Evidence Report

Chapter 1. Introduction

Parkinson's Disease (PD) is a chronic, progressive, neurodegenerative disorder with an estimated prevalence of 31 to 328 per 100,000 people worldwide.[1] A registry of all cases of PD in northern Manhattan from 1988-1993 showed a prevalence rate of 107 per 100,000 people.[2] It is estimated that approximately one to two percent of the population over age 65 have PD;[3] incidence and prevalence increase with age.[1, 4] With the increase in the average age of the population of western countries, an increase in the prevalence of PD is to be expected.

Some studies report that PD affects males and females equally, while others report that PD is somewhat more prevalent in men.[1, 2] All races and ethnic groups are affected.[1] The highest reported prevalences are in Caucasians, and the lowest in Asians and African blacks.[5] The prevalence of PD is reported to be highest in Europe and North America, and lowest in China, Japan and Africa,[1, 5] although lack of standardized diagnostic criteria impair the ability to amass accurate prevalence rates.[3] The mortality for elderly PD patients is two to five times higher than in age-matched controls.[6] The total annual cost for PD in the United States is estimated to be approximately $26 billion, including direct and indirect costs and lost productivity.[7] Clearly, PD places a major burden on both individual and societal healthcare resources.[8]

A discussion of current issues concerning the diagnosis and treatment of PD follows, as an introduction to the specific Objectives, Methods and Results of this systematic review.

Etiology

The clinical syndrome of PD results from idiopathic degeneration of the dopaminergic cells in the pars compacta of the substantia nigra.[9] While the cause of the degeneration is not known, oxidative stress may play a role.[10, 11] This leads to depletion of the neurotransmitter dopamine, which is produced by neurons in the substantia nigra and released in the caudate nucleus and putamen.

The pathogenesis of PD is believed to be multifactorial, caused by environmental factors acting on genetically susceptible individuals as they age.[12, 13, 14] Many studies have examined the impact of environmental exposures on the risk of PD. No infectious etiologic agent has been identified.[1] Some studies have reported that exposures to herbicides, pesticides, welding, or well water may be associated with an increased risk of PD,[15,16] but a cause and effect relationship has not been established.

Studies examining diets in PD patients have generally been inconclusive.[1] Some studies have reported that caffeine, coffee, and smoking are associated with a decreased risk of PD.[17 - 20] It has been hypothesized that antioxidants may be neuroprotective in PD, by preventing neuronal death caused by intracellular free radicals.[10] Some researchers are investigating the role of coenzyme Q in the pathogenesis of PD.[21] Some studies have reported that vitamin E[22] or vitamin C[23] intake was significantly lower in PD patients than in controls, but other studies showed no association between PD and vitamins A, C, or E.[24] Dietary iron intake does not appear to be associated with PD status, while diets high in animal fats and carbohydrates have been associated with increased risk of PD.[23, 24, 25]

Clinical Features

The clinical constellation of resting tremor (3-6 Hz), cogwheel rigidity, and bradykinesia are the hallmarks of parkinsonism.[26] A fourth "cardinal sign" is postural reflex compromise, or gait instability, which usually occurs later in the disease.[26, 27] PD usually presents asymmetrically, although symptoms eventually become bilateral.[26] Although not specific for PD, response to levodopa (L-dopa) is another characteristic finding.[26]

The clinical severity of PD varies, depending on the degree of neuronal loss. Pathologic studies suggest that patients may be symptom free until 60-80 percent of substantia nigral neurons have degenerated.[9] Nonmotor symptoms of PD, such as depression, seborrheic dermatitis, olfactory dysfunction, and autonomic nervous system dysfunction (including constipation, urinary frequency, and orthostatic hypotension) may occur for years prior to the onset of overt motor symptomatology.[28]

As their disease progresses, PD patients become increasingly unable to manage their activities of daily living (ADL) without assistance.[29] Falls are common, as a result of postural instability, dyskinesias, confusion, and dementia. Patients' nutritional status may be sub-optimal, due to difficulty with preparing, chewing, and swallowing foods. Dysphagia is a frequent complication in PD.[30] It is estimated that at least 75 percent of PD patients have speech disorders, which are collectively called hypokinetic or parkinsonian dysarthria, and consist of reduced loudness, monotone, imprecise articulation, and disordered rate.[31, 32, 33] Sleep disturbances are also common in PD.[34]

Psychiatric symptoms are important contributors to the morbidity and mortality of PD.[6] Development of psychopathology in PD is related to multiple factors, including underlying PD disease processes, medication effects, and psychological reaction to illness.[35] Estimates of dementia prevalence in PD range from zero to 93 percent, based on numerous uncontrolled, cross-sectional studies.[36, 37] The prevalence of cognitive decline is higher in patients with older age of PD onset.[37, 38] It may be difficult to distinguish the dementia of Alzheimer's disease from that associated with PD. Published estimates of depression prevalence in PD range from 20 to 90 percent.[39] While the exact prevalence is not known, psychiatric disorders clearly have a major impact on PD patients.

Diagnosis

The abundance of guidelines for PD diagnosis is reflective of the difficulty in diagnosing this condition. One relatively straightforward list of research criteria for probable PD includes:[40]

1. Evidence of disease progression.

2. Presence of at least two of the three cardinal features of parkinsonism (tremor, rigidity, bradykinesia)

3. Presence of at least two of the following:

    a. Marked response to L-dopa (functional improvement or dyskinesia)
    b. Asymmetry of signs

c. Asymmetry at onset

4. Absence of clinical features of alternative diagnosis

5. Absence of etiology known to cause similar features

Other diagnostic guidelines incorporate requirements pertaining to disease duration, and more specifics regarding tremor and response to dopaminergic agonists.[27]

The United Kingdom PD Society Brain Bank has similar, but more stringent, clinical diagnostic criteria, including a specific definition of bradykinesia, and numerous specific exclusion criteria (Appendix A).[41]

A more recent variation of clinical guidelines for PD diagnosis describes an adult-onset, slowly progressive motor disorder combining two or more of: rest tremor, bradykinesia, limb rigidity, and gait instability (late), with dramatic and sustained response to L-dopa. Accepted associated phenomena include depression (early or late), cognitive decline (late), and limited autonomic involvement, such as constipation. Some proposed diagnostic criteria for PD categorize patients as having definite, probable, or possible PD, based on the number of criteria they meet (Appendix A).[26]

The pathologic hallmark of PD is substantia nigra depigmentation and the presence of Lewy bodies, which are neuronal eosinophilic cytoplasmic inclusions. Lewy bodies are believed to be caused by altered neurofilament metabolism or transport. They are not specific for PD, and may be seen in small numbers in other neurodegenerative diseases.[41]

While autopsy provides the pathological gold standard, no clinical gold standard diagnostic test for PD has been identified. Comparisons of clinical and pathological diagnoses have shown that up to 25 percent of patients with clinical diagnoses of PD are found to have different pathological diagnoses at autopsy.[42, 43, 44] Disease presentation may vary, leading to difficulties in making the diagnosis, particularly early in the disease. The marked clinical heterogeneity further complicates ability to accurately diagnose PD.

In the absence of a simple, inexpensive, reliable diagnostic test for PD, some clinicians use acute challenge tests with L-dopa or the dopamine agonist apomorphine to confirm the clinical suspicion of PD.[45] In a meta-analysis of 13 studies of acute apomorphine or L-dopa challenges compared with chronic L-dopa therapy in patients with PD, the authors concluded that the diagnostic accuracy of acute apomorphine and L-dopa challenges did not add additional useful diagnostic information compared with a therapeutic trial of chronic L-dopa.[45]

Researchers have investigated the utility of measuring striatal dopamine levels, in the hopes of diagnosing PD in a preclinical stage, and following the progression of PD after diagnosis. [^{18}F]-fluorodopa positron emission tomography (PET) scans detect changes in presynaptic striatal dopamine function, which is an indirect measure of the striatal storage of dopamine.[46] Single photon emission computed tomography (SPECT) scans use various cocaine analogues to provide a semi-quantitative measure of the concentration of the presynaptic dopamine transporter, which may be decreased in PD, and ^{123}I-iodobenzamide (IBZM) to evaluate the postsynaptic receptor density, which may be normal or increased in PD.[46] PET and SPECT scans are expensive and not always available. The appropriate role for these modalities in the diagnosis and management of PD patients is unclear.[26]

Structural imaging modalities, such as computerized tomography (CT) and magnetic resonance imaging (MRI) have a limited role in diagnosing PD. Increased iron concentration in the substantia nigra causes decreased signal intensity on T_2 weighted images, but these changes are not sufficient to reliably distinguish PD patients from healthy controls.[47] These technologies are more useful for ruling out other conditions than for diagnosing PD.

Olfactory deficits occur early in PD,[48] and do not improve with L-dopa treatment.[49] The University of Pennsylvania Smell Identification Test (UPSIT) is a multiple choice "scratch and sniff" test that is used to evaluate olfactory function (See Appendix A).[49] Olfaction is impaired in other neurodegenerative diseases, such as Huntington's Disease and Alzheimer's dementia (AD).[48] A meta-analysis of 43 studies of olfactory function in PD and AD showed uniform degrees of impairment, and no measure that could help to distinguish between the two entities.[50]

Myriad other tests have been proposed to diagnose and evaluate patients with PD. Depletion of cerebrospinal fluid (CSF) homovanillic acid (HVA) levels indicate dopamine deficiency, but this test has not been shown to reliably discriminate healthy controls from PD patients.[51] Studies of handwriting, tremor analysis, personality, reaction times, and movement velocities have shown differences between patients with PD and normal controls; however, the overlap between the two groups does not enable these tests to reliably diagnose PD in individual patients.

"Red flags" that suggest a diagnosis other than PD include early dementia or apraxia, early instability and falls, prominent autonomic impairment, oculomotor disturbances, and cerebellar signs. The most common atypical parkinsonian syndromes are progressive supranuclear palsy (PSP) and multiple system atrophy (MSA). These conditions are frequently confused with PD, particularly early in their course. One goal of diagnostic testing for PD is to rule out atypical parkinsonian syndromes. Assessment of olfaction may be useful in this regard; olfactory function is normal in PSP, and impaired in MSA.[48]

Patients with PSP generally present with postural instability, often coming to medical attention due to frequent falls. The hallmark of PSP is vertical gaze paralysis. Other symptoms include other visual disturbances, dysarthria, mental changes, speech difficulties, bradykinesia, nuchal dystonia, rigidity, and postural tremors, although resting tremors are uncommon. PSP is progressive, and usually leads to death within five to seven years after diagnosis.[52]

MSA is a sporadic degeneration of the nervous system. In addition to parkinsonian symptoms, which are present in 90 percent of cases, patients present with cerebellar ataxia and autonomic dysfunction. MSA usually begins in the sixth decade, and is associated with a median survival of 9.3 years after diagnosis.[52]

Assessment of PD Severity

Many clinical investigators use different scoring scales to assess the severity of PD symptoms, making it difficult to compare results across studies.[53] The most common scale used to assess PD severity is the Unified Parkinson Disease Rating Scale (UPDRS), which has superceded numerous other scales, including Hoehn & Yahr Disability Scale (H&Y), Schwab & England (S&E) Activities of Daily Living (ADL) scale, Webster scale, Columbia University Rating Scale (CURS), and Northwestern University Disability Scale (NUDS). Appendix A describes the major scales used to assess PD severity.

In the UPDRS, a rating tool that was developed in 1984, points are assigned for a comprehensive list of PD symptoms.[53, 54, 55] Patients may receive a total of 199 points, with 0

representing no disability, and 199 representing total disability. The total score is composed of four major subscales:

I) Mentation, Behavior, and Mood (range 0-16),
II) ADL (range 0-104),
III) Motor Exam (range 0-56), and
IV) Complications of therapy over the past week (range 0-23).

Each of these subscales is broken down into further subscales, which range from 0 (normal) to 4 (maximum severity). Each UPDRS score may be reported in the "off" and "on" state, which refer to presence or absence of L-dopa effectiveness. Practically-defined "off" scores are measured approximately 12 hours after the last dose of L-dopa, although in actual clinical practice, "off" scores often indicate periods when the patients feel their medication is not working. "On" scores are measured shortly after a dose, or when patients feel their medication is working. The UPDRS scales are validated tools that are useful in following the progression of disease and response to interventions.[54, 55]

The H&Y scale divides patients into stages, based on their levels of clinical disability.[56] Stage 0 patients have no signs of disease. Stage I patients have unilateral involvement, with minimal or no functional impairment. Stage II patients have bilateral or midline involvement, without balance impairment. Stage III patients have impaired equilibrium, unsteadiness, and significant slowing of body movements. Stage IV patients have severe symptoms, are still able to walk and stand unassisted, but are extremely incapacitated and unable to live alone. Stage V patients are confined to bed or wheelchair, and require constant nursing care.

The S&E ADL scale has ratings from 0 to 100 percent, where 0 is bedridden with no swallowing, bladder, or bowel function, and 100 percent is completely independent.[57]

Treatment

While there is no cure for PD, the goal of antiparkinsonian pharmacotherapy is to control signs and symptoms of PD while minimizing side effects for as long as possible. Current therapies are aimed toward compensating for decreased striatal dopamine levels, but have not been proven to slow or prevent progression of the disease.[58] Neuroprotective agents, defined as agents that protect vulnerable neurons and slow or stop disease progression, have not been demonstrated for PD.[59, 60] Data are lacking in many areas of PD treatment, and there is currently wide variation in the management of PD.

Patients with early PD require different management strategies from patients with advanced PD. In early PD, the goal is to alleviate symptoms and keep patients functioning independently for as long as possible, using the least amount of medication necessary to achieve this goal. In advanced PD, much of the focus is toward treating medication-related complications, such as dyskinesias, motor fluctuations, and psychiatric problems.[61]

Pharmacological Treatment

Since its introduction in the 1960's,[62] L-dopa has been the mainstay of pharmacological treatment for PD. [7, 58] Taken alone, L-dopa causes nausea. It undergoes rapid catabolism by peripheral decarboxylase, forming dopamine, which is unable to cross the blood-brain barrier. L-

dopa is, therefore, always given with a peripheral decarboxylase inhibitor (PDI), which decreases nausea and limits peripheral metabolism of L-dopa, allowing a small percentage to cross the blood-brain barrier in intact form. In the brain, L-dopa is converted to dopamine by decarboxylase that is stored in the dopaminergic neurons of the substantia nigra.[7] Carbidopa is the only PDI available in the United States, while benserazide is used in other countries.

The optimum daily dosage of L-dopa is highly individualized, depending on symptom severity and side effects. L-dopa and carbidopa are usually given as combined tablets (Sinemet), but may be given individually, if closer dose adjustment is required. Sinemet is available in strengths of 10/100, 25/100, and 25/250, where the first number represents the carbidopa dose and the second number represents the L-dopa dose. Patients with advanced PD rarely require over 1000 mg of L-dopa per day. A low protein diet may enhance the absorption of L-dopa.[63] For the remainder of this report, L-dopa will refer to the combination of L-dopa and a PDI.

L-dopa is the most effective drug in the treatment of PD; however, motor fluctuations and dyskinesias occur in most patients with long-term use.[29] In early PD, patients experience a sustained response to each dose of L-dopa. Over time, however, the duration of response after each dose may decline, resulting in "wearing off." Patients with advanced PD may also suffer from "off" periods, when their medication is not working. These motor fluctuations may be quite unpredictable and disabling.

Another major problem associated with chronic L-dopa therapy is the occurrence of L-dopa-induced dyskinesias (LIDs).[64] Some experts believe that delaying initiation of L-dopa, or combining L-dopa with other antiparkinsonian medications may postpone the onset of dyskinesias, but may result in less improvement of motor symptoms.[65, 66]

Wearing-off and LIDs are believed to be caused by pulsatile stimulation of striatal dopamine receptors. Useful management techniques, therefore, may consist of providing continuous, rather than pulsatile, dopaminergic stimulation. This may be achieved by increasing the frequency of standard L-dopa doses, or by changing to a controlled release (CR) form, although CR forms have lower bioavailability, and usually require an increase in dosage.[58] After LIDs have developed, they may be very difficult to control. Postural instability, autonomic dysfunction, and dementia are aspects of PD that are not responsive to L-dopa.[58]

Some experts believe that to provide maximum clinical benefit, L-dopa should be started early, while others believe that L-dopa is neurotoxic, and try to delay its use until patients' symptoms are severe, starting with other agents instead.[67, 68, 69] L-dopa has been shown to be toxic to neurons *in vitro*, but these findings have not been substantiated in humans.[67, 70] The main reason to delay L-dopa is to limit side effects and delay emergence of on-off phenomena and LIDs.[58]

Dopamine agonists (DAs) are frequently used as monotherapy in early PD, or as adjunctive therapy to L-dopa in more advanced PD, enabling patients to take lower doses of L-dopa. Structurally related to dopamine, DAs act directly on dopamine receptors, mimicking endogenous dopamine.

Bromocriptine, the first DA used in PD patients in the United States, was introduced in 1974 as adjunct therapy to L-dopa for PD patients with motor complications.[71] Two recent systematic reviews of randomized controlled trials (RCTs) evaluating the efficacy and safety of adjunct bromocriptine in PD patients with motor complications were not conclusive, due to methodologic limitations in the studies reviewed.[72, 73]

Other DAs used in PD include pergolide, lisuride, cabergoline, pramipexole, and ropinirole.[74] Apomorphine is the oldest DA, and is not available in the United States. Due to ineffectiveness and increased toxicity when given orally, apomorphine is usually administered subcutaneously. It has a rapid onset and short duration of action, and is sometimes used as rescue therapy in patients on L-dopa with intractable "off" periods.[75] Coadministration with domperidone, which is also unavailable in the United States, may control severe apomorphine-associated nausea and vomiting. Apomorphine is sometimes used as a challenge test to aid in the diagnosis of PD.[45]

Using DAs early in the course of PD may delay the requirement for L-dopa,[74] but all PD patients eventually need to take L-dopa.[75] Patients who begin dopaminergic treatment with DA monotherapy, rather than L-dopa, are at lower risk for developing dyskinesias or motor fluctuations; however, they may experience less motor improvement as measured by UPDRS. Patients with advanced disease may experience motor fluctuations when short-acting DAs are used. Acute adverse events associated with DAs include nausea, vomiting, postural hypotension, and psychiatric manifestations. Several systematic reviews of DAs have been published recently, and they have reported no evidence affirming that one DA is superior to the others.[76 - 79] All currently available DAs are reportedly less effective, less well tolerated in the short term, and more expensive than L-dopa.[29]

The mechanism of action of amantadine, another medication used to treat PD, remains unknown. It has been speculated to increase dopamine release, inhibit reuptake and stimulate dopamine receptors. Some studies have shown that amantadine reduces LIDs. It is associated with numerous side effects, however, including hallucinations, confusion, insomnia, nightmares, livedo reticularis, and ankle edema.[80]

Monoamine oxidase B (MAO-B) inhibitors, including selegiline, lazabemide, and rasagiline, inhibit dopamine catabolism, thereby increasing nigrostriatal dopamine levels. MAO-B inhibitors have been shown to delay the need for dopaminergic therapy in patients with early PD. It is not clear whether this is due to the known symptomatic effect of selegiline or to a possible neuroprotective effect. MAO-B inhibitors probably exert their symptomatic effect by slowing the degradation of dopamine. Several potential neuroprotective effects of MAO-B inhibitors have been suggested. These include protection against oxidative injury, inhibition of apoptosis mediated through the metabolite desmethyl-selegiline, or protection against environmental toxins.[81- 84]

Catechol O-methyl transferase (COMT) is an enzyme required for catabolism of dopamine. Due to the presence of COMT in the periphery, only five to ten percent of oral L-dopa is able to reach the central nervous system, even when L-dopa is taken concomitantly with a PDI.[85] Drugs that inhibit COMT, including entcapone and tolcapone, increase the bioavailability and prolong the action of dopamine. Maintaining stable plasma and brain L-dopa levels may lessen the "wearing off" phenomenon, and enable patients to reduce their L-dopa doses.[86] COMT inhibitors are used only in conjunction with L-dopa. Adverse events associated with COMT inhibitors include exacerbation of LIDs, nausea, sleep disorders, hepatotoxicity, and diarrhea.[86] Fulminant hepatitis has been reported in four patients on tolcapone, and there is now controversy regarding appropriate frequency of liver function test (LFT) monitoring for patients on this medication.[87, 88]

Anticholinergic medications, such as benztropine, procyclidine, and trihexylphenidyl, were used to treat PD before L-dopa and DAs were developed.[89, 90] They relieve tremor and stiffness in PD patients. Their use is limited by anticholinergic effects, such as dry mouth, blurred vision, urinary retention, constipation, and their potential for worsening confusion in PD patients. They are, therefore, not recommended for patients who are cognitively impaired. Due to the numerous

adverse events associated with anticholinergics, some clinicians do not recommend these medications for patients 65 years of age or older.[7] They are typically used in younger, cognitively intact PD patients who have resting tremor as the predominant symptom.

Psychotropic medications are sometimes necessary for PD patients, due to psychiatric effects of the disease process itself, or dopaminergic-induced psychosis. Most antipsychotic medications block dopamine receptors, thereby worsening parkinsonian symptoms.[35] Atypical neuroleptic agents, including clozapine, olanzapine, and quetiapine, may suppress psychosis without worsening motor symptoms. Clozapine may cause orthostatic hypotension or sialorrhea, but the most severe associated risk is that of agranulocytosis, which is not dose related, and may occur in one to two percent of patients.[91, 92]

Many factors, including age, cognitive impairment, disease severity, threatened loss of employment, cost, and likelihood of compliance, influence decisions regarding initial treatment of PD. Medication does not need to be started until symptoms interfere with patients' ADL or quality of life (QoL). Treatment is highly individualized. One strategy is to start L-dopa as monotherapy, then add a DA when the patient requires increased doses of L-dopa, in an attempt to keep L-dopa doses as low as possible. Another option is to start with selegiline or DAs, only adding L-dopa when symptoms cannot be controlled by other medications.[7, 59, 69]

Controversies abound concerning the optimal medical treatment of PD. The major questions regarding early PD management pertain to when treatment should begin and which drug should be used first.[65] For advanced PD, consensus is lacking regarding optimal management of motor fluctuations and LIDs.[61] The recent development of new medications to treat PD has been promising, but has also further complicated decision-making for caregivers managing this chronic, debilitating disease.

Surgical Treatment

The role of surgery in treatment of PD has changed dramatically over the past several decades. In the 1940's and 1950's, pallidotomies and thalamotomies were performed to treat the tremor associated with PD.[93] After the development of L-dopa in the 1960's, neurosurgery was rarely performed to treat PD. Recognition of the limitations of pharmacotherapy and improvement in surgical techniques led to a resurgence of surgery on PD patients in recent years. Surgery is generally reserved for non-demented patients who respond to medical treatment, but suffer from intolerable side effects.[29, 58] Decisions regarding which surgical procedure to perform are based on the severity and pattern of each patient's symptoms.[94] Selection of appropriate surgical procedures for appropriate patients is essential to increase the likelihood of benefit.[95]

Surgical options include ablative procedures (pallidotomy or thalamotomy), deep brain stimulation (DBS), and tissue transplant. In ablative procedures, an abnormally functioning structure (globus pallidus or thalamus) is disrupted. In DBS, an electrode is placed in the globus pallidus, thalamus, or subthalamic nucleus, to stimulate their function.[94]

Pallidotomy may reduce drug-induced dyskinesias and dystonias in PD patients whose parkinsonian symptoms have responded to medical therapy.[96] Surgical candidates are patients who are responsive to L-dopa, because preoperative symptoms that persist in the "on" state generally do not respond well to pallidotomy.[97, 98] Unilateral pallidotomies mainly improve contralateral symptoms.[58] There are conflicting results regarding the safety of bilateral pallidotomy.[29]

Unilateral thalamotomy is effective against contralateral, medically intractable tremor, and may also improve rigidity and dyskinesias. However, thalamotomy doesn't improve, and may worsen, other parkinsonian symptoms, such as bradykinesia, gait problems, postural problems, or speech disorder. Bilateral thalamotomy has a higher incidence of complications.[97]

Targets for deep brain stimulation (DBS) are chosen based on patients' predominant symptoms.[99] Thalamic DBS is effective in reducing parkinsonian tremor, but does not relieve bradykinesia. Thalamic stimulation and thalamotomy have been reported to have equal efficacy for tremor suppression, but thalamic stimulation is associated with fewer adverse effects.[100] Patients with motor fluctuations and dyskinesias may derive comparable benefits by undergoing either pallidotomy or globus pallidus (GPi) stimulation.[101] Initial studies of DBS of the subthalamic nucleus (STN) show favorable results for patients with tremors, akinesia, postural instability, and gait disorders.[97]

Transplantation of autologous adrenal medulla, as a postulated source of dopamine, to the striatum of a PD patient was first performed in Sweden in 1982.[102] The procedure initially appeared to improve motor function, but further investigation demonstrated a lack of efficacy and substantial morbidity. Adrenal medullary transplants are no longer performed to treat PD.[58] Transplantation of fetal brain tissue into the striatum of PD patients, as a source of dopamine-producing cells, initially showed promising results,[97] but more recent studies have cast doubt upon the efficacy and safety of this procedure.[103] Evaluation of the trials concerning surgery is impeded because most publications present the results of uncontrolled trials.

The Core Assessment Program for Intracerebral Transplantations (CAPIT) was devised in 1992, to provide minimal common standards of evaluating the effectiveness of intracerebral grafting.[104] CAPIT consists of recommendations for diagnostic and evaluative procedures to be followed pre- and postoperatively. Transplantation candidates were required to have bradykinesia and at least one other cardinal sign of PD (resting tremor or cogwheel rigidity). MRI was advised, to rule out atypical parkinsonism. Responsiveness to L-dopa was a recommended requirement. The committee recommended recording UPDRS scores ("off" and "on"), H&Y stages ("off" and "on"), Dyskinesia Rating Scale ("on"), self-reporting diary, timed tests of motor function ("off" and "on"), and L-dopa tests ("off") preoperatively and at least four times postoperatively, with a minimum postoperative followup period of one year. They also recommended that PET scans be performed, if available.

In 1999, a broader set of perioperative evaluations, the Core Assessment Program for Surgical Interventional Therapies in Parkinson's Disease (CAPSIT-PD), were developed.[105] The CAPSIT-PD recommendations were similar to the CAPIT recommendations, but applied to evaluation of all types of surgery for PD, not just intracerebral transplants. In addition to the CAPIT diagnostic requirements, the CAPSIT-PD committee advised that patients should have disease duration of at least five years prior to surgery. Instead of "L-dopa responsiveness," they required "dopaminergic responsiveness," which included dopamine agonists as well as L-dopa. Along with regular monitoring of the UPDRS and modified H&Y scales, the committee also recommended regular evaluation of QoL. They made other recommendations to modify the dyskinesia, self-reporting, and timed tests that were advised by CAPIT, and added recommendations for neuropsychological testing. It was advised that patients be evaluated postoperatively at six months, one year, and two years.

Experts generally agree that surgery should only be considered in PD patients who are responsive to medical therapy, but are suffering intolerable side effects from PD medications.

Current controversies in surgical management of PD concern which patients are appropriate candidates for surgery, and indications for the different surgical procedures.

Ancillary Treatment

Caring for patients with PD requires an individualized, multidisciplinary approach. Patients are frequently disabled in many areas of their lives.[106] In addition to medications, they often need psychological and social support, occupational therapy (OT), speech therapy, physical therapy (PT), and other support aimed at maintaining maximal independence and safety.[29, 107] While it is recognized that speech and swallowing difficulties are common in PD patients, referrals to speech therapists are not commonly made.[108, 109] Objective data is needed to establish the efficacy of various ancillary treatments, and, if these treatments are shown to be effective, to encourage caregivers to make appropriate referrals.

Objectives

There are numerous unanswered questions regarding the diagnosis and management of PD. This review of diagnosis and treatment of PD was nominated by the American Academy of Neurology (AAN), and a Task Order was commissioned by the Agency for Healthcare Research and Quality (AHRQ). The purpose of this report is to systematically review the published evidence regarding these issues, in order to answer specific questions posed by the AAN and the AHRQ. This evidence base should be useful to health care providers in developing evidence-based strategies to guide PD management. It will be useful to those planning new clinical trials and making regulatory decisions. Additionally, this evidence base may readily be updated as the literature evolves.

Original Key Questions

The following questions were formulated by AAN and AHRQ:

1. How accurate is the clinical diagnosis of PD? How accurate does the diagnosis need to be for proper clinical decisionmaking?

2. What diagnostic tests improve the accuracy of the clinical diagnosis of PD?

3. What is the role of neuroimaging in the diagnosis of PD? When neuroimaging is indicated, should CT or MRI scan be obtained? Are there data on the cost effectiveness of these diagnostic tests in PD? What is the current or projected role of fluorodopa PET scans in the diagnosis or management of PD? What is the current, or projected, role of SPECT scans using dopamine transporter ligands in the diagnosis or management of PD?

4. When, if ever, is genetic testing indicated in PD?

5. Should the ability of a patient to respond to levodopa be considered a diagnostic tool? From a diagnostic standpoint, what constitutes a levodopa challenge and a diagnostically

positive response? How accurate is this maneuver (i.e., false positives and negatives) and how does it help the differential diagnosis? When is it indicated?

6. Based upon the patient's age and presentation of symptoms, what treatment should a PD patient receive upon initial diagnosis?

7. What is the evidence for neuroprotection with selegiline, Vitamin E, or Vitamin C? How long should neuroprotective therapy be given?

8. What is the role of pharmacotherapy in management of PD?

9. What is the role of Sinemet vs. dopamine agonists based on: age of presentation, cognitive status, symptom profile, duration of illness, and co-morbidities?

10a. What is the appropriate treatment of patients with advancing PD? In patients with moderate PD who are just beginning to experience motor fluctuations and/or dyskinesias, what is the evidence for advancing to the next drug (e.g. more levodopa, Sinemet CR, Mirapex, Requip, Permax, Parlodel, Tasmar, Comtan, Selegiline, Amantadine)?

10b. What is the optimal management of non-psychotic behavioral and psychologic dysfunction in PD? What is the appropriate management of psychotic symptoms? What is the differential diagnosis? How much simplification in antiparkinsonian pharmacotherapy is warranted before the addition of antipsychotics? Can conventional antipsychotics be justified in management of PD? Are atypical antipsychotics the drugs of choice in management of psychotic symptoms in PD? What are the differential effects of atypical antipsychotics in PD? Re: other uses of atypical antipsychotics in PD - are they justified?

11. What is the role of surgery in the management of PD? When should surgery be contemplated in a PD patient? What are the indications for one surgery vs. another? Are there minimal standards of pharmacotherapy that should be observed before contemplating surgery in PD? Re: surgical decisions in depressed or mildly demented patients - where to draw the line?

12. What is the role of rehabilitation in early and late stages of PD? Which patients are the most appropriate candidates for rehabilitation?

13. Does the evidence for Questions 1-12 vary depending on the patient's age, gender, race, or ethnicity, or income level?

After a preliminary review of the literature, the project team at MetaWorks and the co-investigator at Leonard Davis Institute (LDI) worked collaboratively to modify the original key questions, making them more amenable to answers by systematic literature review. The focus of the revised questions was unchanged. In general, where the original questions asked about what kinds of testing or treatment "should" be done, or "what is the role" of a particular test or

treatment, the modified questions asked "what are the results," or "what is the evidence." The following revised questions were reviewed by the Technical Expert Panel (TEP) and the AAN representative, and were approved by the AHRQ Task Order Officer (TOO).

Revised Key Questions

1. What are the results of neuroimaging studies (CT, MRI, PET, SPECT) or other diagnostic tests in determining the diagnosis of PD?

2. What are the results of L-dopa challenge in PD? What is the accuracy, sensitivity and specificity of this test for diagnosing PD?

3. What is the efficacy of medication used to treat early PD? What is the efficacy of initial treatment with L-dopa vs. a dopamine agonist?

4. What is the evidence for neuroprotection with selegiline, Vitamin E, or Vitamin C?

5. What is the efficacy of medication used to treat late PD? What is the efficacy of medication used to treat patients who have an insufficient response to L-dopa? What are the outcomes of treatment of medication-induced side effects?

6. What are the outcomes of treatment for patients who experience motor fluctuations and/or dyskinesias while taking L-dopa?

7. What serious adverse events are associated with medications used to treat PD?

8. What are the outcomes of treatment of PD patients with psychotic symptoms or non-psychotic behavioral and psychological dysfunction?

9. When is surgery performed on PD patients? What types of surgeries are performed and what are their outcomes?

10. What are the outcomes of rehabilitation in PD?

11. What are the results of recent review articles regarding genetic testing in PD?

12. What is the evidence that PD patients are treated differently or have different outcomes based on the following: age, presentation of symptoms, cognitive status, duration of illness, co-morbidities, gender, race, ethnicity, or income level?