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Parkinson Disease in Primary Practice: Keys to Diagnosis and Management

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

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

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

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

DIAGNOSIS

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

Motor Signs and Symptoms

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

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.[1] 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.[2] 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,[3] progressive supranuclear palsy,[4] and dementia with Lewy bodies.[5,6] These parkinsonism-plus syndromes have a worse prognosis than idiopathic PD, respond poorly to antiparkinsonian medication, and carry other features not associated with PD.[7] 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.[8]

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[a]

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

[a] 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. 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.[7]

The investigators came to 3 major conclusions:

- No individual clinical feature has sufficient sensitivity and specificity to serve as the sole basis for distinguishing PD from other diseases with parkinsonian features.
- Despite this, some features are more useful than others.
- The opportunity for diagnostic confusion is greatest early in the clinical course when some of the more distinctive clinical features may not yet have developed.

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

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

From the clinician's perspective, the real potential for aiding the diagnosis lies in[12]:

- 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.[13] 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.[14] The ability to detect some odors remains unchanged, with identification of others significantly impaired.[14] The olfactory deficit in PD appears stable and is not an inherited trait; this suggests the possibility that olfactory tests may be designed specifically 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 confusional episodes, and dribbling were rated the most disabling symptoms, ahead of such cardinal motor features as bradykinesia and tremor.[15]

Depression, which may occur at any stage of PD, affects as many as 50% of patients.[16] 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.[16] Most cognitive abnormalities—including difficulties with complex tasks, long-term planning, and memorizing new information—are common and mostly mild to moderate in severity. It is unknown whether such symptoms form a continuum with the dementias that affect some patients in late-stage PD. Psychotic symptoms affect 6% to 40% of patients with PD.[16]

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

TREATMENT

The goal of treatment should be to obtain optimal reduction of PD symptoms with minimal risk of long-

term 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**).[17-19] 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.[20] 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-

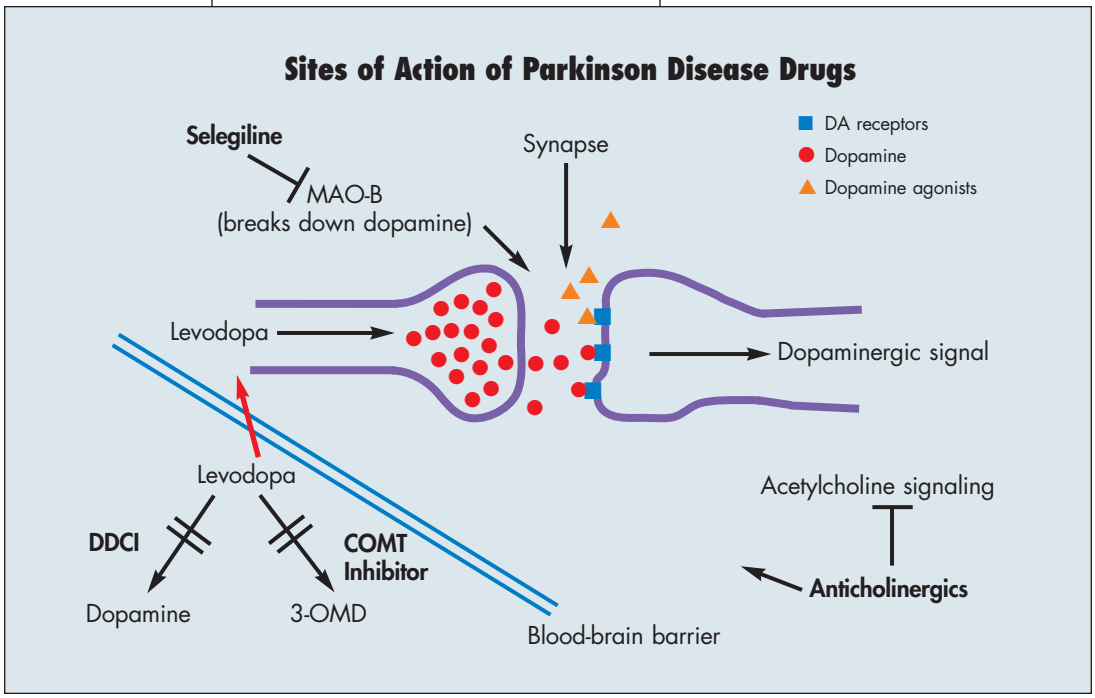

Figure – In this illustration, levodopa passes through the blood-brain barrier to be metabolized to dopamine in dopaminergic neurons. Dopa-decarboxylase (DDC) and COMT (catechol-*O*-methyltransferase) inhibitors prevent the peripheral metabolism of extrinsic levodopa, thus allowing it to reach the brain. (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.[20]

Dopamine Agonists

Dopamine receptor agonists were introduced as adjuncts to levodopa therapy to help control the motor fluctuations that occur in PD. Unlike levodopa, however, their initiation in early disease as monotherapy is believed to reduce motor fluctuations in later years. In fact, dopamine agonist treatment of patients requiring dopaminergic therapy results in fewer motor complications than levodopa therapy after 2.5 years of follow-up.[20] 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),[21] 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.[22] Rasagiline is similarly useful as monotherapy and in combination with levodopa.

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

Amantadine

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

Anticholinergic Agents

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

COMT Inhibitors

Dopamine and its precursor, levodopa, are both metabolized by the enzyme catechol-*O*-methyltransferase (COMT) in the liver, GI tract, and other organs. By preventing this breakdown, COMT inhibitors, like the decarboxylase inhibitor 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 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.[24] 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.[25]

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.[26] 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.[27] Ongoing studies are examining whether initiation of therapy with the combination agent will result in a lower dyskinesia rate.[1]

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_{10}, and the dopamine agonists pramipexole and ropinirole to provide neuroprotective benefits in PD.[28] 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%.[29] 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.[30] Transplantation of an alternative tissue, human retinal pigment epithelial cells, is now being studied.[31]

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.[32] 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.[33] A subsequent phase 2, double-blind, placebo-controlled study involving 34 patients with advanced PD failed to show clinical improvement, however.[34]

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). ■

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