for on-off fluctuations in parkinsonism: preliminary observation. *Ann Neurol.* 1986;20:262-265.

**18.** Kurth MC, Tetrud JW, Tanner CM, et al. Double-blind, placebo-controlled, crossover study of duodenal infusion of levodopa-carbidopa in Parkinson's disease patients with "on-off" fluctuations. *Neurology.* 1993;43:1698-1703.

**19.** Nutt JG, Carter JH, Lea ES, Woodward WR. Motor fluctuations during continuous levodopa infusions in patients with Parkinson's disease. *Mov Disord.* 1997;12:285-292.

**20.** Nilsson D, Hansson LE, Johansson, et al. Long-term intraduodenal infusion of a water based levodopa-carbidopa dispersion in very advanced Parkinson's disease. *Acta Neurol Scand.* 1998;97:175-183.

**21.** Syed N, Murphy J, Zimmerman T Jr, et al. Ten years' experience with enteral levodopa infusions for motor fluctuations in Parkinson's disease. *Mov Disord.* 1998;13:336-338.

**22.** Olanow CW, Watts RL, Diller WC. An algorithm (decision tree) for the management of Parkinson's disease (2001): treatment guidelines. *Neurology.* 2001;56(suppl 5):S1-S88.

**23.** Olanow CW. The role of dopamine agonists in the treatment of early Parkinson's disease. *Neurology.* 2002;58(suppl 1):S33-S41.

**24.** Bonuccelli U, Pavese N. Dopamine agonists in the treatment of Parkinson's disease. *Expert Rev Neurother.* 2006;6:81-89.

**25.** Kartzinell R, Teychenne P, Gillespie MM, et al. Bromocriptine and levodopa (with or without carbidopa) in parkinsonism. *Lancet.* 1976;2:272-275.

**26.** Lieberman AN, Kupersmith M, Gopinathan G, et al. Bromocriptine in PD: further studies. *Neurology.* 1979;29:363-369.

**27.** Olanow CW, Fahn S, Muenter M, et al. A multicenter double-blind placebo-controlled trial of pergolide as an adjunct to Sinemet in Parkinson's disease. *Mov Disord.* 1994;9:40-47.

**28.** Lieberman A, Ranhosky A, Korts D. Clinical evaluation of pramipexole in advanced Parkinson's disease: results of a double-blind, placebo-controlled, parallel-group study. *Neurology.* 1997;49:162-168.

**29.** Lieberman A, Olanow CW, Sethi K, et al. A multicenter trial of ropinirole as adjunct treatment for Parkinson's disease. Ropinirole Study Group. *Neurology.* 1998;51:1057-1062.

**30.** Oertel WH, Wolters E, Sampaio C, et al. Pergolide versus levodopa monotherapy in early Parkinson's disease patients: the PELMOPET study. *Mov Disord.* 2006;21:343-353.

**31.** Bracco F, Battaglia A, Chouze C, et al. The long-acting dopamine receptor agonist cabergoline in early Parkinson's disease: final results of a 5-year, double-blind, levodopa-controlled study. *CNS Drugs.* 2004;18:733-746.

**32.** Hutton JT, Morris JL, Brewer MA. Controlled study of the antiparkinsonian activity and tolerability of cabergoline. *Neurology.* 1993;43:613-616.

**33.** Rascol O, Lees AJ, Senard JM, et al. A placebo-controlled study of ropinirole, a new D2 agonist, in the treatment of motor fluctuations of L-DOPA-treated parkinsonian patients. *Adv Neurol.* 1996;69:531-534.

**34.** Przuntek H, Weizel D, Gerlach M, et al. Early institution of bromocriptine in Parkinson's disease inhibits the emergence of levodopa-associated motor side effects. Long-term results of the PRADO study. *J Neurol Transm.* 1996;103:699-715.

**35.** Brunton LL, Lazo JS, Parker KL, eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics.* 11th ed. Minneapolis: McGraw-Hill Professional; 2005.

**36.** Kvernmø T, Haertter S, Bueger E. A review of the receptor-binding and pharmacokinetic properties of dopamine agonists. *Clin Ther.* 2006;28:1065-1078.

**37.** Jimenez-Jimenez FJ, Lopez-Alvarez J, Sanchez-Chapado M, et al. Retroperitoneal fibrosis in a patient with Parkinson's disease treated with pergolide. *Clin Neuropharmacol.* 1995;18:277-279.

**38.** Mondal BK, Suri S. Pergolide-induced retroperitoneal fibrosis. *Int J Clin Pract.* 2000;54:403.

**39.** Shaunak S, Wilkins A, Pilling JB, Dick DJ. Pericardial, retroperitoneal, and pleural fibrosis induced by pergolide. *J Neurol Neurosurg Psychiatry.* 1999;66:79-81.

**40.** Pritchett AM, Morrison JF, Edwards WD, et al. Valvular heart disease in patients taking pergolide. *Mayo Clin Proc.* 2002;77:1280-1286.

**41.** Flowers CM, Racoosin JA, Lu SL, Beitz JG. The US Food and Drug Administration's registry of patients with pergolide-associated valvular heart disease. *Mayo Clin Proc.* 2003;78:720-731.

**42.** Baseman DG, O'Suilleabhain PE, Reimold SC, et al. Pergolide use in PD is associated with cardiac valve regurgitation. *Neurology.* 2004;63:301-304.

**43.** Van Camp G, Flamez A, Cosyns B, et al. Heart valvular disease in patients with Parkinson's disease treated with high-dose pergolide. *Neurology.* 2003;61:859-861.

**44.** Waller EA, Kaplan J, Heckman MG. Valvular heart disease in patients taking pergolide. *Mayo Clin Proc.* 2005;80:1016-1020.

**45.** Schade R, Andersohn F, Suissa S, et al. Dopamine agonists and the risk of cardiac-valve regurgitation. *N Engl J Med.* 2007;356:29-38.

**46.** Zenetini R, Antonini A, Gatto G, et al. Valvular heart disease: the use of dopamine agonists for Parkinson's disease. *N Engl J Med.* 2007;356:39-46.

**47.** Wheadon DE, Wilson-Lynch K, Gardiner D, Kreider MS. Ropinirole, a non-ergoline D<sub>2</sub> agonist, is effective in early parkinsonian patients not treated with L-dopa. *Mov Disord.* 1996;11:162. Abstract P601.

**48.** Lieberman A, Olanow CW, Sethi K, et al. A multicenter trial of ropinirole as adjunct treatment for Parkinson's disease. Ropinirole Study Group. *Neurology.* 1998;51:1057-1062.

**49.** The Parkinson Study Group. A controlled trial of rotigotine monotherapy in early Parkinson's disease. *Arch Neurol.* 2003;60:1721-1728.

**50.** Reynolds NA, Wellington K, Easthope SE. Rotigotine in Parkinson's disease. *CNS Drugs.* 2005;19:973-981.

**51.** Morgan JC, Sethi KD. Rotigotine for the treatment of Parkinson's disease. *Expert Rev Neurother.* 2006;6:1275-1282.

**52.** Ling ZD, Robie HC, Tong CW, Carvey PM. Both the antioxidant and D3 agonist actions of pramipexole mediate its neuroprotective actions in mesence-

phalic cultures. *J Pharmacol Exp Ther.* 1999;289:202-210.

**53.** Mirapex. In *Physicians' Desk Reference.* 55th ed. Montvale, NJ: Thomson; 2001:2626-2630.

**54.** Shannon KM, Bennett JP Jr, Friedman JH. Efficacy of pramipexole, a novel dopamine agonist, as monotherapy in mild to moderate Parkinson's disease. *Neurology.* 1997;49:724-728.

**55.** Parkinson Study Group. Pramipexole vs levodopa as initial treatment for PD. *JAMA.* 2000;284:1931-1938

**56.** Parkinson Study Group. Dopamine transporter brain imaging to assess the effects of pramipexole vs levodopa on PD progression. *JAMA.* 2002;287:1653-1661.

**57.** Moeller JC, Oertel WH, Koester J, et al. Long-term efficacy and safety of pramipexole in advanced Parkinson's disease: results from a European multicenter trial. *Mov Disord.* 2005;20:602-610.

**58.** Kunig G, Pogarell O, Moeller JC, et al. Pramipexole, a nonergot dopamine agonist, is effective against rest tremor in intermediate to advanced Parkinson's disease. *Clin Neuropharmacol.* 1999;22:301-305.

**59.** Pogarell O, Gasser T, van Hilten JJ, et al. Pramipexole in patients with Parkinson's disease and marked drug resistant tremor: a randomized, double blind, placebo controlled multicentre study. *J Neurol Neurosurg Psychiatry.* 2002;72:713-720.

**60.** Dewey RB Jr. 10 questions about using apomorphine for PD. *Neurologist.* 2005;11:190-192.

**61.** Gancher S. Pharmacokinetics of apomorphine in Parkinson's disease. *J Neural Transm Suppl.* 1995;45:137-141.

**62.** Dewey RB. Management of motor complications in Parkinson's disease. *Neurology.* 2004;62(suppl 4):S3-S7.

**63.** Dewey RB Jr, Hutton JT, LeWitt PA, Factor SA. A randomized, double-blind, placebo-controlled trial of subcutaneously injected apomorphine for parkinsonian off-state events. *Arch Neurol.* 2001;58:1385-1392.

**64.** Rinne UK, Bracco F, Chouze C, et al. Cabergoline in the treatment of early Parkinson's disease: results of the first year of treatment in a double-blind comparison of cabergoline and levodopa. *Neurology.* 1997;48:363-368.

**65.** Rinne UK, Bracco F, Chouze C, et al. Early treatment of Parkinson's disease with cabergoline delays the onset of motor complications: results of a double-blind levodopa controlled trial. *Drugs.* 1998;55(suppl 1):23-30.

**66.** Inzelberg R, Nisipeanu P, Rabey JM, et al. Double-blind comparison of cabergoline and bromocriptine in Parkinson's disease patients with motor fluctuations. *Neurology.* 1996;47:785-788.

**67.** Hutton JT, Koller WC, Ahlskog JE, et al. Multicenter, placebo-controlled trial of cabergoline taken once daily in the treatment of Parkinson's disease. *Neurology.* 1996;46:1062-1065.

**68.** Townsend M, MacIver DH. Constrictive pericarditis and pleuropulmonary fibrosis secondary to cabergoline treatment for Parkinson's disease. *Heart.* 2004;90:e47.

**69.** Horvath J, Fross RD, Kleiner-Fisman G, et al. Severe multivalvular heart disease: a new complication of the ergot derivative dopamine agonists. *Mov Disord.* 2004;19:656-662.

**70.** Pinero A, Marcos-Alberca P, Fortes J. Cabergoline-related severe restrictive mitral regurgitation. *N Engl J Med.* 2005;353:1976-1977.

**71.** Peralta C, Wolf E, Alber H, et al. Valvular heart disease in Parkinson's disease vs controls: an echocardiographic study. *Mov Disord.* 2006;21:1109-1113.

**72.** Bergamasco B, Frattola L, Muratorio A, et al. Alpha-dihydroergocryptine in the treatment of de novo parkinsonian patients: results of a multicenter, randomized, double-blind, placebo-controlled study. *Acta Neurol Scand.* 2000;101:372-380.

## Dopamine Agonists in Parkinson Disease:

### Special Focus on Pramipexole

- 73.** Albanese A, Colosimo C. Dihydroergocriptine in Parkinson's disease: clinical efficacy and comparison with other dopamine agonists. *Acta Neurol Scand.* 2003;107:349-355.
- 74.** Goinathan G, Teräväinen H, Dambrosia JM, et al. Lisuride in parkinsonism. *Neurology.* 1981;31:371-376.
- 75.** Clarke CE, Speller JM. Lisuride for levodopa-induced complications in Parkinson's disease. *Cochrane Database Syst Rev.* 2000;(2):CD001515.
- 76.** Obeso JA, Luquin MR, Vaamonde J, et al. Subcutaneous administration of lisuride in the treatment of complex motor fluctuations in Parkinson's disease. *J Neural Transm Suppl.* 1988;27:17-25.
- 77.** Vaamonde J, Luquin MR, Obeso JA. Subcutaneous lisuride infusion in Parkinson's disease. *Brain.* 1991;114:601-614.
- 78.** Stocchi F, Ruggieri S, Vacca L, Olanow CW. Prospective randomized trial of lisuride infusion versus oral levodopa in patients with Parkinson's disease. *Brain.* 2002;125:2058-2066.
- 79.** Obeso JA, Luquin MR, Martinez Lage JM. Intravenous lisuride corrects oscillations of motor performance in Parkinson's disease. *Ann Neurol.* 1986;19:31-35.
- 80.** Hofmann C, Penner U, Dorow R, et al. Lisuride, a dopamine receptor agonist with 5-HT<sub>2B</sub> receptor antagonist properties: absence of cardiac valvulopathy adverse drug reaction reports supports the concept of a crucial role for 5HT<sub>2B</sub> receptor drug agonism in cardiac valvular fibrosis. *Clin Neuropharmacol.* 2006;29:80-86.
- 81.** Woitalla D, Muller T, Benz S, et al. Transdermal lisuride delivery in the treatment of Parkinson's disease. *J Neural Transm Suppl.* 2004;68:89-95.
- 82.** Reichmann H, Bilsing A, Ehret R, et al. Ergoline and non-ergoline derivatives in the treatment of Parkinson's disease. *J Neurol.* 2006;253(suppl 4):iv36-iv38.
- 83.** Arnsten AF. Catecholamine regulation of the prefrontal cortex. *J Psychopharmacol.* 1997;11:151-162.
- 84.** Kable JW, Murrin LC, Bylund DB. In vivo gene modification elucidates subtype-specific functions of alpha<sub>2</sub>-adrenergic receptors. *J Pharmacol Exp Ther.* 2000;293:1-7.
- 85.** Millan MJ, Cussac D, Milligan G. Antiparkinsonian agent pibredil displays antagonist properties at native, rat, and cloned, human alpha<sub>2</sub>-adrenoceptors: cellular and functional characterization. *J Pharmacol Exp Ther.* 2001;297:876-887.
- 86.** Newman-Tancredi A, Cussac D, Audinot V, et al. Differential actions of antiparkinson agents at multiple classes of monoaminergic receptor, II. Agonist and antagonist properties at subtypes of dopamine D<sub>2</sub>-like receptor and alpha<sub>1</sub>/alpha<sub>2</sub>-adrenoceptor. *J Pharmacol Exp Ther.* 2002;303:805-814.
- 87.** Lebrun-Frenay C, Borg M. Choosing the right dopamine agonist for patients with Parkinson's disease. *Curr Med Res Opin.* 2002;4:209-214.
- 88.** Simon N, Micallef J, Reynier JC, et al. End-of-dose akinesia after a single intravenous infusion of the dopaminergic agonist pibredil in Parkinson's disease patients: a pharmacokinetic/pharmacodynamic, randomized, double-blind study. *Mov Disord.* 2005;20:803-809.
- 89.** Castro-Caldas A, Delwaide P, Jost W, et al. The Parkinson-Control study: a 1-year randomized, double-blind trial comparing pibredil (159 mg/day) with bromocriptine (25 mg/day) in early combination with levodopa in Parkinson's disease. *Mov Disord.* 2006;21:500-509.
- 90.** Rajput AH. Adverse effects of ergot-derivative dopamine agonists. In: Olanow CW, Obeso JA, eds. *Dopamine Agonists in Early Parkinson's Disease.* Kent, UK: Wells Medical; 1997:109-218.
- 91.** Junghanns S, Fuhrmann JT, Simonis G, et al. Valvular heart disease in Parkinson's disease patients treated with dopamine agonists: a reader-blinded monocenter echocardiography study. *Mov Disord.* 2007;22:234-238.
- 92.** Frucht S, Rogers JD, Greene PE, et al. Falling asleep at the wheel: motor vehicle mishaps in persons taking pramipexole and ropinirole. *Neurology.* 1999;52:1908-1910.
- 93.** Zesiewicz TA, Hauser RA. Sleep attacks and dopamine agonists for Parkinson's disease: what is currently known? *CNS Drugs.* 2003;17:593-600.
- 94.** Paus S, Brecht HM, Koester J, et al. Sleep attacks, daytime sleepiness, and dopamine agonists in Parkinson's disease. *Mov Disord.* 2003;18:659-667.
- 95.** Fénelon G, Mahieux F, Huon R, Ziegler M. Hallucinations in Parkinson's disease: prevalence, phenomenology and risk factors. *Brain.* 2000;123(pt 4):733-745.
- 96.** Poewe W. Psychosis in Parkinson's disease. *Mov Disord.* 2003;18(suppl 6):580-587.
- 97.** Evans AH, Lees AJ. Dopamine dysregulation syndrome in Parkinson's disease. *Curr Opin Neurol.* 2004;17:393-398.
- 98.** Factor SA, Molho ES, Podskainy GD, Brown D. Parkinson's disease: drug-induced psychiatric status. *Adv Neurol.* 1999;65:115-138.
- 99.** Friedman JH. Management of psychosis in Parkinson's disease. In: Koller WC, Paulson G, eds. *Therapy of Parkinson's Disease.* New York: Marcel Dekker; 1995:521-532.
- 100.** Holroyd S, Currie L, Wooten GF. Prospective study of hallucinations and delusions in Parkinson's disease. *J Neurol Neurosurg Psychiatry.* 2001;70:734-738.
- 101.** Tanner CM, Vogel C, Goetz CG, Klawans HL. Hallucinations in Parkinson's disease: a population study. *Ann Neurol.* 1983;14:136. Abstract.
- 102.** Fox SH, Visanji NP, Johnston TH, et al. Dopamine receptor agonists and levodopa and inducing psychosis-like behavior in the MPTP primate model of Parkinson's disease. *Arch Neurol.* 2006;61:1343-1344.
- 103.** Voon V, Hassan K, Zurowski M, et al. Prospective prevalence of pathologic gambling and medication association in PD. *Neurology.* 2006;66:1750-1752.
- 104.** Klos KJ, Bower JH, Josephs KA, et al. Pathological hypersexuality predominantly linked to adjunct dopamine agonist therapy in Parkinson's disease and multiple system atrophy. *Parkinsonism Relat Disord.* 2005;11:381-386.
- 105.** Lawrence AJ, Blackwell AD, Barker RA, et al. Predictors of punding in Parkinson's disease: results from a questionnaire survey. *Mov Disord.* 2007;22:2339-2345.
- 106.** Nirenberg MJ, Waters C. Compulsive eating and weight gain related to dopamine agonist use. *Mov Disord.* 2006;21:524-529.
- 107.** Pontone G, Williams JR, Bassett SS, Marsh L. Clinical features associated with impulse control disorders in Parkinson disease. *Neurology.* 2006;67:1258-1261.
- 108.** Giovannoni G, O'Sullivan JD, Turner K, et al. Hedonistic homeostatic dysregulation in patients with Parkinson's disease on dopamine replacement therapies. *J Neurol Neurosurg Psychiatry.* 2000;68:423-428.
- 109.** Weintraub D, Potenza MN. Impulse control disorders in Parkinson's disease. *Curr Neurol Neurosci Rep.* 2006;6:302-306.
- 110.** Voon V, Hassan K, Zurowski M, et al. Prevalence of repetitive and reward-seeking behaviors in Parkinson disease. *Neurology.* 2006;67:1-4.
- 111.** Hollander E, Evers M. New developments in impulsivity. *Lancet.* 2001;358:949-950.
- 112.** Green J, McDonald WM, Vitek JL, et al. Cognitive impairments in advanced PD without dementia. *Neurology.* 2002;59:1320-1324.
- 113.** Dubois B, Pillon B. Cognitive deficits in Parkinson's disease. *J Neurol.* 1997;244:2-8.
- 114.** Gerlach M, Double K, Arzberger T, et al. Dopamine receptor agonists in current clinical use: comparative dopamine receptor binding profiles defines in the human striatum. *J Neural Transm.* 2003;110:1119-1127.
- 115.** Sokoloff P, Giros B, Martres MP, et al. Molecular cloning and characterization of a novel dopamine receptor (D<sub>3</sub>) as a target for neuroleptics. *Nature.* 1990;347:146-151.
- 116.** 2006 California problem gambling prevalence survey. NORC at the University of Chicago; August 2006. [http://www.adp.ca.gov/opg/pdf/CA\\_Problem\\_Gambling\\_Prevalence\\_Survey-Final\\_Report](http://www.adp.ca.gov/opg/pdf/CA_Problem_Gambling_Prevalence_Survey-Final_Report). Accessed July 17, 2008.
- 117.** Silveira-Moriyama L, Evans AH, Katzenschlager R, Lees AJ. Punding and dyskinesias. *Mov Disord.* 2006;21:2214-2217.
- 118.** Voon V. Repetition, repetition, and repetition: compulsive and punding behaviors in Parkinson's disease. *Mov Disord.* 2004;19:367-370.
- 119.** Mirapex [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc; 2006.
- 120.** Goetz CG, Blasucci L, Stebbins GT. Switching dopamine agonists in advanced Parkinson's disease: is rapid titration preferable to slow? *Neurology.* 1999;52:1227-1229.
- 121.** Linzasoro G. Conversion from dopamine agonists to pramipexole. An open-label trial in 227 patients with advanced Parkinson's disease. *J Neurol.* 2004;251:335-339.