Evidence Report/Technology Assessment

Number 57

Diagnosis and Treatment of Parkinson's Disease: A Systematic Review of the Literature

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Prepared by:
MetaWorks, Inc., Evidence-based Practice Center
Medford, MA

Investigators
Cindy B. Levine, MD
Kyle R. Fahrbach, PhD
Andrew D. Siderowf, MD
Rhonda P. Estok, RN, BSN
Veronica M. Ludensky, BA
Susan D. Ross, MD, FRCPC

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review prior to their release.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome written comments on this evidence report. They may be sent to: Director, Center for Practice and Technoloy Assessment, Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850.

Carolyn Clancy, M.D.
Director
Agency for Healthcare Research and Quality

Jean Slutsky, P.A., M.S.P.H.
Acting Director, Center for Practice and Technology Assessment
Agency for Healthcare Research and Quality

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Structured Abstract

Objectives. Parkinson's Disease (PD) is estimated to affect over 1 percent of the population over age 65. The objective of this systematic review is to assess the quantity and quality of published evidence regarding diagnosis and treatment of patients with PD.

Search Strategy. English-language literature published from 1990 to 2000 was searched using electronic databases. Searches were supplemented by manually reviewing bibliographies of all accepted studies and selected review articles.

Selection Criteria. Studies were required to evaluate at least 10 human patients and address pre-defined areas of interest. Only randomized controlled trials (RCTs) were accepted for studies regarding pharmacological treatment.

Data Collection and Analysis. Pertinent data were evaluated for quality and level of evidence, extracted from accepted studies by one researcher, and reviewed by a second. Data were summarized and synthesized qualitatively. Meta-analyses were performed, comparing standardized mean changes from baseline to outcome in PD severity rating scales.

Main Results. The database includes 59 studies (3,369 patients) regarding diagnosis, 49 studies (9,968 patients) on pharmacological treatment, 42 studies (1,380 patients) on surgery, 10 studies (392 patients) on psychiatric treatment, and 20 studies (1,049 patients) on ancillary treatment of PD.

PD is diagnosed clinically; evidence does not show that specific tests improve diagnostic accuracy. There is no evidence that different dopamine agonists (DAs) vary in treatment effects. Meta-analysis suggests that in early PD, treatment with DAs plus levodopa (L-dopa) may control PD symptoms better than treatment with L-dopa alone, but this was not a consistent finding. Similarly, no consistent difference in symptom control was found between L-dopa alone and the combination therapy of L-dopa plus selegiline. In patients with advanced disease, treatment with catechol O-methyl transferase (COMT) inhibitors combined with L-dopa provides significantly greater PD symptom control than treatment with L-dopa alone and is associated with lower L-dopa doses; however, long-term (greater than 7 months) results are lacking, and hepatotoxicity is a rare but potentially lethal side effect associated with tolcapone.

For pallidotomy and deep brain stimulation (DBS), endpoint PD scale scores are significantly better than baseline scores. DBS of the subthalamic nucleus (STN) and globus pallidus (GPi) result in significant improvement in PD symptoms, but only STN DBS is associated with decreased L-dopa doses. There are insufficient studies of thalamotomy and tissue transplantation to draw any conclusions regarding their efficacy and safety.

Ancillary treatments, such as physical therapy, improve some symptoms on a short-term basis, but long-term data are lacking. Intensive speech therapy has been shown to improve vocal intensity up to 12 months after treatment; however, long-term results are from only one study of 22 patients.

Conclusions. PD is diagnosed clinically; there is currently no gold standard premorbid diagnostic test for PD. Meta-analyses of different pharmacological treatments showed that the only medication that consistently controlled PD symptoms better than L-dopa alone was the

combination of L-dopa plus COMT inhibitors in patients with advanced PD. Meta-analyses suggest that pallidotomy and DBS result in improvement of PD rating scores. The published literature regarding PD suffers from lack of reporting standardized outcomes.

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Summary

Overview

Parkinson's Disease (PD) is a chronic, progressive, neurodegenerative disorder with an estimated prevalence of 31 to 328 per 100,000 people worldwide. It is estimated that more than 1 percent of the population over age 65 are afflicted with PD; incidence and prevalence increase with age.

PD is caused by idiopathic degeneration of dopamine-producing cells in the substantia nigra, located in the midbrain. Three "cardinal signs" of PD are resting tremor, cogwheel rigidity, and bradykinesia. Postural instability, typically a late finding in PD, is the fourth cardinal sign. Additional common findings are asymmetrical onset of symptoms and symptomatic response to L-dopa (levodopa). Diagnosis of PD is problematic because of the lack of a reference standard test. The diagnosis is generally made clinically, although up to 25 percent of patients with clinical diagnoses of PD have received different pathological diagnoses at autopsy.

L-dopa is the mainstay of pharmacological treatment for PD; however, its use is limited by the development of motor fluctuations and drug-induced dyskinesias. Dopamine agonists (DAs) are also used, either alone or in combination with L-dopa. DAs act directly on dopamine receptors, mimicking endogenous dopamine. Monoamine oxidase B (MAO-B) inhibitors act by inhibiting dopamine catabolism, increasing dopamine levels in the basal ganglia. Catechol O-methyl transferase (COMT) inhibitors act by inhibiting catabolism of dopamine, thereby extending L-dopa's peripheral half-life. Despite the large selection of medications available to treat PD, all PD patients ultimately require L-dopa.

In patients with early PD, the goal of treatment is to alleviate symptoms and maintain independent function. In advanced PD, the focus is aimed toward maximizing "on" time (time when medication is effective), minimizing "off" time (time when medication is not effective), and treating medication-related complications, such as dyskinesias, motor fluctuations, and psychiatric problems.

Surgical treatment for PD is generally considered for patients who respond to medications but have intolerable side effects. Surgical options include ablative procedures (pallidotomy or thalamotomy), deep brain stimulation (DBS), and tissue transplantation.

There are numerous unanswered questions regarding the diagnosis and management of PD. MetaWorks investigators developed an evidence base through a systematic review of the English-language literature from 1990 to 2000 pertinent to patients with PD. This synthesis of the best available and most recent evidence is intended to serve as an information resource for decisionmakers and developers of practice guidelines and recommendations. It also should serve to highlight gaps in the literature and areas that require future research.

Reporting the Evidence

This report presents the results of a systematic review of published studies of adult patients with PD. The following key questions guided this review.

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1. What are the results of neuroimaging studies or other diagnostic tests in determining the diagnosis of PD?
2. What are the results of L-dopa challenge in PD? What are 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 nonpsychotic 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, comorbidities, gender, race, ethnicity, or income level?

Methodology

MetaWorks investigators applied methods derived from the evolving science of systematic review research. The review followed a work plan that had been developed a priori and shared with the Task Order Officer at the Agency for Healthcare Research and Quality (AHRQ), the project's nominator (American Academy of Neurology), and a multidisciplinary Technical Expert Panel.

The work plan outlined the methods to be used for the literature search, study eligibility criteria, data elements for extraction, and methodological strategies employed both to minimize bias and to maximize precision during the process of data collection and synthesis.

The published literature from January 1, 1990, to December 31, 2000, was searched using Medline, Current Contents®, and Cochrane Library databases. The electronic searches were supplemented by a manual search of the reference lists of all accepted articles, recent review articles, and relevant Internet sites.

Two levels of screening were applied. Level I screening involved rejection of abstracts on the basis of predefined exclusion criteria, such as animal studies, case reports, or ineligible languages. Level II screening involved assessment for fit with inclusion criteria. To be eligible, a study had to be published in English. Only randomized controlled trials (RCTs) were accepted for pharmacological treatment. For other areas, due to rarity of RCTs, other study designs were accepted, including nonrandomized controlled trials (NRCTs), uncontrolled case series (UCSs), and observational studies. Each study was required to include a minimum of 10 patients.

Relevant data from all accepted studies were entered onto data extraction forms designed specifically for this project. All data elements were extracted by one investigator and reviewed by a second investigator. One hundred percent agreement between the two reviewers was required prior to entry of data elements into the database. At least one physician reviewed all data elements extracted from every study.

All accepted studies were evaluated for quality by using the previously published methods of Level of Evidence and the Jadad Quality Score Assessment.

The information captured from each study included date of publication, location and type of study, primary objective of study, description of interventions (e.g., medications or surgery), PD scale measurements at baseline and after treatment, and adverse events. Summary statistics were calculated and meta-analyses were performed, comparing standardized mean changes in PD severity rating scales.

A group of 19 peer reviewers was assembled to review and provide suggestions for the draft final report describing this project. Their comments, in addition to those of the Technical Expert Panel, were incorporated into the final report.

Findings

Diagnosis

The studies covered by the review of the literature on diagnosis of PD and review findings are:

- Fifty-nine studies, 141 treatment arms, 3,369 patients.
- Study designs: 46 cross-sectional studies, 5 UCSs, 2 NRCTs, 6 others.
- Five studies of apomorphine challenges: insufficient evidence to support role in diagnosing PD.
- Six autopsy studies: evidence to support role in confirming clinical diagnosis of PD.
- Ten studies of clinical or laboratory evaluation: inconclusive evidence to determine role in diagnosing PD.

- Two studies of color vision testing: inconclusive evidence to determine role in diagnosing PD.
- Three studies of magnetic resonance imaging (MRI): insufficient evidence to determine role in diagnosing PD.
- Seven studies of olfactory function: evidence to support ability to distinguish parkinsonism from healthy controls but not to distinguish PD from atypical parkinsonism.
- Three studies of PD test battery (includes tests of motor function, olfaction, and depression): preliminary evidence suggesting usefulness in diagnosing PD, but long-term confirmatory studies are needed.
- Eight studies of positron emission tomography (PET) scans: insufficient evidence to determine role in diagnosing PD.
- Thirteen studies of single photon emission computed tomography (SPECT) scans: insufficient evidence to support role in diagnosing PD.
- Two studies of other scans (nuclear magnetic resonance (NMR), ultrasound): insufficient evidence to support role in diagnosing PD.

Pharmacological Treatment

The review of pharmacological treatment included:

- Forty-nine studies (all RCTs), 111 treatment arms, 9,968 patients.
- Thirty-two studies regarding patients with early PD (disease duration 5 years or less), 17 with advanced PD.

While most studies reported Unified Parkinson Disease Rating Scale (UPDRS) scores or other common PD rating scales, comparison of different treatments across studies presented numerous methodologic obstacles. It was not always possible to discern the number of patients who received L-dopa or the doses they received because many studies simply reported that L-dopa was given to patients as needed. Studies were not consistent in reporting the same PD rating scales or in reporting both baseline and endpoint scores, with standard deviations, for all parameters. Studies did not consistently report whether the PD scale scores were measured when patients were in the "off" or "on" state. Given these limitations, however, the following associations were noted:

- Meta-analysis suggests that in early PD, treatment with DAs plus L-dopa may control PD symptoms better than treatment with L-dopa alone, but this was not a consistent finding.
- In studies in which patients were randomized to L-dopa vs. L-dopa plus DAs, the combination of L-dopa plus DAs resulted in better UPDRS scores than L-dopa alone. This was true in both short- and long-term (over 1 year) studies.
- In studies where patients were randomized to L-dopa vs. DAs, where additional L-dopa was discretionary, L-dopa alone resulted in better UPDRS scores than DAs (with or without additional L-dopa).
- There was no evidence that different DAs varied in treatment effects.
- Meta-analysis did not suggest that treatment with selegiline plus L-dopa controlled PD symptoms better than treatment with L-dopa alone.
- Meta-analysis showed that in patients with advanced disease, treatment with COMT inhibitors combined with L-dopa provided significantly greater PD symptom control than L-dopa alone and was associated with lower L-dopa doses. However, long-term (over 7 months) results are lacking, and hepatotoxicity is a rare but potentially lethal side effect that has been associated with tolcapone.
- These meta-analysis results should be viewed with caution, as they are based on the small number of RCTs that met the inclusion criteria for this systematic review. Due to the small number of studies within each meta-analysis, these findings are sensitive to possible publication bias in the literature.

Surgical Treatment

The review of surgical treatment included:

- Forty-two studies, 52 treatment arms, 1,380 patients.
- Study designs: 35 UCSs, 4 RCTs, 2 NRCTs, 1 other.
  - Pallidotomy: 20 treatment groups, 764 patients.
  - Thalamotomy: 5 treatment groups, 134 patients.
  - DBS: 16 treatment groups, 288 patients.
    - Globus pallidus (GPi): 4 treatment groups, 22 patients.
    - Subthalamic nucleus (STN): 8 treatment groups, 135 patients.
    - Thalamus: 4 treatment groups, 131 patients.
  - Tissue transplants: 9 treatment groups, 165 patients.
    - Adrenal medulla: 3 treatment groups, 91 patients.
    - Human fetal tissue: 5 treatment groups, 62 patients.
    - Porcine fetal tissue: 1 treatment group, 12 patients.
  - No surgery: 2 treatment groups, 29 patients.

The findings were:

- The overall quality of the surgery literature was lower than the quality of the pharmacology literature, as very few RCTs were done to evaluate the efficacy and safety of surgical procedures. It must be recognized, however, that it is very difficult to perform RCTs of surgical procedures, and other study designs may have to suffice.
- For all surgical procedures, "off" scores improved to a greater degree than "on" scores.
- On average, endpoint PD scale scores for pallidotomy and DBS treatment were significantly better than baseline scores.

- DBS of the STN and GPi both improved PD scores, but only STN DBS was associated with decreased L-dopa dosages.
- There were insufficient studies of thalamotomy to draw any conclusions regarding efficacy or safety.
- An insufficent number of studies have been done to make more than tentative conclusions about the effectiveness of fetal brain transplantation. A recent RCT comparing tissue transplant to sham surgery raised important questions regarding the long-term efficacy and safety of the procedure.
- Due to the small number of studies within each meta-analysis, these findings are sensitive to possible publication bias in the literature.

Treatment of Psychiatric Disorders

The review of treatment of psychiatric disorders covered:

- Ten studies, 12 treatment arms, 392 patients.
- Study designs: 6 UCSs, 2 RCTs, 2 others.

The findings were:

- Evidence from 6 studies (314 patients) supports the efficacy of clozapine in improving symptoms of psychosis in PD patients.
- There was insufficient evidence regarding treatment of depression in PD patients.

Ancillary Treatment of PD

The review of ancillary treatment covered:

- Twenty studies, 37 treatment arms, 1,049 patients.
- Study designs: 13 RCTs, 3 UCSs, 2 NRCTs, 2 cross-sectional studies.
  - Physical therapy: 7 studies.
  - Speech, swallowing, or voice therapy: 5 studies.
  - Multidisciplinary rehabilitation programs: 4 studies.
  - Other: 4 studies.

It was found that:

- Short-term efficacy was demonstrated in all of the above ancillary treatments, but long-term trials are needed.
- Intensive speech treatment has been shown to improve vocal intensity up to 12 months after treatment; however these long-term results are from only one study of 22 patients.

Future Research

Standardization of reporting results is essential. Investigators should consistently report baseline, endpoint, and change in UPDRS scores, along with standard deviations. The number of patients who receive L-dopa should be clearly stated, as well as the L-dopa doses. Patients with comorbidities should be included in clinical trials. As nearly all of the studies in the database excluded patients with serious illnesses, the generalizability of study results is limited. In particular, studies should include more elderly patients, patients with young age of disease onset, and members of different racial and ethnic groups. RCTs should be performed to evaluate surgical procedures. Further studies of physical therapy, occupational therapy, speech therapy, and other nonpharmacologic and nonsurgical treatment modalities should be of longer duration and should measure standardized, clinically meaningful outcomes.

Given the large volume of studies that are published regarding PD, semiannual updates are recommended to keep this database current.

Availability of the Full Report

The full evidence report from which this summary was taken was prepared for the Agency for Healthcare Research and Quality (AHRQ) by the MetaWorks, Inc., Evidence-based Practice Center (EPC) in Medford, MA, under Contract No. 290-97-0016. It will be available in June 2003. Printed copies may be obtained free of charge from the AHRQ Publications Clearinghouse by calling 800-358-9295. Requesters should ask for Evidence Report/Technology Assessment No. 57, *Diagnosis and Treatment of Parkinson's Disease: A Systematic Review of the Literature.* In addition, Internet users will be able to access the report and this summary online through AHRQ's Web site at www.ahrq.gov

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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?

Chapter 2. Methodology

MetaWorks investigators used systematic review methods derived from the evolving science of review research.[110, 111] These methods were generally applied according to standard operating procedures at MetaWorks and are displayed in Figure 1.

A Task Order, containing the original questions described above, was developed by AAN, submitted to AHRQ, then presented to MetaWorks. From this Task Order, MetaWorks researchers developed a Work Plan (see Appendix B), which was then reviewed by AHRQ, AAN, and the TEP. The work plan outlined the methods to be used for the literature search, study eligibility criteria, data elements for extraction, and methodological strategies to minimize bias and maximize precision during the process of data extraction and synthesis. After a preliminary review of the literature, a Topic Assessment and Refinement report was submitted to the AHRQ, AAN, and TEP, discussing the revised key questions and preliminary results of the literature searches (Appendix C).

Causal pathways relevant to the above questions were then developed (Appendix D). These pathways were not designed to function as clinical practice guidelines or algorithms for patient care decisions. They were constructed solely to guide the systematic review process for this project, and with the expectation that they might change as the project developed.

Literature Search

The published literature was searched from January 1, 1990 to December 31, 2000, using Medline, Current Contents®, and Cochrane Library databases. A manual search was performed of the bibliographies of all publications accepted for inclusion into the evidence base. In addition, the bibliographies of recent review articles were searched for potentially relevant citations. The retrieval cut-off date was February 1, 2001.

The Medline search included the following search strategies, with limits of publication dates 01/01/1990 to 12/31/2000, English language, Clinical Trial, and Human:

Diagnosis: *(Parkinson disease OR parkinson syndrome OR parkinsonism) AND (diagnosis OR medical errors OR accuracy OR sensitivity OR specificity) OR (diagnosis AND antiparkinsonian agents).*

Pharmacological Treatment: *(Parkinson disease OR parkinson syndrome OR parkinsonism) AND (treatment OR levodopa OR carbidopa OR amantadine OR anticholinergic OR selegiline OR deprenyl OR dopamine agonist OR bromocriptine OR pergolide or lisuride OR cabergoline OR pramipexole OR ropinirole OR tolcapone OR entacapone).*
(Parkinson disease OR parkinson syndrome OR parkinsonism) AND (selegiline OR Vitamin E OR Vitamin C OR neuroprotective agents).

The search cut-off date for pharmacologic studies was initially 1985, for the purpose of including studies of anticholinergic agents. However, no acceptable studies of anticholinergic agents were published between 1985 and 1990; therefore the search cut-off date was changed back to 1990, in accordance with the search cut-off date established for the other questions.

Surgical Treatment: *(Parkinson disease OR parkinson syndrome OR parkinsonism) AND (surgery OR pallidotomy OR brain tissue transplant OR deep brain stimulation)*

Psychiatric Treatment: *(Parkinson disease OR parkinson syndrome OR parkinsonism) AND (psychological OR psychotic OR mental disorder) AND (drug therapy OR drug interactions).*

Ancillary Treatment: *(Parkinson disease OR parkinson syndrome OR parkinsonism) AND rehabilitation.*

Genetics: *(Parkinson Disease OR parkinsonism OR Parkinson) AND genetics AND limit to review articles January 1, 1997-August 1, 2000.*

The search of the Current Contents CD-ROM database employed the same strategies. The Cochrane Controlled Trials Register search strategy was "Parkinson's Disease."

All citations and abstracts resulting from the above searches in Medline and Current Contents were downloaded and printed at MetaWorks.

To assist with the development of the evidence base, pertinent articles from the following Internet sites were reviewed:

American Parkinson Disease Association (http://apdaparkinson.com)
Medscape (http://www.medscape.com)
National Guidelines Clearinghouse (NGC; http://www.guideline.gov)
National Parkinson Foundation (http://www.parkinson.org)
Parkinson's Action Network (http://www.parkinsonsaction.org)
Parkinson's Disease Foundation (http://www.parkinsons-foundation.org)
United Parkinson Foundation (http://www.aoa.dhhs.gov/aoa/dir/221.html)
Clinical trials information (http://www.parkinson-study-group.org)

A list of potentially relevant studies was provided by the American Speech-Language-Hearing Association (ASHA). These citations were screened in the same manner as those identified by electronic searches.

Exclusion Criteria

During Level I screening, all abstracts were downloaded, reviewed and evaluated for the following exclusion criteria:

- Reviews, meta-analyses (except those regarding diagnosis and genetics)
- Letters, case reports, editorials, and commentaries.
- Abstracts and unpublished study reports.
- Pharmacokinetic and pharmacodynamic studies.

- Animal or *in vitro* studies.
- Studies written in languages other than English.
- Studies published prior to 1990.
- Studies with < 10 patients.
- Cross-over studies.
- Studies where results for PD population cannot be separated from results from other populations.
- Studies not pertaining to diagnosis or treatment of PD.
- Treatment studies with < 24 weeks of treatment and followup.

Cross-over studies were excluded for several reasons. It is frequently difficult to extract information from the mid-point of the trial, before the cross-over occurs. The patient response in the second phase of a study of cross-over design may be impacted by treatment administered during the first phase. When patients drop out in the first phase, the patients entering the second phase may be different from the baseline population, introducing selection bias. Additionally, the number of parallel design RCTs that met the inclusion criteria comprised a large enough evidence base to justify the exclusion of studies of cross-over design, with all of their attendant difficulties in data extraction and interpretation.

Given that PD is a chronic condition, and that patients stay on medications for years, the most clinically relevant data comes from long-term trials. For this reason, treatment trials had to be greater than or equal to 24 weeks duration for acceptance. Furthermore, the most useful data for analysis concerning pharmacological treatment of PD are in randomized controlled trials (RCTs); therefore, only RCTs were accepted for studies pertaining to pharmacological treatment. For trials pertaining to surgical treatment, 24 weeks of followup were required; however, study designs other than RCTs were accepted, due to the scarcity of RCTs evaluating surgical procedures for PD. For trials pertaining to diagnosis, study duration and design were not restricted.

Full articles were retrieved for all abstracts passing Level I screening. The articles then underwent Level II screening, which consisted of evaluating the articles for the following inclusion criteria (See Appendix E):

Inclusion Criteria

Diagnosis:

- The following study designs: observational [prospective, retrospective, and cross sectional (XS)], or interventional [RCTs, non-randomized controlled trials (nRCTs), uncontrolled case series (UCSs), XS].

- Adult patients with potential diagnosis of PD.
- Studies addressing any diagnostic test to establish or support a diagnosis of PD.

Pharmacological Treatment:

- RCTs only.
- $\geq$ 24 weeks treatment and followup duration.
- Studies reporting at least one objective clinical outcome measure (efficacy or safety) on at least one of the following drugs or category of drugs:
    - L-dopa/Carbidopa (Sinemet)
    - L-dopa/Benserazide (Madopar)
    - Amantadine (Symmetrel)
    - Dopamine agonists: Bromocriptine (Parlodel), Pergolide (Permax), Ropinirole (Requip), Pramipexole (Mirapex), Andropinole, Cabergoline (Dostinex), Apomorphine, Lisuride (Dopergin)
    - Monoamine oxidase B (MAO-B) inhibitors: Selegiline (Deprenyl), Rasagiline (TVP-1012), Lazabemide
    - Catechol-O-methyltransferase (COMT) inhibitors: Tolcapone (Tasmar), Entacapone (Comtan)
    - Anticholinergic agents: Trihexylphenidyl (Artane), Benztropine (Cogentin), Procyclidine
- Studies involving neuroprotection with selegiline, Vitamin E (tocopherol), or Vitamin C.

Surgical Treatment:

- The following study designs: interventional (RCTs, nRCTs, and UCSs).
- $\geq$ 24 weeks study and followup duration.
- Must report at least one objective clinical outcome measure.
- Studies addressing surgery in adult patients with PD including:
    - Ablative or destructive surgery (thalamotomy, pallidotomy),

- Stimulation surgery or Deep Brain Stimulation (DBS),
- Transplantation surgery.

Psychiatric Treatment:

- The following study designs: interventional (RCTs, nRCTs, and UCSs).
- $\geq$ 24 weeks study and followup duration.
- Studies addressing treatment of non-psychotic behavioral and psychological dysfunction in adult patients with PD.
- Studies addressing treatment of psychotic symptoms in adult patients with PD.
- Studies addressing use of antipsychotic medications in conjunction with antiparkinsonian agents.
- Studies addressing the use of atypical antipsychotic medications in management of adult patients with PD.
    - Clozapine (Clozaril)
    - Olanzapine (Zyprexa)
    - Quetiapine (Seroquel)

Ancillary treatment:

- The following study designs: interventional (RCTs, nRCTs, and UCSs).
- No minimum study duration.
- Studies reporting at least one of the following specific interventions:
    - Allied health interventions.
        - Occupational therapy (OT).
        - Physical therapy (PT).
        - Psychotherapy (counseling).
        - Speech therapy.

- Studies reporting at least one of the following specific outcomes:
    - Acute hospitalization.
    - Rehabilitation hospitalization.
    - Nursing home admission.
    - Work absenteeism.
    - Quality of Life (QoL).
    - Activities of Daily Life (ADL) assessment.

Genetics:

- Study design limited to recent review articles only.
- Adult patients undergoing genetic testing to support a diagnosis of PD.

General Considerations:

Studies pertaining to diagnosis were initially required to report sensitivity and specificity; however, as very few studies met this requirement, it was removed. Some of the peer reviewers commented that the inclusion criteria for surgical studies were less rigid than those for pharmacological studies. This disparity was due to the relative scarcity of RCTs pertaining to surgical treatment of PD.

For studies regarding ancillary treatment to be accepted, the initial requirement was that the study duration be at least 24 weeks. This resulted in acceptance of only six studies; therefore, this requirement was removed, and studies of < 24 weeks duration were also accepted.

Linked Studies

After the accepted studies were determined, linked studies were identified. These were studies in which the same patient population was reported in more than one publication. “Parent” studies were assigned, which contained primary data. “Child” studies contained supplemental information, such as followup data or additional analyses. Data elements were extracted from the parent studies, and supplemented by information presented in kin studies, when appropriate.

Rating the Evidence

All eligible studies were rated for both quality and level of evidence at the time of data extraction. Two established methods: 1) the Jadad method,[112] and 2) the Level of Evidence method[113] were used (see Appendix B, Attachments B and C).

Data Extraction

Data Extraction Forms (DEFs) were designed in advance (see Appendix E), and pilot tested on a small sample of eligible studies. The pilot test allowed for necessary edits to the DEF to be made prior to implementation on all studies. Key data from each eligible study were extracted by a researcher recording data from original reports onto a DEF, and reviewed by a second researcher checking all DEF fields against the original report. Differences were resolved prior to data entry. In all cases, at least one physician reviewed each study. Dual review of all data served to reduce error and bias in the data extraction process. The data were then entered into MetaWorks' relational database of clinical studies, MetaHub™.

When trials consisting of several phases with different study designs were encountered, only data from the randomized phase was captured.

Key data elements sought for extraction from each study are listed in the Work Plan (Appendix B).

Database Development

Data were entered from the DEFs into a relational database of clinical trials. At the time each DEF was entered, 100 percent of the data entries were checked back against the original DEFs. In addition, a 20 percent random sample of data in the completed database was checked against the DEFs. Error rates in excess of 2 percent of QC-checked data would have triggered a 100 percent recheck of all data elements entered into the database.

Statistical Methods

The main goal of the statistical analysis was to estimate the difference in efficacy of various treatments for PD.

Summary Statistics

Data listings and summary data were prepared for study level characteristics, patient and treatment level characteristics, outcomes of interest, and safety data. When the database was complete, verified, and locked, data were entered into table shells. In general, study and patient characteristics and outcomes variables were summarized using standard descriptive statistics weighted by study sample size.

Diagnosis

Studies pertaining to diagnosis were synthesized with summary statistics only.

Pharmacologic Treatment

The medications with sufficient data for comparisons were L-dopa, DAs, selegiline, and COMT inhibitors. The primary efficacy outcomes of interest were the standardized mean changes from baseline to common followup time points, as evaluated on the UPDRS scales. If total UPDRS score was not reported, scores from UPDRS III (Motor) or II (ADLs) were used. Both "off" and "on" scores were captured when reported. Most studies, however, did not report whether scores were "off" or "on."

When UPDRS scores were not available, S&E ADL scores, Webster, Columbia University Rating Scale (CURS),[114] or H&Y scores were used instead, in the above order of preference. This order was based on frequency of reporting the different scales. Validation studies show that scores on the various PD rating scales are generally very highly correlated. For example, one study found a correlation of 0.79 between total UPDRS score and H&Y score, a correlation of -0.88 between S&E and UPDRS, and a correlation of 0.76 between scores on the Webster scale and the total UPDRS score.[54]

We had initially intended to include the Northwestern University Disability Scale (NUDS), in the above evaluations; however, inconsistency in reporting methods prevented pooling results from different studies that used this scale.[54, 115] This did not result in exclusion of any studies; while 19 treatment arms reported NUDS scores, all of them reported results of at least one other scale as well.

Placebo treatment arms frequently allowed discretionary L-dopa administration. For the purposes of analysis, placebo arms with discretionary L-dopa were categorized as L-dopa arms, despite incomplete reporting of the actual number of patients treated, or their specific results. In the DA meta-analysis, a separate analysis was performed comparing studies in which patients received discretionary L-dopa to studies in which patients were randomized to L-dopa.

Surgery

The surgical procedures analyzed were pallidotomy, DBS, and fetal cell transplants. Studies of thalamotomy were synthesized with summary statistics only, due to the small number of studies.

The primary efficacy outcomes of interest for surgery studies were the standardized mean changes from baseline to outcome, as evaluated on the UPDRS scores. If total UPDRS score was not reported, scores from UPDRS III (Motor) or II (ADLs) were used. When UPDRS scores were not available, S&E ADL, Webster, CURS, or H&Y scores were used instead, in the above order of preference.

For both pharmacological and surgical studies, safety outcomes were reported with summary statistics.

Ancillary Treatments

Results of ancillary treatments were synthesized with summary statistics only, due to the small number of accepted studies and the variety of evaluative techniques presented in the different studies.

Meta-Analyses

Meta-analysis of efficacy outcomes of pharmacological studies was performed for all RCTs reporting outcome data on at least one of the PD rating scales mentioned above. Meta-analysis of the primary efficacy outcomes of the surgery studies was also performed for all studies reporting the necessary outcome data. The effect sizes calculated and meta-analyzed were standardized mean differences.[116] Appendix F describes interpretation of the size of standardized mean differences.

Effect sizes for pharmacological studies. In the meta-analyses of pharmacological studies, the effect size represents the standardized difference between two groups on the change in patients' scores from the beginning of the treatment to the end of the treatment. Optimally, this effect size was calculated from baseline and outcome data for the two treatment groups, and (preferably) change-score standard deviations; however, in some cases calculations were possible from study *p*-values.

Unbiased change-score effect sizes were calculated using the standard formula:

$$d_{CHANGE} = \left(1 - \frac{3}{4N - 9}\right) \frac{(\overline{Y}_{T\_OUTCOME} - \overline{Y}_{T\_BASELINE}) - (\overline{Y}_{C\_OUTCOME} - \overline{Y}_{C\_BASELINE})}{\sqrt{s^2_{pooled\_CHANGE}}},$$

where N is the total study sample size.[116] The numerator represents the difference between the treatment and control groups on the amount of change each underwent from the beginning of the study. The denominator contains the pooled variance of the treatment and control change-scores. See Appendix F for a description of how this variance was estimated when the source studies reported baseline and outcome data but failed to report change-score standard deviations. The change-score effect sizes measured the standardized difference in change between a treatment and a control group, to see if one treatment led to more improvement (or less decline) in PD than the other. Effect sizes were scaled such that a positive effect size indicated that the treatment under investigation worked better than the control, where the control was always therapy with L-dopa alone.

Effect sizes for surgery studies. The meta-analysis of surgery data examined pre-post surgery standardized mean differences in PD scores:

$$d_{PRE->POST} = \left(1 - \frac{3}{4N - 9}\right) \frac{(\overline{Y}_{T\_OUTCOME} - \overline{Y}_{T\_BASELINE})}{\sqrt{s^2_{pooled\_PRE->POST}}}.$$

These effect sizes simply compare pre-test to post-test scores to determine if there was any improvement at all due to the surgery. This means that the only comparisons between the efficacies of different types of treatment (e.g., pallidotomy versus DBS) that can be made are indirect comparisons.

Meta-analyses of pharmacological and surgery studies. Based upon available data, three sets of meta-analyses were conducted for the pharmacological studies: one that compared the efficacy of DAs (with L-dopa allowed) to L-dopa given alone, one that compared the efficacy of selegiline (with L-dopa allowed) to L-dopa given alone, and one that compared the efficacy of COMT inhibitors (with L-dopa allowed) to L-dopa given alone.

There were insufficient studies to allow a meta-analysis of any pharmacological treatment against placebo, with no L-dopa involved.

Based upon available data, three sets of meta-analyses were calculated for the surgery studies: one that investigated whether pallidotomy was associated with improved "off" or "on" scores, one that investigated whether DBS was associated with improved "off" or "on" scores, and one that investigated whether fetal brain cell transplants were associated with improved "off" or "on" scores. There were insufficient studies to perform a similar meta-analysis on thalamotomy treatment arms.

After effect sizes and their expected variances were calculated for a given set of studies, a fixed-effects meta-analysis was conducted within each set.[116] The chi-square homogeneity statistic (Q_E) was calculated for each meta-analysis to determine whether there was any variation in the study effects that could not be explained due to sampling error. Given the low number of studies in each meta-analysis, there was very low power to detect effect heterogeneity. Thus, a more conservative random-effects model was utilized to calculate the final estimates and confidence intervals when the estimate of random-effects variation (defined as τ or Δ^2) was greater than zero.[117] The random-effects model accounts for treatment variation not explainable due to sampling error, and thus leads to wider confidence intervals for its parameters than the fixed-effects model. When data permitted, fixed-effects and/or random-effects meta-regressions (mixed-model meta-analyses that consider study characteristics as predictors of treatment effect) were examined as well.[117, 118] Common study characteristics investigated were mean patient age, severity of disease at baseline, disease duration, and the time between initial treatment and post-test.

All meta-analyses and meta-regressions were performed using SPSS 10.1 and procedures written in SAS/IML 8.1.

Sensitivity Analysis. When the number of studies in the meta-analysis permitted, sensitivity analysis was performed to examine whether any design characteristics were associated with treatment effects. Characteristics (covariates) of interest included:

1) whether study data were intention-to-treat (ITT) or completers

2) adequacy of blinding, as reflected in Jadad score.[112]

The data were also inspected for "outliers" – study effects that were extreme enough, either in their value or in the value of their study characteristics, that they might by themselves "skew" the estimate of the mean effect, the estimate of effect size heterogeneity, or the relationship between a study characteristic and the study effects.

Role of Consultants

Eight people from both academic and community settings comprised the TEP (Appendix G). They all received copies of the Work Plan and its revision, causal pathways, topic refinement, study listings, and draft report. When TEP members provided feedback, MetaWorks investigators reviewed their comments, and applied them as deemed appropriate. Additionally, during the course of the project, monthly conference calls were instituted among MetaWorks, the topic nominator (AAN), the TOO, and the co-investigator from LDI. During these conference calls, project updates were provided and issues of concern were addressed.

Peer Review

A group of 19 peer reviewers (Appendix G) was assembled to review a draft version of this report. The panel was composed of neurologists, a neurosurgeon, an internist, two statisticians, a speech-language pathologist, and two PD patients. All reviewers were asked to complete peer review form relative to the content of the first draft of this report (Appendix G), and were also invited to provide additional written comments. Seven of the eight TEP members and 13 of the 19 peer reviewers provided feedback on the draft Evidence Report. All responses from the TEP and peer reviewers were reviewed and, where appropriate, incorporated into the final report.

Chapter 3. Results

In the following results, “k” refers to the number of studies, "t" refers to the number of treatment arms, and “n” refers to the number of PD patients.

Searches

The numbers of abstracts obtained from searches in Medline and Current Contents are displayed in Figure 2. The primary search in Medline (search window: 1990-2000) yielded 957 abstracts, the search in Current Contents (search window: 1990-2000) yielded 397, and the Cochrane Library search yielded 590, for a total of 1,944 citations. After 614 duplicates were identified, a total of 1,330 abstracts were downloaded into Reference Manager at MetaWorks. Another 174 potentially relevant citations were identified from manual bibliography checks. Thus, over the duration of this project, 1,504 abstracts identified from electronic searches and bibliography checks were screened against protocol-defined exclusion criteria. This does not include the searches for review articles and genetics, which yielded 377 and 149 citations, respectively. Of the 1,504 citations pertaining to diagnosis and treatment of PD, 791 were rejected during Level I screening of abstracts. The main reasons for Level I rejection were: studies not pertinent to PD, studies with less than ten patients or with study duration less than 24 weeks, studies not pertaining to diagnosis or treatment, and cross-over studies. Full-text papers of the remaining 713 studies were retrieved and screened at MetaWorks.

During Level II screening of full-text papers, 465 were rejected, resulting in 248 accepted studies. Evidence Table 1 summarizes the number of studies rejected during Level II screening or data extraction, organized by rejection reason. Comprehensive bibliographies for accepted studies may be found in Appendix H. Appendix I contains full bibliographies for rejected studies, organized by rejection reason.

The screening strategies were reviewed *a priori* with the TEP, TOO, and AAN representative. A few studies did not meet inclusion criteria, but the consulting PD experts believed they should be mentioned in this review. These studies are discussed in Appendix J, but were not extracted, entered into the database, or included in the statistical analyses.

Studies

Study Characteristics

Evidence Table 2 summarizes the main study-level characteristics of the 248 studies accepted for data extraction. These studies consisted of 180 parents and 68 kin studies. In the 180 parent studies, there were a total of 353 treatment groups, and 16,158 patients. Of the accepted studies, 59 parents (and 6 kins) pertained to diagnosis (t=141, n=3,369), 49 parents (and 36 kins) to pharmacological treatment (t=111, n=9,968), 42 parents (and 23 kins) to surgery (t=52, n=1,380), ten parents (and one kin) to psychiatric treatment (t=12, n=392), and 20 parents (and two kins) to ancillary treatment (t=37, n=1,049). The genetics section of this report was based on the contents of 16 papers which were reviewed, although not formally extracted.

Evidence Table 3 shows baseline treatment level characteristics of patients in all accepted studies. One study excluded patients < 60 years of age,[119] but most studies did not focus specifically on elderly or young patients. The evidence base in both pharmacological and surgical studies is heavily weighted towards people under age 65.

Further details regarding treatment level variables will be described in the individual sections concerning diagnosis, pharmacological treatment, surgical treatment, psychiatric treatment, and ancillary treatment.

Diagnosis

There were 59 parent and six kin studies concerning diagnosis, consisting of 3,369 patients, 1,108 healthy controls, and 859 patients with other neurological diagnoses, such as secondary parkinsonism or essential tremor. The vast majority of studies were cross-sectional studies (k=46, n=2,055), six were retrospective observational studies (n=953), five were UCSs (n=278), and two were nRCTs (n=83). All were graded as level III evidence, and quality score could not be calculated because there were no RCTs.

Evidence Table 4 shows the number of studies, treatment arms, and patients who were evaluated by different diagnostic tests. The categories of diagnostic testing included: apomorphine or L-dopa challenge tests (k=5, t=6, n=229), autopsy studies (k=6, t=15, n=253), clinical or laboratory tests (k=10, t=26, n=1,412), color vision testing (k=2, t=3, n=35), MRI (k=3, t=8, n=140), olfactory testing (k=7, t=21, n=355), PD Test Battery (k=3, t=7, n=180), PET scans (k=8, t=21, n=185), SPECT scans (k=13, t=29, n=460), and other scans (k=2, t= 5, n=120).

An estimate of the diagnostic accuracy of any test should compare the test with a reference standard, which should be the best available method of assessing the presence or absence of the disease of interest.[120] The major difficulty in assessing diagnostic tests for PD is the lack of a validated reference standard for comparison.

Apomorphine and L-Dopa Challenge Tests

All five studies evaluating challenge tests with apomorphine or L-dopa were conducted in Europe: three in the United Kingdom[121, 122, 123] and one each in Germany[124] and Italy.[125] Three studies were cross-sectional, and two were UCSs. They included 229 PD patients and 43 patients with other neurological diagnoses. Comparison of these studies is hampered by heterogeneity in many areas, including reference standard, study design, challenge test methodology, definitions of positive results, and outcomes reported.

In all five studies, patients were reported as having positive or negative apomorphine tests, and presence or absence of PD, based on long-term response to L-dopa. The sensitivities of the apomorphine tests ranged from 87 to 95 percent, and the specificities ranged from 75 to 95 percent. There are several problems, however, with comparing the sensitivity and specificity results from different studies. The major limitation is lack of a constant reference standard. In two studies, the reference standard was response to chronic L-dopa use. Apomorphine is a rapidly acting DA. Patients who respond to apomorphine would be expected to also respond to other DAs or to L-dopa, but it is not valid to equate L-dopa response with a diagnosis of PD, as other conditions may also respond to L-dopa. In three studies, the reference standard was clinical diagnosis of PD. The problem with using clinical diagnosis as the reference standard is that

autopsy studies have shown that clinical diagnosis may be wrong in up to 25 percent of cases.[42] Until there is a valid reference standard, it will remain difficult to evaluate any diagnostic test for PD.

There are several other areas of heterogeneity among the apomorphine studies. The dosage of apomorphine varied, ranging from one to ten mg given subcutaneously, and the time interval between doses ranged from 30 to 120 minutes. In some studies, the apomorphine dose was adjusted for weight. Some studies used placebo, while others reported that the acute side effects associated with apomorphine would make blinding impractical. Criteria for positive results also varied from study to study, and included improvements of 15 or 25 percent in the tapping test, walking test, tremor scale, rigidity scale, or modified Webster score to define positive apomorphine test results. In several studies, some patients had equivocal results. The studies concluded, in general, that the apomorphine test might be predictive of response to L-dopa, but is not diagnostic of PD.

SPECT Scans

Thirteen studies, consisting of 460 PD patients, 191 healthy controls, and 64 patients with other neurological disorders, evaluated the use of SPECT scans in PD patients.[126 - 138] Eleven of these studies were performed in Europe (eight in Germany (six by the same author), two in Italy, and one in the Netherlands), one in the US, and one in Japan. Ten studies were cross sectional, two were UCSs, and one was a nRCT. Five studies evaluated patients with early PD only,[126 - 130] and eight evaluated patients with various stages of PD. Five of the studies compared SPECT results before and after administration of apomorphine,[127, 128, 130, 131, 132] and one compared SPECT results to PET results.[129]

Three studies evaluated presynaptic dopamine transporters, using the cocaine analogues [123]β-carboxymethoxy-tropane (β-CIT),[138] fluoropropyl-carbomethoxy-tropane (FP-CIT),[133] or iodopropenyl-carbomethoxy-tropane (IPT)[126] as radioligands. In all three studies, early PD patients had decreased presynaptic uptake compared with normal controls.

Nine studies evaluated postsynaptic dopamine receptors, using the ligand IBZM.[127 - 132, 134, 135, 136] The results showed that normal or increased receptor binding of IBZM corresponded to positive response to L-dopa or apomorphine,[129-132] and decreased binding corresponded to negative response to L-dopa or apomorphine.[127, 128, 130, 132, 136] There was, however, considerable overlap between patients with PD, atypical parkinsonism, and normal controls.[127, 128, 132, 134]

One study using the ligand IBZM reported increased uptake in patients with early PD compared with normal controls, but decreased uptake in patients with more severe PD.[135] The authors theorized that in patients with advanced PD, there may be down-regulation of striatal post-synaptic dopamine receptors due to chronic exposure to exogenous L-dopa.

In one study, changes in global and regional cerebral blood flow (CBF) were measured.[135] Global CBF was lower in PD patients than in normal controls, and decreased with more advanced disease.

Combining the results of the SPECT scan studies is problematic because they varied in many ways. Some evaluated pre-synaptic function, while others evaluated post-synaptic function, and one evaluated cerebral blood flow. Some compared PD patients to normal controls, and some compared SPECT results to the results of apomorphine or L-dopa challenges. In many cases, there was overlap between the results of PD patients and controls. The great variation in

reporting results of SPECT scan studies precludes any conclusion regarding the utility of SPECT scans in diagnosis or management of PD.

PET Scans

Eight studies, including 185 patients, 144 healthy controls, and 52 patients with other neurological disorders, evaluated the use of PET scans in PD patients. Three studies were conducted in Finland,[139, 140, 141] three in the United Kingdom,[142, 143, 144] one in the United States,[145] and one in Japan.[146] All were cross-sectional studies.

As was true with the SPECT scan studies, the studies of PET scans reported their results in inconsistent fashion. Six studies reported that [^{18}F] fluorodopa uptake was lower in the caudate and putamen nuclei of PD patients than in healthy controls.[140, 142, 143, 144, 145, 146] One study reported that PET scans of patients with PD vs. atypical parkinsonism had different amounts of caudate ^{18}F-Dopa uptake, blood flow, and glucose metabolism in the striatum,[146] while another reported that it was difficult to distinguish PD from atypical parkinsonian syndromes using PET scans.[142] Two studies evaluated presence of striatal dopamine D2 receptors in PD patients. One reported that there were increased D_2 receptors in the putamen, but not the caudate, of patients with early PD.[141] The other study reported that there were decreased D2 receptors outside the striatum in advanced, but not early, PD.[139] Further research is needed to evaluate the appropriate role of PET scans in diagnosis of PD.

Other Scans

Five studies presented results of imaging studies other than SPECT or PET scans. Three studies pertained to MRI scans,[47, 147, 148] and one study each described results of proton nuclear magnetic resonance (NMR) spectroscopy[149] and transcranial color-coded real-time sonography (TCCS).[150] All studies were performed in Europe, although the NMR study was multicentric, and included sites in the United States. All studies were of cross sectional design.

The three studies of MRI scans in PD patients all reported their results differently. One study reported shortening of T_2 relaxation times in the substantia nigra, caudate, and putamen of PD patients compared with healthy controls, but there was some overlap between PD patients and controls, and the values did not correlate with disease severity.[47] One study showed significant differences in T_2 relaxation times between healthy controls and patients who had PD for greater than ten years, but not patients who had PD for shorter durations.[148] One study comparing MRI results in patients with PD, PSP, and MSA, showed hypointense and hyperintense signal changes in the putamen of nine of the 15 MSA patients, but none of the ten PSP or 65 PD patients, suggesting that this finding effectively rules out a diagnosis of PD.[147] These results suggest that MRI may be useful to rule out conditions other than PD, but are not useful in diagnosing PD.

The study on proton NMR spectroscopy showed no significant difference between patients and healthy controls, but subgroup analyses showed differences between elderly PD patients and controls and in treated vs. untreated patients.[149] There is insufficient evidence to determine the appropriate use of proton NMR spectroscopy to diagnose PD.

One study compared the results of TCCS in PD patients vs. normal controls.[150] The substantia nigra was undetectable by TCCS in 28 of 30 controls and 13 of 30 PD patients, because its echogenicity was identical to that of the adjacent brain tissue. Some PD patients with more severe disease had increased echogenicity of the substantia nigra, but the sensitivity of this

finding was only 40 percent, while the specificity was reported as 100 percent. There is insufficent evidence to determine the appropriate use of TCCS to diagnose PD.

Clinical Diagnosis

In current practice, the diagnosis of PD is made clinically. Two studies evaluated the accuracy of clinical diagnosis in PD. In one study, 402 patients who had been diagnosed with PD by general practitioners in North Wales were examined by PD specialists, using the UKPDS Brain Bank clinical diagnostic criteria outlined in Appendix A.[151] Of the 402 patients, the diagnosis of parkinsonism was confirmed in 299 (213 with PD and 86 with possible PD or atypical parkinsonism), and 103 patients were found not to have parkinsonism (25.6 percent). The authors concluded that patients suspected of having parkinsonism should be referred early to a specialist for evaluation, given the apparent inaccuracy of clinical diagnosis by general practitioners.

There may be a measurable error rate for initial diagnosis by a specialist, as well. The 800 patients who had been involved in the Deprenyl and Tocopherol Antioxidative Therapy for Parkinson's Disease (DATATOP) study were observed for a mean of 6.0 ± 1.4 years (range 0.2 - 7.6 years).[152] Of the 800 patients who had been diagnosed by experts as having PD, 65 (8.1 percent) subsequently received an alternative diagnosis.

Color vision discrimination in PD patients was evaluated in two studies. In one study, 16 patients with previously untreated PD and 16 age-matched controls were given color vision tests.[153] The PD patients had significantly worse color vision than the controls. In the second study, color vision was tested in 19 PD patients before and after treatment with L-dopa.[154] Nine control subjects were also tested twice, without L-dopa administration. Color discrimination improved significantly in PD patients after treatment with L-dopa, and did not change in the controls. Further testing is required to determine whether color vision testing is useful in diagnosing patients with PD.

In one study, visual evoked potentials (VEPs) were measured to compare visual impairment in 12 patients with PD, 12 with MSA, and 9 healthy controls.[155] The VEP patterns between PD and MSA were significantly different, leading the authors to speculate that VEPs might be useful in distinguishing PD from MSA.

Quantification of rigidity was reported in two studies. One study evaluated a computerized elbow device to quantify rigidity in 24 PD patients and 103 age-matched controls.[156] Basal (at rest) and activated (nontest arm performing flexion and extension exercises) rigidity values in both arms were significantly higher in PD patients than controls. In PD patients, activated rigidity values were higher than basal values, but the opposite was true in controls. In a similar study, basal and activated angular impulse scores, which reflect the relationship between change in force and time, were calculated in 20 PD patients and ten controls.[157] Angular impulse scores were significantly higher in PD patients than controls, and were higher with activation in patients, but not in controls. These studies suggest that objective measures of rigidity in PD patients may be useful in diagnosing and following disease progression in PD patients. Patients with atypical parkinsonism were not included in these studies.

Blood and CSF Tests

Three studies reported results of blood tests in PD patients. Peripheral blood lymphocyte (PBL) levels of dopamine were measured in 25 PD patients and 12 healthy controls.[158] PBL dopamine levels were significantly lower in untreated PD patients than in controls, and much higher in PD patients on L-dopa. The authors concluded that measuring PBL dopamine levels might be useful in diagnosing early PD.

A prospective double blind study of ^{3}H-spiperone binding capacity to PBLs showed no significant differences in binding between patients with *de novo* PD, other parkinsonian syndromes, and healthy controls.[159]

Plasma levels of pituitary and adrenal hormones were measured in 15 untreated PD patients and 12 healthy controls.[160] Integrated levels of adrenocorticotropic hormone (ACTH), growth hormone (GH), and cortisol were significantly lower in PD patients than controls. Random prolactin (PRL) levels were nonsignificantly higher in PD patients, and nocturnal peak PRL levels were significantly higher in PD patients than controls. These results suggest abnormal pituitary function in PD patients, but do not provide useful tools for diagnostic testing in PD.

Two studies reported results of CSF analyses in PD patients. In one study, CSF somatostatin-like immunoreactivity (SLI) was measured in 15 patients with early PD, 8 with other forms of parkinsonism, and 26 controls.[161] SLI was significantly higher in patients with PD than in controls. In patients with other forms of parkinsonism, SLI levels were higher, but the difference was not significant. When the PD patients were subgrouped according to degree of memory impairment, only patients with severe memory impairment had higher levels of SLI. Another study compared the CSF and plasma carnitine levels in 29 PD patients and 29 age-matched controls, and found no significant differences between patients and controls.[162] There is insufficient evidence regarding the usefulness of testing CSF levels of somatostatin or carnitine in diagnosing PD.

Olfactory Tests

Seven studies, including 355 patients, 127 healthy controls, and 197 patients with other neurologic disorders, evaluated olfactory function in the diagnosis of PD. Two studies were performed in Japan,[163, 164] two in the United States,[165, 166] and one each in the United Kingdom,[167] France,[168] and Austria.[169] All were cross-sectional studies. All studies reported their results differently.

Three studies reported UPSIT results, but their reporting methods varied. One reported the number of PD patients with abnormal UPSIT scores (126 of 155 PD patients, or 81 percent.[167] Abnormal UPSIT scores were also reported in 11 of 72 patients with multiple sclerosis (15.3 percent), nine of 58 patients with motor neuron disease (15.5 percent), and eight of eight patients with AD (100 percent). The second study reported the bilateral UPSIT scores for 20 treated and 20 untreated PD patients compared with 20 controls.[165] Both treated and untreated patients had symmetrical significantly decreased olfactory function compared to controls. The third study[166] reported the mean UPSIT score for odor identification in 21 PD patients, 21 PSP patients, and 21 controls. The PD patients had significantly lower scores than the PSP patients or the controls.

The other studies of olfaction varied in their techniques of measurement. One study tested olfactory evoked potentials, and reported presence of olfactory dysfunction in ten of 20 PD patients, and zero of nine patients with AD.[164] One study reported the number of patients with

correct results in odor identification tests (OIT) and odor discrimination tests (ODT).[168] Thirty-seven of 80 PD patients had abnormal OIT results (46.3 percent), compared with five of 40 controls (12.5 percent). This difference was significant, but the percent of patients with abnormal ODT results did not differ significantly between PD patients and controls (28.0 vs. 16.4 percent). The authors concluded that PD patients have a defect in olfactory identification, but not in olfactory discrimination. Another study found that olfactory threshold and odor identification were significantly impaired in 21 PD patients compared with 19 controls, although there was no significant difference between the PD patients and 22 patients with AD.[169] One study compared odor detection threshold and recognition threshold, and found both to be significantly impaired in 18 PD patients compared with 10 controls.[163]

Although all of the studies of olfactory function used different methods of measurement and reporting, they all were consistent in reporting that olfactory function is impaired in PD patients compared with healthy controls. There was not as much consistency in comparing results in patients with PD vs. atypical parkinsonism; therefore, there is insufficient evidence to support olfactory function testing to be used as a diagnostic tool at this time.

PD Test Battery

Three studies, all by the same author, evaluated the usefulness of a PD test battery in diagnosing PD.[170, 171, 172] Two of these studies reported the performance of the PD test battery in PD patients,[170, 171] and one reported its performance in first degree relatives of PD patients.[172]

The PD test battery includes tests of motor function, olfaction, and depression. Results are combined in a logistic regression analysis into an equation that provides a "PD score," between 0 and 1.0. Scores ≤ 0.6 are considered to be suggestive of PD. The initial cross-sectional study, which evaluated 18 PD patients and 19 controls, showed a sensitivity of 94 percent and a specificity of 95 percent. The tests were then performed in a "validation group" of 103 PD patients and 122 controls, and the sensitivity and specificity decreased to 69 and 88 percent, respectively.[170]

In a subsequent publication, the same authors performed the PD test battery on 205 patients with undiagnosed neurological conditions, and then followed the patients for at least one year, until they were diagnosed with a specific neurologic disease or determined to be neurologically normal.[171] Fifty-nine of the 205 patients were subsequently diagnosed with PD, 106 with other neurologic diagnoses, and 40 were neurologically normal. Forty of the 59 PD patients had a PD test battery score consistent with the diagnosis of PD, and 37 of the 40 neurologically normal patients had a PD test battery score in the normal range. The authors reported that the test battery showed a sensitivity of 92 percent and a specificity of 68 percent, although they did not account for the 106 patients with other neurological diagnoses. These results are not adequate to consider the PD test battery to be the reference standard for PD diagnosis.

In one study, the PD test battery was administered to 78 asymptomatic first degree relatives of PD patients and 100 healthy controls.[172] Eighteen of the 78 relatives and nine of the normal controls had abnormal PD test battery scores. These subjects would need to be followed over time to determine the predictive value of the test battery in asymptomatic people.

Autopsy

Six studies, including 253 patients with PD, 124 patients with other neurological disorders, and 76 controls without neurological disorders, reported results of autopsy data. Two of the studies were conducted in Canada,[44, 173] two in the United States,[174, 175] one in the United Kingdom,[42] and one was multinational.[176]

A commonly cited statistic is that up to 25 percent of patients with clinical diagnoses of PD are found to have different pathological diagnoses at autopsy. This stems from a study in which the brains from one hundred consecutive patients with clinically diagnosed PD were collected from sites within the United Kingdom, between 1987 and 1990.[42] Neurologists had prospectively diagnosed the patients with PD. Autopsies of all 100 brains showed that 76 of the brains had a pathological diagnosis of PD, and 24 had been clinically misdiagnosed. The misdiagnoses included PSP, AD, MSA, vascular disease, isolated nigral atrophy without Lewy bodies, postencephalitic parkinsonism, and one case without abnormal findings. The authors then evaluated the sensitivity and specificity of various clinical manifestations of PD. If patients were required to have two of the three cardinal signs of PD for diagnosis (resting tremor, cogwheel rigidity, and bradykinesia), the sensitivity of clinical assessment was 99 percent, but the specificity was only eight percent. If they were required to have all three cardinal signs, the sensitivity decreased to 65 percent, but the specificity increased to 71 percent.

Another study reviewed autopsy results in 59 patients who had been clinically diagnosed with parkinsonian syndromes over a 22-year period.[44] The initial clinical diagnosis was PD in 43 patients, and decreased to 41 patients in the final diagnosis. The diagnosis of PD was confirmed by autopsy in 28 of the 43 patients with an initial diagnosis of PD (65 percent) and 31 of the 41 patients with a final clinical diagnosis of PD (76 percent). The remaining pathological diagnoses included MSA, PSP, neurofibrillary tangle parkinsonism, drug-induced parkinsonism, substantia nigra cell loss without inclusions, and Jakob-Creutzfeldt's disease. The authors concluded that the clinical diagnosis of PD is more accurate in patients who have been affected for more than five years.

One study retrospectively reviewed clinical data on 34 patients with a pathologic diagnosis of PD, and 31 patients with a pathologic diagnosis of diffuse Lewy body disease (DLBD).[175] Significant differences between the two conditions included older mean age of onset and presence of myoclonus for DLBD patients, and presence of rest tremor and clinical response to L-dopa in PD patients.

A retrospective chart review for history of falling was performed in 77 patients with autopsy-confirmed diagnoses of parkinsonian disorders.[176] Only 11 of these patients had PD; the remainder had PSP, MSA, DLBD, or corticobasal degeneration (CBD). The frequency of recurrent falls was similar in all groups, but falls occurring at the onset of parkinsonian symptoms were common in PSP and absent in PD and DLBD. These results suggest that it may be important to include questions about falling when taking a history in patients with suspected PD, in order to rule out atypical parkinsonism.

One study sought to show the absence of resting tremor in a large proportion of PD patients; however, the opposite result was noted.[173] The authors reviewed clinical data from 22 years of observation in 47 patients with pathologically-confirmed parkinsonism, of which 30 had a pathological diagnosis of PD. All 30 patients had been noted to have resting tremor at some point during their disease (100 percent), while only six of the 17 patients with other forms of parkinsonism had a history of resting tremor (35 percent). This suggests that most patients with

PD have rest tremor at some point during the course of PD, while this may not be the case for patients with alternative diagnoses.

Interrater reliability for diagnosing PD was tested in a clinicopathologic study.[174] Six neurologists analyzed 105 clinical scenarios of patients with diagnoses blinded: PD (n=15), DLBD (n=14), or neither (n=76). Diagnoses had been confirmed by autopsy. The neurologists reviewed the clinical vignettes extracted from records of the patients' first and last clinic visits. For each patient, the neurologists gave an initial impression, based on clinical judgment after the first visit, without laboratory or neuroimaging data, and a final diagnosis, based on all information available at the last clinic visit. The median sensitivity and specificity of clinical diagnosis of PD at the first visit were 73.3 (range 53.5-80.0) and 85.6 (range 74.4-94.4) percent, respectively. At the last visit, these values increased to 80.0 (range 60.0-86.6) and 92.2 (range 82.2-96.7) percent. The median positive predictive value (PPV) increased from 45.9 (range 34.2 to 61.5) percent at the first visit to 64.0 (range 42.8-75.0) percent at the last visit. The median negative predictive value (NPV) was over 95 percent at both visits. The authors concluded that the low PPV and relatively high sensitivity suggest overdiagnosis of PD by neurologists.

In summary, the autopsy studies showed clinical diagnosis of PD to have a modest degree of accuracy, which may be improved by following patients over time. Aside from autopsy, there is insufficient evidence that any diagnostic tests have sufficient sensitivity or specificity to qualify as reference standards for the diagnosis of PD.

Pharmacological Treatment of PD

Forty-nine parent studies, composed of 111 treatment arms and 9,968 patients, were accepted for the pharmacological treatment section of this project (See Evidence Table 2). Twenty-six were graded as level I evidence, and 23 were Level II. None were Level III-V. The mean quality score was 3.6 (where 5 is best), and the median was 4, suggesting moderate to high validity of studies in this set.

The mean age of all patients in pharmacological treatment groups was 63.0 years (t=97, n=8,605, range 55.4-80.0 years). As shown in Evidence Table 3, gender was reported in 36 studies (t=82, n=7,774); 59.6 percent of patients were male and 40.4 percent were female. Race was reported in only two studies, and the vast majority of patients in these two studies were Caucasian.[66, 177]

The mean disease duration of all patients in pharmacological treatment groups that reported this parameter was 5.0 years (t=84, n=6,369, range 0.6 –13.6 years). Disease duration was distributed as follows: 23 treatment arms reported a mean disease duration of < 2 years, 26 reported 2-5 years, 14 reported 5-10 years, and 21 reported ≥ 10 years.

Seven studies reported "on" UPDRS scores only,[66, 178 - 183] two reported both "off" and "on" scores,[184, 185] one reported the average of "off" and "on" scores.[186] The remainder did not specify whether their UPDRS scores were "off" or "on."

Studies were divided into early or advanced PD, based on the study authors' classification or disease characteristics reported in the studies. Thirty-two studies (t=74, n=7,405) that referred to patients as having "early" or "*de novo*" PD, or mean disease duration < 5 years were classified as early. Seventeen studies (t=37, n=2,563) that reported patients with "advanced" PD, mean disease duration > 5 years, or patients who suffered from fluctuations and dyskinesias due to long-term L-dopa treatment were classified as advanced. It must be recognized that this categorization has limitations. Disease duration is useful in classifying individual patients as

having early vs. advanced disease, but mean disease duration of < 5 years does not mean that all patients have short disease duration. Studies that reported mean disease duration did not always report the range of disease duration in the individual patients.

Motor fluctuations are typically seen in patients with advanced PD; however some studies in which the patients were identified as having "early" PD reported motor fluctuations and "off" times. Given these limitations, three of the 32 studies that were classified as early,[187, 188, 189] and five of the 17 studies that were classified as advanced[185, 190, 192, 193, 194] may have actually contained mixed populations of patients with early and advanced disease.

Numbers of treatment arms with each treatment combination are shown in Evidence Table 5. Determining the number of studies in which L-dopa was used was problematic, because some studies used L-dopa as a comparator drug, while others merely allowed investigators to give patients L-dopa as needed. This was further complicated by the fact that in the studies where L-dopa was discretionary, the number of patients who received L-dopa, and their dosage of L-dopa, was frequently not reported. In 41 treatment arms (n=3,927), L-dopa was the only anti-Parkinson drug prescribed. These include treatment arms that were labeled as placebo arms, but patients received L-dopa as needed.

In studies of patients with early PD, it was often difficult to ascertain whether or not patients had previously taken L-dopa. This is important to distinguish, because it may be assumed that patients who never received L-dopa have less severe PD symptoms than patients who had received L-dopa. In 12 studies, inclusion criteria required that patients had never received L-dopa prior to study entry.[119, 180, 195 - 204] In 15 studies, some patients may have received L-dopa prior to study entrance, but it was not always possible to ascertain which patients had been on L-dopa.[65, 66, 82, 178, 181, 188, 205 - 213] In five studies of patients with early PD,[187, 189, 214, 215, 216] and all 17 studies of patients with advanced PD, all patients were on L-dopa prior to study enrollment.

As shown in Evidence Table 5, treatment with DAs alone was reported in six treatment arms (n=508), MAO-B inhibitors alone in five treatment arms (n=336), and placebo alone in four treatment arms (n=374). The small number of pure placebo arms is due to the fact that most placebo groups in the pharmacological literature are groups in which patients received both active drug and placebo.

L-dopa was combined with DAs in 33 treatment arms (n=2,935), with MAO-B inhibitors in seven treatment arms (n=700), and with COMT inhibitors in eight treatment arms (n=639). Seven treatment arms contained other combinations, including L-dopa/DA/MAO-B inhibitor (t=2, n=68), DA/MAO-B inhibitor (t=1, n=10), α-dihydroergocryptine (α-DHEC; t=1, n=62), α-DHEC and L-dopa (t=1, n=10), L-dopa/vitamin E (t=1, n=202), and L-dopa/vitamin E/MAO-B inhibitor (t=1, n=197). No studies of amantadine or anticholinergic medications met the criteria for inclusion into this systematic review.

Rejected pharmacological studies of interest that were not accepted for this review, but were deemed to be of interest by the TEP, are discussed in Appendix J. These studies were rejected mainly due to publication date prior to 1990, inadequate study duration, or cross-over design, and include studies of anticholinergic medications, pramipexole, pergolide, tolcapone, selegiline, and GM1 ganglioside.

Pharmacological Treatment: Early PD

The 32 studies that focused on patients with early PD consisted of 74 treatment groups and 7,405 patients. There were 58.4 percent males and 41.6 percent females (t=59, n=5,670). Mean

age, weighted by sample size, was 62.6 years, and ranged from 55.4 to 80 years (t=68, n=6,969). Mean disease duration, weighted by sample size, was 2.3 years, and ranged from 0.6 to 4.2 years (t=53, n=4,015).

The studies that were classified as describing patients with early PD included:

- ten studies of bromocriptine (with or without L-dopa) vs. L-dopa[188, 195, 199, 204, 205, 209, 214, 215, 216]
- one study comparing two different doses of bromocriptine[119]
- two studies comparing different formulations of L-dopa[197, 198]
- four studies of selegeline plus L-dopa vs. L-dopa alone[181, 207, 210]
- one study of bromocriptine vs. selegiline plus L-dopa vs. L-dopa alone vs. selegiline plus bromocripine[208]
- two studies of selegeline vs. placebo[200, 202]
- two studies of ropinerole plus L-dopa vs. L-dopa alone[65, 212]
- one study of ropinerole plus L-dopa vs. bromocriptine plus L-dopa[206]
- one study of pramipexole vs. placebo[213]
- one study of pramipexole plus L-dopa vs. L-dopa[66]
- one study of cabergoline plus L-dopa vs. L-dopa alone[203]
- one study of lisuride plus selegeline vs. lisuride alone[201]
- one study of pergolide plus L-dopa vs. L-dopa alone[180]
- one study of lisuride plus L-dopa vs. L-dopa alone[178]
- one study of L-dopa alone vs. tocopherol plus L-dopa vs. selegeline plus L-dopa vs. selegeline, tocopherol, and L-dopa[82]
- one study comparing four doses of lazabemide vs. placebo[211]
- one study of L-dopa vs two doses of tolcapone plus L-dopa[189]
- one study of α-dihydroergocryptine (ADHEC) vs. placebo[196]
- one study of ADHEC plus L-dopa vs. L-dopa[187]

Pharmacological Treatment: Advanced PD

The 17 studies that focused on patients with advanced PD consisted of 37 treatment groups and 2,563 patients. There were 62.7 percent males and 37.3 percent females (t=23, n=2,104). Mean age, weighted by sample size, was 64.0 years, and ranged from 56.0 to 75.8 years (t=29, n=2,232). Mean disease duration, weighted by sample size, was 9.6 years, and ranged from 5.5 to 13.6 years (t=31, n=2,354).

The studies that were classified as describing patients with advanced PD included:

- one study comparing two doses of bromocriptine plus L-dopa[192]
- two studies of cabergoline plus L-dopa vs. placebo plus L-dopa[185, 190]
- one study of cabergoline plus L-dopa vs. bromocriptine plus L-dopa[191]
- two studies comparing different preparations of L-dopa[194, 217]
- two studies comparing pramipexole plus L-dopa vs. placebo plus L-dopa[182, 184]
- one study comparing pramipexole plus L-dopa vs. bromocriptine plus L-dopa vs. placebo plus L-dopa[186]
- one study comparing lisuride vs apomorphine[218]
- one study comparing lisuride plus L-dopa vs L-dopa alone[193]
- one study comparing pergolide plus L-dopa vs. placebo plus L-dopa[183]
- one study comparing ropinirole plus L-dopa vs. placebo plus L-dopa[219]
- two studies comparing entcapone plus L-dopa vs. placebo plus L-dopa[177, 220]
- two studies comparing tolcapone plus L-dopa vs. placebo plus L-dopa[86, 179]

Pharmacological Treatment of PD: Meta-analyses

Meta-analysis of DAs (plus L-dopa) vs. L-dopa alone. As shown in Evidence Table 6, seventeen studies provided sufficient data on one of the PD rating scales to calculate standardized mean differences between the pre-test/post-test change scores for a DA + L-dopa group and the pre-test/post-test change scores for an L-dopa group.[65, 66, 178, 180, 182, 183, 185, 188, 190, 193, 195, 203, 208, 209, 212, 215, 216] Six studies investigated the effect of a DA+L-dopa versus L-dopa alone, but did not report enough data to allow the calculation of a pre-post effect size.[184, 199, 204, 205, 214, 219]

Three of the studies in the meta-analysis examined patients naïve to L-dopa before the trial (all were studies of patients with early disease),[180, 195, 203] seven of the studies examined patients with a mix of previous exposure to L-dopa (all early disease studies),[65, 66, 178, 188, 208, 209, 212] and seven of the studies examined patients that were all previously exposed to L-dopa (all but two were studies of patients with advanced disease).[182, 183, 185, 190, 193, 215, 216]
Twelve of the studies in the meta-analysis examined treatment arms of patients with mean disease duration ≤ five years (i.e., early disease),[65, 66, 178, 180, 188, 195, 203, 208, 209, 212, 215, 216] and five studies examined treatment arms of patients with mean disease duration greater than five years (i.e., advanced disease).[182, 183, 185, 190, 193] Six studies investigated bromocriptine,[188, 195, 208, 209, 215, 216] while no other agonist was investigated more than three times.

In 11 of the studies in the meta-analyses, L-dopa was mandatory (i.e., patients were randomized to receive L-dopa or L-dopa plus a DA),[178, 182, 183, 185, 188, 190, 193, 195, 209, 215, 216] and in five studies, the L-dopa was discretionary (i.e., patients were randomized to receive L-dopa or a DA, but L-dopa could be added at the practioner's discretion).[65, 66, 180, 203, 208]

A meta-analysis of differences between change in PD scores was performed. Figure 3 shows point estimates and 95 percent confidence interval error bars for the individual studies.

A fixed-effects meta-analysis showed that the change-score effect sizes (CHESs) were heterogeneous after sampling error was taken into account ($Q_E = 87.95$, $p<0.001$). A random-effects model led to slightly positive but only marginally statistically significant effect for treatment with a DA + L-dopa versus L-dopa alone ($\hat{\delta} = 0.16$, SE($\hat{\delta}$) = 0.09), where $\hat{\delta}$ represents the estimate of the mean effect size and SE ($\hat{\delta}$) represents its standard error. The 95 percent confidence intervals for this estimate are presented in Figure 3.

Given the presence of considerable heterogeneity, examination of study characteristics was warranted; however, multivariate analysis was made difficult by the presence of collinearity between the numerous predictors and the low number of studies. For instance, there was a strong relationship between stage of disease (early vs. advanced) and previous exposure to L-dopa. There was also a strong (yet unexplained) correlation between stage of disease and whether the DA investigated was bromocriptine; there were no studies in which bromocriptine was used and patients had a long disease duration. To simplify interpretation, univariate analyses for each study characteristic were conducted.

There were two study characteristics that were statistically significant: time of evaluation (p=0.009) and type of L-dopa delivery (p<0.001) (discretionary vs. mandatory). Studies with a duration of greater than one year had significantly lower effect sizes than studies with a duration of less than one year; studies with discretionary L-dopa delivery had significantly lower effect sizes than studies in which L-dopa delivery was mandatory in the dopamine agonist arm.

These findings suggest two different mechanisms at work. The first suggests that the effect of treatment with a DA+L-dopa, relative to L-dopa alone, may decline over time. The latter suggests that treatment which mandates L-dopa as an adjunct to a DA controls PD symptoms better than treatment which merely allows doctors to give L-dopa when they think it might be needed.

While the mechanisms are different, their individual impacts cannot be measured in this meta-analysis; these two variables were highly correlated (r=.60, p=.015), making it very difficult to separate their respective influences. Among the studies in which L-dopa delivery was mandatory, there was a mix of short- and long-term study durations; however, when L-dopa delivery was discretionary, the only studies present were long-term ones.

Meta-analyses within each level of each key study characteristic (e.g., a meta-analysis of studies with short disease duration, a meta-analysis of studies with long disease duration, a meta-analysis of studies with *de novo* patients, etc.) are presented in Figure 3. Studies in which the DA used was bromocriptine had a higher average effect size than those in which another DA was investigated. Studies of patients with advanced PD had a higher average effect size than those with patients with early PD, and studies with non-*de novo* patients had a higher average effect size than studies with *de novo* patients or patients with a mixed background. However, none of these differences were statistically significant.

Two groups of sensitivity analyses were conducted. In the first, three design characteristics (whether LOCF measurements were used, whether the study was blinded, and whether the study effect was known to be "on" or whether it was merely assumed to be "on") were investigated univariately. None were close to being statistically significant (p>0.30 for each). In the second group of sensitivity analyses, re-analyses of the data were conducted to determine whether any particularly large or small effect sizes were having an unbalancing effect on the overall results. The first set of re-analyses deleted the largest effect size from one study,[215] and the second set deleted the smallest effect size from a different study.[65] All meta-regressions using the new subsets of studies found substantively what the initial meta-regressions found: a significant negative effect for treatment duration, suggesting that DAs work better in studies of short duration.

There were three studies in which head-to-head comparisons between bromocriptine and other DAs were performed. The comparator drugs were cabergoline,[191] ropinirole,[206] and pramipexole.[186] All studies used L-dopa as a supplementary treatment. Two studies were in patients with advanced disease[186, 191] and one in patients with early disase.[206] Effect size could only be calculated for two of the studies. The average effect size (positive indicating that bromocriptine performed better) was not significantly different from zero.

Conclusions of DA+L-dopa vs. L-dopa meta-analyses. There is no evidence that different DAs vary in treatment effects. Meta-analysis suggests that in early PD, treatment with DAs plus L-dopa may control PD symptoms better than treatment with L-dopa alone, but this was not a consistent finding. However, given the wide heterogeneity in this small group of studies in type of treatment, focus of treatment, duration of treatment, and patient characteristics, it would be very difficult to detect such effects if they indeed existed.

Meta-analysis of selegiline (plus L-dopa) vs. L-dopa alone. Evidence Table 7 shows the three studies that compared the effect of selegiline and L-dopa versus the effect of L-dopa alone in patients with early PD.[181, 207, 208] All studies looked at patients with short disease duration. Figure 4 shows point estimates and 95 percent confidence interval error bars for the individual studies, as well as for the overall meta-analysis.

A fixed-effects meta-analysis showed that the CHESs were heterogeneous (Q_E = 11.79, p=0.003). A random-effects model led to a moderate sized estimate of mean effect that was statistically insignificant ($\hat{\delta}$ = 0.47, SE($\hat{\delta}$) = 0.25). Due to the small numbers of studies involved, reliable examination of the impact of study characteristics on treatment efficacy and sensitivity analysis were not possible.

Conclusions of Selegiline+L-dopa vs. L-dopa meta-analyses. While there is some evidence to suggest that selegiline + L-dopa may work better than L-dopa alone in controlling symptoms of PD, the difference between the two therapies in efficacy in controlling PD symptoms was statistically insignificant. However, the power to detect a difference between these two therapies was very small given the low number of studies involved and the wide variation between them.

Studies not included in selegiline meta-analysis. One study investigated the efficacy of the MAO-B inhibitor lazabemide relative to the efficacy of a placebo (as opposed to an L-dopa treatment).[211] The average lazabemide effect was 0.302 (p<0.05), suggesting that lazabemide performed somewhat better than placebo. Two studies examined the effect of selegiline versus the efficacy of placebo.[200, 202] In these placebo-controlled trials, the primary efficacy outcome was time until L-dopa treatment was required. In both cases, patients in the placebo arms needed L-dopa sooner than patients in the selegiline treatment arms.

In the DATATOP study, 800 patients with early PD were randomized to receive selegiline, vitamin E, the combination, or placebo.[82] The primary endpoint was the time when L-dopa was required. Selegiline significantly delayed the L-dopa requirement, while vitamin E showed no evidence of benefit. This study could not be included in the meta-analysis because UPDRS scores at uniform time points prior to starting L-dopa were not available in the published literature.

Meta-analysis of COMT-inhibitors (plus L-dopa) vs. L-dopa alone. Five studies compared the effect of COMT inhibitors with L-dopa versus the effect of L-dopa alone in patients with PD.[86, 177, 179,189, 220] Except for one study,[189] all were in the setting of advanced disease. As shown in Evidence Table 8, three of the studies provided a pair of effects (each for a different dose of tolcapone: 100mg and 200mg). The remaining two studies investigated entacapone as a treatment. A total of six of the eight study arms investigated patients with disease duration of > 10 years. Figure 5 shows point estimates and 95 percent confidence interval error bars for the individual studies, as well as for the overall meta-analysis.

The fixed-effects meta-analysis of CHESs were homogeneous (Q_E = 5.32, p=0.62). The estimate of the mean was 0.33 (SE($\hat{\delta}$) = 0.056), which was statistically significantly greater than zero (p<0.001). Error bars for each meta-analysis are presented in Figure 5.

There was little variance on most of the study characteristics, making the investigation of the impact of study duration, severity of disease, and baseline exposure of patients to L-dopa difficult. It is likely that this minimal variation in study characteristics contributed to the reason that the effect sizes were so homogenous. There was no statistically significant difference between the effect sizes of the three 100 mg tolcapone arms and the three 200 mg tolcapone arms (p>0.50), and no statistically significant difference between the effect sizes of the two arms in which average disease duration was less than five years and the six arms in which average disease duration was greater than ten years (p=0.25).

The significantly positive mean CHES for the COMT inhibitors remained significantly positive after the largest change-score effect was deleted (p<0.001).

Conclusions of COMT+L-dopa vs. L-dopa meta-analyses. Unlike the meta-analyses of the DAs and selegiline, the studies in the meta-analysis of treatment with COMT were very homogeneous with regard to disease duration, treatment duration, and baseline exposure of

patients to L-dopa. It is likely that this led to the consistent moderately positive effect for COMT + L-dopa versus L-dopa. It can safely be concluded that in the short term (≤ seven months), patients with advanced PD who receive combination treatment with COMT and L-dopa can expect a reduction in PD symptoms substantively greater than similar patients who are treated with L-dopa alone. Most of the studies examined the COMT inhibitor tolcapone; however, there was no evidence that tolcapone treatment was better or worse than treatment with entcapone. Also, there was no evidence that treatment with 200mg of tolcapone alleviated symptoms more than treatment with 100mg of tolcapone.

Due to reports of hepatotoxicity associated with tolcapone, the three tolcapone studies were reviewed for mention of hepatotoxicity.[86, 179, 189] Of the 451 patients taking tolcapone, 16 patients were reported to have transient elevations in LFTs (3.5 percent), leading to withdrawal of six patients from the three studies (1.3 percent). Of the 227 patients on the lower dose of tolcapone (100 mg per day), seven patients had reports of elevated LFTs (3.1 percent), and one patient withdrew from the study (0.4 percent). Of the 224 patients on the higher dose of tolcapone (200 mg per day), nine patients had reports of elevated LFTs (4.0 percent), and five patients withdrew from the studies (2.2 percent). All of the COMT studies had a duration of seven months or less; therefore, no conclusions may be made regarding long-term safety.

Pharmacological Treatment of PD: On-Off Time

"On" and "off" time were captured, when reported, but these results were not amenable to meta-analysis because they were reported in non-standardized ways. While motor fluctuation assessment is an important component of determining optimal treatment of PD, the variation in methods of reporting this parameter precluded pooling results from different studies.

Pharmacological Treatment of PD: L-Dopa Doses

When L-dopa is used in combination with another drug to treat PD, one measure of efficacy is the dose of L-dopa required by patients on combination therapy. Where both baseline and outcome mean L-dopa doses were reported, the L-dopa doses prior to and after treatment were compared. In studies comparing DAs plus L-dopa to L-dopa alone, the mean daily L-dopa dose in the DA/L-dopa arms decreased from 624.7 mg (range 250.0 - 1,305.8) to 488.5 mg (range 136.0 – 940.4), whereas in the L-dopa monotherapy arms, the mean L-dopa dose decreased minimally, from 608.8 (range 242.7-940.4) to 594.0 mg (range 306.0 – 889.0).

In studies comparing COMT inhibitors plus L-dopa to L-dopa alone, the mean daily L-dopa dose in the COMT inhibitor/L-dopa arms decreased from 621.6 (range 270.6 – 865.8) to 514.8 mg (range 249.8 – 658.7), whereas in the L-dopa monotherapy arms, the mean daily L-dopa dose increased from 669.5 (range 364.3 – 948.0) to 681.9 mg (range 410.9 – 963.5).

In studies comparing selegiline plus L-dopa to L-dopa alone, many of the patients were not on L-dopa prior to the study. Therefore, the mean baseline dose of L-dopa is not available, but after treatment, the mean daily L-dopa dose in the selegiline/L-dopa arms was 388.0 mg (range 356.0 – 424.0), while in the L-dopa monotherapy group, it was 478.5 mg (range 426.0 – 543.0). All of these results suggest that combination therapy has greater efficacy than L-dopa alone in lowering L-dopa doses.

Pharmacological Treatment of PD: Dyskinesia Scores

While dyskinesia scores are of interest, particularly in patients with advanced PD, they could not be analyzed because only two pharmacologic studies reported dyskinesia scores.[191, 193] Other studies described dyskinesias in a more qualitative fashion, which did not allow for evaluation with meta-analytic methods.

Pharmacological Treatment of PD: Safety

Heterogeneity in methods of reporting safety outcomes leads to imprecision in summarizing data from multiple studies. Some studies reported safety outcomes in terms of numbers of patients, while others reported numbers of adverse events (AEs). These values are not interchangeable, as one patient may suffer more than one event. Other studies reported only the most common or the most severe events. Numbers of AEs are also affected by the aggressiveness of the methods by which the investigators identify events. If investigators specifically ask about a particular AE (i.e., active monitoring), they are more likely to discover it than if they wait for patients to volunteer the information (i.e., passive monitoring).

For the purposes of this summary data, only AEs reported in terms of numbers of patients (not events) have been captured, except when zero or one event was reported, in which case zero or one patient was substituted, respectively.

The number of deaths, withdrawals, and most common AEs, classified by body system, are listed in Evidence Table 9. While withdrawals occurred more commonly for issues of safety rather than lack of efficacy, no studies reported treatment-related deaths. The table lists the most common or clinically important AEs, but is by no means comprehensive.

Due to the frequency and clinical relevance of neurological and psychiatric AEs, these have been reported separately, along with the incidence of the most common neurological and psychiatric symptoms (Evidence Table 10). Overall, the most common neurological AEs reported were aggravation of PD, dyskinesias, and akinesia. Sleeping disorders were the most commonly reported psychiatric AEs reported. Gastrointestinal AEs were the most common non-neurological, non-psychiatric AEs reported. As L-dopa was given concomitantly in most groups, it is difficult to separate the L-dopa AEs from those caused by other drugs.

Dizziness was more common in advanced than early disease (incidence 22.5 vs. 17.4 percent), as was dyskinesia (incidence 35.3 vs. 17.7 percent) and PD aggravation (33.7 vs. 15.4 percent). Thus, while efficacy did not differ between early and advanced disease, AEs were much more frequent in treatment groups of patients with advanced disease.

Surgical Treatment of PD

There were 42 parent and 16 kin studies concerning surgical treatment, encompassing 52 treatment arms and 1,380 patients (See Evidence Table 2).

The vast majority of studies were UCSs (k=35, n=1,145), and the remainder were RCTs (k=4, t=8, n=105), nRCTs (k=2, t=7, n=117), and one case-control retrospective study (t=2, n=13). Thirty-eight of the studies were graded as level III evidence, and four were level II. Quality score could be calculated only for the four RCTs, and was a mean of 3, reflecting moderate quality.

As shown in Evidence Table 3, gender was reported in 32 of the 42 surgery studies (t=40, n=891). There were 573 males (64.3 percent) and 318 females (35.7 percent). Mean age was reported in 41 studies (t=51, n=1,336). The mean age, weighted by sample size, was 60.8 years, with a range of 46.5 to 73.3 years. In 41 treatment arms, mean age was reported to be < 65, and ten treatment arms reported a mean age of ≥ 65, suggesting that younger patients tended to be enrolled in surgery trials. Disease duration was reported in 34 studies (t=43, n=1,058). The mean disease duration was 12.8 years, and ranged from 4.8 to 17.5 years. This was not unexpected, given that surgery is generally not performed until patients have become intolerant to medical therapy. Mean age of disease onset was reported in six treatment arms; three reported mean age of disease onset ≥ 50 years (n=102), and three reported mean age of disease onset < 50 years (n=49).

Treatment level characteristics of surgical studies are summarized in Evidence Table 11. Pallidotomy was evaluated in 20 treatment arms (n=764), thalamotomy in five treatment arms (n=134), DBS in 16 treatment arms (n=288), and tissue transplant in nine treatment arms (n=165). No surgery was performed on patients in two treatment arms (n=29).

Thirteen studies reported dyskinesia scores (t=16, n=426). This is an important outcome to assess in surgical patients, because patients commonly undergo surgery to reduce medication complications, such as dyskinesias. As dyskinesia is a medication side effect, dyskinesia scale results are reported in the "on" state. Pooling of these scales across studies is problematic, because studies reported different variations of the scales, the scales were not always defined, and standard deviations were generally not reported. Nearly all treatment arms showed improvement in mean dyskinesia scores, particularly contralateral scores, after surgery.

Scores that were reported less frequently include Beck Depression Inventory (BDI; t=4, n=62), postural instability and gait disturbances (PIGD; t=3, n=102), Perdue Pegboard Test (t=2, n=46), and Webster Score (t=1, n=12).

Two studies included concurrent control groups of patients who did not undergo surgery (n=29).[221, 222] In both of these control groups, baseline UPDRS scores were lower (better) than post-study scores, the opposite pattern from that seen in all surgical groups, suggesting that patients who did not undergo surgery deteriorated clinically.

Timing of post-surgical evaluation may affect results, and may give an indication of duration of postoperative benefit. Approximately half of the surgical treatment arms reported results at less than one year, and the other half reported results at greater than one year. No consistent pattern emerged in comparing earlier vs. later results.

"On-off" time was of interest, because surgical patients have advanced PD, where motor fluctuations are particularly problematic; however, it was only reported in ten studies, using inconsistent methods of measuring this phenomenon.

Pallidotomy

Results of pallidotomy were reported in 20 treatment arms (n=764).[221-240] There were 16 treatment arms in which patients underwent unilateral procedures (n=491) and four in which patients underwent a mixture of unilateral and bilateral procedures (n=273; 107 were bilateral procedures).[222, 228, 230, 240] Of the four studies that included results on patients with bilateral pallidotomies, two did not distinguish the results of the patients with unilateral vs. bilateral procedures,[228, 240] one reported that there was no difference in outcome between the patients with

unilateral and bilateral procedures,[230] and one reported that the patients who underwent bilateral procedures had symptoms of greater severity prior to the pallidotomies, and did not improve significantly after the procedures.[222]

Mean L-dopa dose in the nine pallidotomy studies that reported both baseline and outcome doses did not change significantly. The mean dose at baseline was 923.8 mg (range 545 – 1,125), and at endpoint was 921.6 mg (range 627 – 1,174).

Five pallidotomy studies reported "on-off" time. One study reported the number of patients with shorter "off" periods,[224] one study reported the mean "off" time,[228] one reported the number of patients whose "off" time improved, worsened, or was unchanged,[234] one reported the percent of hours "on" and "off,"[231] and one used a study-specific scale, which was not defined.[230] These results could not be pooled in a meaningful way, but all of these studies reported overall improvement in this parameter.

Thalamotomy

Thalamotomy was described in five treatment arms (n=134), [100, 222, 241, 242, 243] the vast majority of which were unilateral procedures. Most studies of thalamotomy were published prior to 1990; therefore, this database, with its search cut-off date of 1990, contains limited information regarding this procedure.

Very few treatment arms reported UPDRS, S&E, or H&Y scores in thalamotomy studies, and only one reported both preoperative and postoperative scores. The low number of studies that reported these parameters prevents any conclusion about the efficacy of thalamotomy to be drawn based on PD rating scales. All studies, however, reported overall improvement in tremor.

Deep Brain Stimulation

DBS was reported in 16 treatment arms (n=288), including stimulation of subthalamic nuclei (STN; t=8, n=135), [244 - 250] globus pallidus (GPi, t=4, n=22), [244, 246, 248] and thalamic nuclei (t=4, n=131). [100, 251, 252 ,253]

L-dopa doses decreased significantly after DBS: from a baseline daily mean of 1,018.8 mg (range 442 – 1,560 mg) to an endpoint mean of 455.2 mg (range 262 – 1,110 mg) per day. When the DBS studies were divided by nucleus location, the mean daily L-dopa dose decreased from 1,208.5 mg (range 729 – 1,560 mg) to 555.3 mg (range 262 – 850 mg) in the STN DBS groups (t=8), and increased from 863.0 mg (range 856 – 870 mg) to 1006.5 mg (range 903 – 1,110 mg) in the GPi DBS groups (t=2). Mean pre- and post-DBS L-dopa doses in the thalamic DBS groups were only reported in one study, and decreased slightly, from 649 to 610 mg per day.

Five DBS treatment arms reported mean dyskinesia scores, which improved after surgery in all cases.[246-250] One STN study reported transient exacerbation of dyskinesias in the first postoperative weeks, which resolved with decreasing the dose of L-dopa and increasing the voltage of the stimulation.[248]

Tissue Transplants

Cell transplants were described in nine treatment arms (n=165), and included three groups of adrenal medulla transplants (n=91),[254, 255, 256] five groups of human fetal brain cell transplants (n=62),[257 - 260] and one group of porcine fetal brain cell transplants (n=12).[261] Results from the

studies of adrenal transplantation[254, 255, 256] are not addressed in this report, as this procedure is no longer performed in PD patients, due to lack of efficacy and substantial morbidity.[97] Due to the small number of transplant studies, drawing conclusions regarding the efficacy of transplantation is problematic. One important study that was published too late to meet the inclusion criteria for this systematic review was an RCT comparing the outcomes of human embryonic tissue transplantation to sham surgery.[103] Some clinical improvement was noted in patients ≤ 60 years of age, but not in older patients. This study, which was notable for the development of late dystonias and dyskinesias in the active treatment arm, is discussed in detail in Appendix J.

Surgical Treatment: Meta-analyses

Pallidotomy. Fifteen pallidotomy treatment arms provided sufficient pre-post data on any of the PD rating scales to calculate pre-post standardized mean differences for "off" scores, and 12 treatment arms provided sufficient pre-post data to calculate standardized mean differences for "on" scores (Evidence Table 12). Figures 6 and 7 show point estimates and 95 percent confidence interval error bars for the individual study effect sizes for "off" and "on" scores, respectively.

Meta-analyses - "Off" effects. A fixed-effects meta-analysis showed that the "off" effect sizes were heterogeneous (Q_E = 37.94, p<0.001). A random-effects model suggested that pallidotomy is effective in reducing "off" scores ($\hat{\delta}$=0.77, SE($\hat{\delta}$) = 0.12). Given the heterogeneity of effects, examination of study characteristics was warranted. Univariate meta-regressions were conducted which investigated three study characteristics: time since surgery (≤ one year vs. > one year), average age of the participants, and average patient H&Y score at baseline. No predictors were statistically significant, although there was a marginally significant (p=0.095) effect for time since surgery; the estimated effect size of pallidotomy on PD scale scores was 0.87 in studies with a duration of one year or less, and 0.36 in studies with a duration greater than one year. This suggests that pallidotomy may be effective mainly for the first year, but the number of long-term studies is too limited to make more than a tentative conclusion. The 95 percent confidence intervals for estimates of the mean effect size are in Figure 6.

Meta-analyses - "On" effects. A fixed-effects meta-analysis showed that the "on" effect sizes seemed homogeneous (Q_E = 11.18, p=0.43). As mentioned previously, our rule was to use a random-effects model if the estimate of random-effects variation was greater than zero. In this case, the random-effect results are almost identical to those of the fixed-effects model. The random-effects model led to a small and statistically insignificant estimate of average effect for pallidotomy "on" scores ($\hat{\delta}$=0.13, SE($\hat{\delta}$) = 0.08). Univariate meta-regressions were conducted for three study characteristics: time since surgery (≤ one year vs. > one year), average age of the participants, and average patient H&Y score at baseline. No study characteristics explained the significant amount of variation.

Sensitivity analyses were conducted to determine if any of the results seemed dependent on the inclusion of any one study. The only finding was that the effect of time since surgery was statistically significant if the largest effect size was deleted.[229] The effect in this study is quite large (0.93), as opposed to the effects from the two other studies with surgery followups exceeding one year; the effect in one is 0.20,[228] and the effect in the other is 0.10.[223] The

followup times in these three studies were 16, 24, and 48 months, respectively. It might be that the effect of pallidotomy on “off” scores does not decline until after at least a year and a half (or more) has passed. This result is suggestive at best, but may be worthy of future within-study investigation. The 95 percent confidence intervals for estimates of the mean effect size are in Figure 7.

Deep Brain Stimulation. Fourteen DBS treatment arms provided sufficient pre-post data on any of the PD rating scales to calculate pre-post standardized mean differences for "off” scores, and eight treatment arms provided sufficient pre-post data to calculate standardized mean differences for “on” scores (Evidence Table 13). Figures 8 and 9 show point estimates and 95 percent confidence interval error bars for the individual studies for "off" and "on" scores, respectively.

Meta-analyses - “Off” effects. Given that DBS takes place at three different sites (the GPi, the STN, and the thalamus), three separate meta-analyses were conducted. The “off” scores of the four studies of DBS of the GPi were very homogeneous (Q_E = 0.88, p>0.50). The fixed-effects estimated average effect of DBS-GPi on PD scale scores was significant and very large ($\hat{\delta}$=1.31 (SE($\hat{\delta}$) = 0.33). The eight studies of DBS of the STN were quite heterogeneous (Q_E = 55.68, p<0.001). A random-effects model led to a large and statistically significant estimate of average effect ($\hat{\delta}$=2.00, SE($\hat{\delta}$) = 0.47). Finally, the two studies of thalamic DBS seemed homogenous (Q_E = 0.27, p>0.50), but the fixed-effects estimated average effect was near zero ($\hat{\delta}$= -0.08, SE($\hat{\delta}$) = 0.16). This latter result is not surprising, as DBS of the thalamus is generally done for different reasons than DBS of the other two sites, i.e., it is not done to control severe PD, but to control tremor.[97]

Three study characteristics (time since implantation of the DBS device, average age of patients, and average H&Y score at baseline) were explored as possible explanations for the heterogeneity in the STN effect sizes. Three univariate meta-regressions were conducted to test whether any of these characteristics explained significant variation; however, no characteristics did (p>0.05). Sensitivity analyses were conducted to investigate whether any one study effect might be responsible for the excess variation; however, this was not the case.

Overall, meta-analyses of "off" effects showed that DBS led to significant improvement in "off" scores when performed on GPi or STN, and no significant change when performed on thalamic nuclei.

Meta-analyses - “On” effects. Two meta-analyses were conducted (there were no reports of “on” scores for thalamic DBS). The two studies of “on” effect sizes for DBS of the GPi were somewhat homogeneous (Q_E = 1.56, p=0.21). A random-effects model led to a mean effect size near zero ($\hat{\delta}$= 0.01, SE($\hat{\delta}$) = 0.61). The eight studies of DBS of the STN were heterogeneous (Q_E = 14.96, p=0.01). A random-effects model led to a statistically significant estimate of average effect ($\hat{\delta}$=0.79, SE($\hat{\delta}$) = 0.30).

Three study characteristics (time since implantation of the DBS device, average age of patients, and average H&Y score at baseline) were explored as possible explanations for the heterogeneity in the STN effect sizes. Three univariate meta-regressions were conducted to test whether any of these characteristics explained significant variation; however, no characteristics did (p>0.05). Sensitivity analyses were conducted to investigate whether any one study effect

might be responsible for the excess variation. The analyses showed that the “on” effect from one study (2.47) was causing most of the heterogeneity;[245] a re-analysis without this effect size resulted in a meta-analysis showing little heterogeneity (Q_E = 4.63, p=0.33). The mean effect size ($\hat{\delta}$=0.49) was just short of being statistically significant (p=0.06). This suggests the possibility that DBS does not significantly impact "on" scores; a finding which would not be surprising, given that surgery is only performed on patients who are responsive to medication.

Tissue Transplant. Four tissue transplant treatment arms provided sufficient pre-post data on any of the PD rating scales to calculate pre-post standardized mean differences for “off” scores, and five treatment arms provided sufficient pre-post data to calculate standardized mean differences for “on” scores (Evidence Table 14). Figures 10 and 11 show point estimates and 95 percent confidence interval error bars for the individual studies for "off" and "on" scores, respectively.

Meta-analyses - “Off” scores. Meta-analysis showed that the “off” score effect sizes may be homogeneous (Q_E = 3.18, p=0.36). However, given the low number of studies in these meta-analyses, the power to detect heterogeneity was very low. To be conservative, a random-effects model was employed. Random-effects modeling shows a positive and statistically significant benefit for tissue transplants ($\hat{\delta}$=0.88, SE($\hat{\delta}$) = 0.21). The 95 percent confidence intervals for these estimates are presented in Figure 10.

Meta-analyses - “On” scores. A fixed-effects meta-analysis showed that the “on” score effect sizes were heterogeneous after sampling error was taken into account (Q_E = 9.36, p=0.05). A random-effects model suggested a positive and statistically significant effect for tissue transplants ($\hat{\delta}$ =1.09, SE($\hat{\delta}$) = 0.34), indicating that tissue transplants led to improvement in "on" scores. There were not enough studies to investigate whether variation in study characteristics might be responsible for the heterogeneity in the study effects (See Figure 11).

Conclusions of Surgery Meta-Analyses. Pallidotomy resulted in significant improvement in "off" scores and insignificant improvement in "on" scores. DBS of GPi and STN resulted in significant improvement in "off" scores, but no significant change in "on" scores. Thalamic DBS resulted in no significant change in "off" or "on" scores. Fetal cell transplantation resulted in significant improvement in both "off" and "on" scores.

The mean “off” effect size for pallidotomy (0.77) is lower than the mean effect size for DBS of the GPi (1.31). This implies that DBS of the GPi may be better than pallidotomy in controlling PD symptoms in the “off” state. Without head-to-head RCTs, however, any conclusions are tentative at best. It is also worthwhile to note that there are other possible benefits to surgery, such as reduction of dyskinesias and motor fluctuations, that could not be investigated in these meta-analyses. Finally, while current results of tissue transplantation are promising, too few studies have been done on fetal brain surgery to make any more than tentative conclusions about its effectiveness, and the recent RCT comparing tissue transplant to sham surgery raised important questions regarding the long-term safety of the procedure.[103]

Surgery: Safety

Due to missing data and heterogeneity in methods of reporting AEs, summarization of surgical safety data suffers from the same limitations as summarization of pharmacological safety data. For the purposes of this summary data, only AEs reported in terms of numbers of patients (not events) have been captured, except when zero or one event was reported, in which case zero or one patient was substituted, respectively.

Evidence Table 15 lists the most common or clinically important AEs, but is by no means comprehensive. Transient AEs were not captured, as it was believed that decisions regarding the safety of surgery would be based mainly on long-term outcomes, not on transient perioperative complications.

Eighteen treatment arms reported the occurrence or absence of treatment-related deaths, which were uncommon except in tissue transplant studies, in which an 8.2 percent incidence of treatment-related deaths was reported. All of these deaths, however, were in adrenal transplant groups, and this procedure is no longer performed.

Reported AEs were primarily neurological or psychiatric, and included speech disorders (t=12, n=362, incidence = 6.1 percent); motor abnormalities (t=12, n=450, incidence = 5.6 percent); visual disturbances (t=8, n=320, incidence = 3.4 percent); depression (t=4, n=143, incidence = 6.3 percent); confusion, hallucinations, or psychosis (t=11, n=379, incidence = 4.2 percent); and dementia or impaired intellect (t=4, n=99, incidence = 5.1 percent). Some studies reported cerebral hemorrhage (t=11, n=266, incidence = 6.0 percent) and cerebrovascular events (t=4, n=106, incidence = 6.6 percent). The highest incidence of neurological AEs was reported in thalamotomy treatment groups (15.3 percent), but as these numbers were based on only two studies and 59 patients, the clinical relevance is unclear.

Psychiatric Treatment

There were ten accepted studies and one kin concerning treatment of psychiatric disorders in patients with advanced PD. Six studies were UCSs (n=114), two were RCTs (n=57), and two were retrospective observational studies (n=221). Eight studies were graded as level III evidence, and two were level II. Quality score could only be calculated for two studies, and was four in one study[262] and two in the other.[263]

Six accepted studies evaluated the efficacy of the atypical antipsychotic medication clozapine in managing PD patients with psychosis.[264 - 269] None were RCTs. Four were UCSs (n=93), lasting from 12 to 24 months.[264 - 267] Over seventy-five percent of patients in these studies demonstrated improvement in their psychotic behavior on a daily dose of 6.25 to 150 mg clozapine. The main adverse events reported were sialorrhea (reported in zero to 59 percent of patients), sedation (reported in two to 53 percent of patients), and confusion (reported in zero to 82 percent of patients). There were no reported cases of agranulocytosis. In the two retrospective reviews, charts of 221 PD patients on clozapine for control of psychotic symptoms were reviewed.[268, 269] Patients received clozapine for one to 76 months (mean duration 15.2 months). There was a decrease in the number of patients with agitation, delirium, delusions, dementia, depression, visual hallucinations, psychosis sundowning, insomnia, vivid dreams, daytime napping, disorientation, memory loss, and abulia, although none of these symptoms resolved completely in all patients. Forty-six of 221 patients (20.8 percent) withdrew from the drug due to

adverse events. The most common adverse events were somnolence, amnesia, delirium, sialorrhea, and orthostatic hypotension. Granulocytopenia was reported in six patients, but all resolved with discontinuation of the drug, and there were no cases of agranulocytosis.

The efficacy and safety of risperidone,[270] quetiapine,[271] piracetam,[263] and citalopram[262] were evaluated in one study each. In a UCS of ten patients with advanced PD, cognitive decline and psychiatric symptoms, patients were treated with low doses of the atypical antipsychotic drug risperidone for 16 to 48 weeks (mean 34.8 weeks).[270] While there was improvement in psychiatric symptoms in most subjects, two patients discontinued risperidone due to worsening of parkinsonism, and two developed delirium. The small size and uncontrolled design of this study does not allow conclusions to be drawn regarding the efficacy and safety of risperidone.

Quetiapine, another atypical antipsychotic, was openly administered for 12 months to 11 PD patients with psychosis.[271] Only five of the 11 patients completed one year of treatment. Withdrawals were due to dizziness, falling, obstipation, cerebrovascular accident, and lack of efficacy. Four of the five patients who completed the trial had improvement in their psychotic symptoms, particularly visual hallucinations. The small trial size and high dropout rate make these results difficult to interpret.

Piracetam, a drug that is structurally similar to γ-aminobutyric acid, was investigated in an RCT of 20 patients who were randomized to piracetam or placebo for 24 weeks, for treatment of intellectual impairment.[263] There were no significant effects on any motor or cognitive features of PD.

Thirty-seven PD patients suffering from major depression participated in an RCT comparing citalopram, a serotonin-specific reuptake inhibitor (SSRI), to placebo.[262] After six, ten, 14, 26, 39, and 52 weeks, the citalopram was well tolerated, but no more efficacious than placebo.

Ancillary Treatment

For the purposes of this report, ancillary treatment included interventions other than medication or surgery. Eight studies concerning ancillary PD treatments were initially accepted for inclusion into the database.[31, 272 - 278] Twelve additional studies and two kins were identified that did not meet the initial criteria for acceptance because they were less than 24 weeks in duration.[279 - 292] When the study duration requirement was dropped for this category, the 12 studies were accepted. The results of the studies of ancillary treatments are presented in Evidence Table 16.

Of the 20 studies ultimately accepted, the majority were RCTs (k=13, t=28, n=866). Three were single-blinded, and the others were not blinded. There were two nRCTs (t=4, n=73), two cross-sectional studies (t=2, n=20), and three UCSs (n=90). Studies were graded as level I (k=2), II (k=11), or III (k=7) evidence, where I is best. The mean quality score for the 13 RCTs was 1.5 of a possible 5, where 5 is best, reflecting low quality.

Physical Therapy (PT)

PT was evaluated in six studies,[272, 280, 282, 286, 288, 290] and one study compared music therapy (MT) to PT.[285] Speech therapy was evaluated in four studies,[31, 279, 281, 287] and swallowing therapy in one study.[284] Facial mobility training was evaluated in one study.[283] A health management program for PD was evaluated in two studies,[275, 276] nurse practitioner participation in patient

care was evaluated in two studies,[273, 277] and intensive, multidisciplinary, inpatient rehabilitation programs were evaluated in two studies.[278, 289]

In the only long-term study of PT, 40 PD patients were divided into two groups of twenty patients each.[272] One group received conventional physiotherapy, which consisted of active and passive mobilization exercises to enhance postural control, balance, walking, and range of motion. The second group underwent sensory-enhanced physiotherapy, which consisted of coupling tasks with visual or auditory reinforcements, such as colored squares on the floor, or tones associated with certain movements. Each group had three four-week cycles of physiotherapy, with three months in between cycles. Baseline scores for H&Y, walking, dressing, eating, feeding, and hygiene were comparable between the two groups. At each endpoint tested (one, four, and 12 months), patients in the enhanced physiotherapy group performed better than the conventional physiotherapy group, in all scores. The scores in both groups improved immediately after each month of therapy, but returned to baseline in the conventional group after three months of no therapy, while the enhanced physiotherapy group's scores remained improved compared to baseline. The authors concluded that coupling rehabilitation with sensory stimulation leads to learning and retention of motor strategies in PD patients. Limitations of this study include its small size and the lack of randomization and blinding.

The remaining PT studies were all of less than three months duration. In one randomized, single-blind crossover study, advanced PD patients underwent intensive rehabilitation for one hour, three times a week, for four consecutive weeks.[280] At the end of the month, patients were instructed to continue the exercise program at home. The control group received no specific instructions, and underwent the same rehabilitation program six months later. In both groups, the UPDRS total, mental, ADL, and motor scores were significantly improved immediately after the one month of rehabilitation, but returned to baseline six months later, suggesting that the beneficial effects of PT are not sustained when patients resume their usual activities.

One study compared a group of 16 PD patients who were treated with PT and various antiparkinson medications, with a group of 17 patients who were treated with medications only.[282] The PT group received PT for one hour, three times a week, for four months. After four months, patients in the PT group showed greater improvements than the control group in clinical rating scales and motor performance tests. Similar degrees of improvement were seen in patients with different degrees of symptom severity. Limitations of this study include the lack of randomization, and lack of followup after the PT had been discontinued.

In one study, 15 PD patients were randomly assigned to two training groups in which they were trained to perform specific arm movements.[286] The patients in one group received auditory rhythmic cues, which consisted of tones to guide the timing of their movements. A group of age-matched volunteers who underwent the same training served as the control group. Speed of aimed movements was tested immediately after training and one hour later. Movement time improved to a similar degree in all groups, and did not change significantly after one hour. The short duration of this trial does not permit conclusions to be drawn about possible long-term efficacy of this type of training in PD patients.

In another study, 51 patients with early or mid-stage PD were randomized to participate in a ten-week program of exercises to improve spinal flexibility and axial mobility, or receive usual care.[288] The therapy consisted of 30 individual sessions with a physical therapist, each session lasting 45 minutes to one hour. The usual care group was "wait listed" for therapy, and invited to participate in the program after the study was completed. After ten weeks, participants in the

exercise regimen improved in all three primary outcome variables, which were functional axial rotation (in degrees), functional reach (in inches) and time to go from supine to standing (in seconds). The control group did not change significantly in functional axial rotation or functional reach, although their time for moving from supine to standing increased to a similar degree as did the active patients. Limitations in this study include short duration, use of surrogate outcomes which may not reflect meaningful clinical changes, and lack of followup to determine if improvement was maintained.

In an RCT of 37 PD patients with gait impairments, 15 patients were randomized to a three-week home-based rhythmic auditory stimulation (RAS) program, which consisted of walking 30 minutes each day on a flat surface, stairs, and stop-and-go exercises to music at different tempos.[290] One control group was given the same exercises without RAS, and the second control group was given no training. After three weeks, gait velocity on flat and inclined surfaces, cadence, and stride length all increased in the RAS group, velocity and stride length increased to a lesser degree in the exercise alone group, and did not change markedly in the untrained group. Some EMG patterns improved as well, but the changes were small and not consistent across muscles. Interpretation of the results of this study is limited by its short duration.

The effect of MT on emotional well being and QoL was evaluated in a single-blinded RCT in which 32 PD patients were randomized to participate in sessions of MT or PT weekly for two months.[285] At three months, MT patients demonstrated improvements in UPDRS ADL, motor, and bradykinesia scores, although rigidity scores were unchanged. PT patients demonstrated no significant change in UPDRS ADL, motor, or bradykinesia scores, but the rigidity score improved significantly. QoL was measured by a happiness measurement scale, and was improved in the MT group, but unchanged in PT patients. One limitation of this study is the validity of comparing these two very different therapies. The PT sessions consisted of group exercises, and involved minimal interaction among participants. The MT sessions were of longer duration than the PT sessions, and involved more active participation. Another limitation is that the final UPDRS and QoL measurements were taken only one month after completion of the programs; therefore, the durability of the improvements cannot be assessed.

Speech/Swallowing Therapy

Two studies, both by the same author, evaluated the effects on intensive speech treatment in PD patients.[31, 287] The two trials evaluated a total of 80 patients. Forty-eight patients were treated with the Lee Silverman Voice Treatment (LSVT), an intensive speech therapy program in which high-effort loud phonation is emphasized, with the goal of improving respiratory, laryngeal, and articulatory functions during speech. Patients received four weekly one-hour sessions of LSVT. Thirty-two patients had the same number of placebo speech therapy sessions, in which they were trained to increase their respiratory muscle activity during inspiration and expiration. The study durations were one and twelve months. A variety of measures of auditory function were performed in the different studies. Both studies supported the efficacy of LSVT for improving vocal intensity and decreasing the impact of PD on communication. Respiratory treatments alone were not effective. In the 12-month study, the LSVT group improved or maintained vocal intensity above pretreatment levels 12 months after their training was completed, whereas the placebo group had statistically significant deterioration of vocal intensity levels from before treatment. However, the 12-month study contained only 22 PD patients, and the generalizability of these results is unclear.

The Lombard effect, which describes the phenomenon that most people will increase their voice intensity when speaking in the presence of masking noise, was tested in a cross-sectional study of ten patients.[279] All patients had been judged to have low vocal intensity by a speech-language pathologist. They were instructed to read a paragraph aloud with "normal auditory feedback," then read it again while listening to white noise through headphones. All ten PD patients showed a marked increase in speech intensity while listening to white noise. Speaking rate and speech intelligibility did not improve consistently with the white noise, and in fact worsened in some cases. It is not possible to extrapolate the effects of a one-time exposure to white noise on long-term voice intensity of PD patients.

A longer-term study evaluated the effect of a one-month voice rehabilitation program on 20 moderate-severity PD patients with complaints regarding their oral communication skills.[281] H&Y stage 1 patients were excluded, because they generally do not have speech difficulties, and stage 5 patients were excluded because their severe motor impairment would make participation difficult. After the one-month program, patients had increased vocal intensity, and decreased complaints of weak, monotonous, and unintelligible speech. Twelve of the patients complained of dysphagia prior to the program, compared with zero complaints afterwards. While these results are promising, longer-term trials are needed to adequately assess the efficacy of this treatment.

The effect of swallowing training on PD patients with swallowing disorders was evaluated in ten PD patients and 12 healthy volunteers.[284] Subjects underwent an initial evaluation which consisted of a modified barium swallow and electromyogram (EMG) to evaluate the time it took to initiate their swallowing reflex (premotor time, or PMT). Subjects were then given one session of swallowing training. PMTs were initially elongated in the PD patients, and decreased significantly after the training, while they were normal and unchanged in healthy controls. Studies of longer duration are needed to assess the clinical significance and durability of these results.

Other Therapies

One study evaluated the effects of orofacial physiotherapeutic treatment (OPT) on facial mobility of PD patients.[283] OPT consisted of brushing and applying ice to muscles, blowing through a straw, and other exercises to stimulate the facial muscles. Eight patients were randomized to receive OPT twice a week for four weeks, and eight patients received no therapy. After four weeks, measurements of facial movement were significantly improved in the OPT group patients, but there were no significant differences in the measurements of the control group patients. Repeat measurements one month after treatment completion showed similar findings.

One study reported the results of transcranial magnetic stimulation (TMS), a procedure in which a magnetic coil was positioned over the motor cortices of ten PD patients, who then received 30 stimuli twice a day for ten days.[274] Mean UPDRS scores improved by 20.9 to 33.3 percent in total, mentation, ADL, and motor scales, and the improvements persisted after six months of followup. No adverse events were reported. Given the small number of patients in this study, no definitive statements may be made regarding the efficacy of TMS; however, these preliminary results appear favorable.

Two studies evaluated the effectiveness of PROPATH, a patient education and health promotion program designed for PD patients.[275, 276] PROPATH participants receive an introductory videotape and educational pamphlets that provide detailed advice on daily coping with physical, emotional, and psychological aspects of PD. Patients periodically complete detailed questionnaires in which they rate the severity of their symptoms and their ability to perform ADL. Both studies were unblinded RCTs, in which patients were randomized to PROPATH participation or usual care. Patients were followed for six months in one study (n=400), and 12 months in the other study (n=50). In the six-month study, medical utilization was lower in PROPATH patients, when measured by numbers of doctor visits, hospital days, or sick days, although only the change in number of doctor visits was statistically significant. The control group had no change in the numbers of doctor visits or hospital days, and a decrease in sick days. QoL scores improved in patient global assessment in the PROPATH group, but the change was not statistically significant. In the 12-month study, patient perception of general health and psychological well-being improved significantly in the PROPATH group and worsened in the control group. Patient satisfaction with care and health care utilization was not significantly different between the two groups. Thus, there are some inconsistencies between the results of the two PROPATH studies.

Two studies assessed the value of a nurse practitioner or PD nurse specialist in management of PD.[273, 277] Both studies were unblinded RCTs, involving a total of 225 PD patients. In one study, patients were randomized to see a PD nurse specialist or a neurologist. Minimal differences were noted in a one-year followup of these patients. In another study, patients were randomized to receive home visits from a nurse practitioner or usual care. After six months, there was no significant difference in psychosocial functioning between the two groups.

In a single-blinded RCT, 12 patients with moderately advanced PD were randomized to participate in a four-week, inpatient, multidisciplinary rehabilitation program administered by physical, occupational, and speech therapists.[278] The eight control patients received no rehabilitation. UPDRS total, Webster, and scales of functional independence all improved significantly in the active group after the four weeks of treatment, but did not change significantly in the control group. Five months after the program had been discontinued, the above scores were still improved from prior to the intervention, but worse than they were immediately following the rehabilitation program.

An uncontrolled study of a five to ten-day inpatient multidisciplinary rehabilitation program evaluated QoL, using the Nottingham Health Profile (NHP), in 58 PD patients before and one month after completion of the program.[289] Patients showed significant improvement in total score, pain, emotional reactions, and physical mobility, but no significant change in energy, sleep, or social isolation. The authors did not report whether this improvement lasted for longer than one month.

In summary, the 20 studies of ancillary treatment in PD reviewed in this Evidence Report showed modest improvement in some parameters after treatment with PT or MT, and significant improvement in vocal intensity after LSVT. Studies of multidisciplinary rehabilitation programs, PROPATH, or nurse practitioner interventions yielded mixed efficacy results. Evaluation of literature pertaining to ancillary treatment of PD is hampered by poor quality studies.

Genetics

Due to the lack of prospective trials regarding genetic testing for PD, it was decided that the genetics review would be presented as a summary of recent articles on the topic, including review articles. Evidence for the existence of a genetic component for PD has been reported since the 1880s, when a neurologist described a family history of PD in up to 15 percent of his patients.[293, 294] However, experts currently believe that most cases of PD are sporadic, and that family history does not appear to confer increased risk of developing PD.[295]

Early twin studies showed low concordance rates, and argued against a genetic etiology of PD. More recent studies have refuted this claim.[295] In a study of nearly 200 twin pairs in which at least one twin had PD, there was increased concordance in monozygotic twins, but only in patients who were diagnosed with PD before age 50.[296] The authors concluded that genetics do not appear to play a major role in PD with typical age of onset (age > 50), but may be more important for cases with younger age of onset (≤ 50).

Another twin study evaluated the [18-F] fluorodopa PET scans of 34 patients and their monozygotic or dizygotic twins who did not have PD.[297] Ten of the 18 monozygotic twins and three of the 17 dizygotic twins had PET scans that showed decreased uptake of fluorodopa in the striatum, consistent with PD, although none of them had clinical evidence of PD. Subjects were followed for up to seven years after their initial evaluation. All asymptomatic monozygotic co-twins showed progressive loss of dopaminergic function over seven years, and four developed clinical PD, but none of the dizygotic twin pairs became clinically concordant. This study suggests that there is a substantial genetic component to the etiology of PD that has been unrecognized because standard clinical diagnostic criteria are insufficiently sensitive. It also shows that functional imaging modalities, such as [F-18] Fluorodopa PET, may be useful tools for future studies of genetic or environmental risk factors for PD.

In an epidemiologic study using a comprehensive genealogic computerized database of over 600,000 Iceland residents over the past 11 centuries, all relatives of PD patients were traced, to examine the evidence for a genetic component of PD risk.[298] Risk ratios (RRs) were calculated for the relatives of all 772 PD patients, and also for the subgroup of PD patients with late-onset PD (n=560). Siblings of PD patients had the highest RRs (6.3 for all PD patients, 6.7 for patients with late-onset PD), followed by offspring (3.0 and 3.2, respectively), and nieces and nephews (2.3 and 2.7, respectively). The results of this study suggest that there may be a substantial genetic contribution (at least in this highly interrelated ethnic population), not only in patients with "young-onset" disease (as has been the finding in twin studies), but also in PD patients with typical age of onset.

Mutations associated with PD have been identified in several genes, and it appears that different mutations can produce the same parkinsonian phenotype. The *α-synuclein* gene on chromosome 4q21-23, and the *parkin* gene on chromosome 6q25-27 have been studied extensively.[294] α-synuclein is a protein that has been identified as a major component of Lewy bodies and a part of the amyloid plaque in AD.[295] A point mutation in the *α-synuclein* gene has been identified in some cases of autosomal dominant familial PD in families of Greek or Italian descent.[294] Many mutations in the *parkin* gene are associated with early-onset, autosomal-recessive PD in Japanese and European families[299 - 302] while other *parkin* mutations may be associated with a protective factor for sporadic (non-familial) PD.[303]

It is likely that other genes will be identified that are involved with familial PD, but the currently available evidence suggests that the vast majority of PD cases are not familial, and have no known associated genetic component.[295] When more information is known about the specific genetic abnormalities in PD patients, specific intracellular genetic manipulation may become possible, with the goal of treating, curing, and even preventing PD.[304, 305]

Chapter 4. Answers to 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?

The use of CT to diagnose PD was not addressed in any of the studies in the database. Evidence suggests that MRI may be useful to rule out conditions other than PD, but not for diagnosing PD. Evidence regarding SPECT and PET scans was inconsistent. Some studies reported these scans could distinguish advanced PD from normal controls; however, these conditions should be clinically distinguishable without the need for neuroimaging studies. Differentiating atypical parkinsonism from PD is clinically more difficult, but studies were inconsistent in their conclusions regarding ability of SPECT or PET scans to distinguish between these conditions. The role of SPECT and PET scans in diagnosing PD remains unclear. More research should be done looking at combinations of tests for diagnosing PD.

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

Lack of a reference standard limits the ability to quantify accuracy, sensitivity, and specificity of the apomorphine and L-dopa challenge tests. Current published evidence does not support the use of L-dopa or apomorphine challenge tests 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?

- Meta-analysis suggests that treatment with DAs plus L-dopa may control PD symptoms better than treatment with L-dopa alone, but this was not a consistent finding.

- In studies in which patients were randomized to L-dopa vs. L-dopa plus DAs, the combination of L-dopa plus DAs resulted in better UPDRS scores than L-dopa alone. This was true in both short and long-term (greater than one year) studies.

- In studies where patients were randomized to L-dopa vs. DAs, where additional L-dopa was discretionary, L-dopa alone resulted in better UPDRS scores than DAs (with or without additional L-dopa).

- Treatment with DAs was associated with lower L-dopa doses.

- There is no evidence that different DAs vary in treatment effects in patients with early PD.

- This review found no consistent evidence that treatment with DAs plus selegiline controlled PD symptoms better than treatment with L-dopa alone in patients with early PD; however, treatment with selegiline was associated with a delay in requirement for L-dopa.

- These meta-analysis results should be viewed with caution, as they are based on the small number of RCTs that met the inclusion criteria for this systematic review. Due to the small number of studies within each meta-analysis, these findings are sensitive to possible publication bias in the literature.

- With regard to initial treatment of L-dopa vs. DAs, only one study compares a DA to placebo without the addition of L-dopa as needed.[213] In this study, the DA clearly performed better than placebo. In another study, bromocriptine and L-dopa were compared as monotherapy and combination therapy.[204] While dystonia was less frequent in the bromocriptine monotherapy group, no other significant differences were observed. These studies do not provide enough evidence to make a conclusion regarding the efficacy of initial treatment with L-dopa vs. a DA.

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

There is evidence that vitamin E is not neuroprotective in PD. There is insufficient evidence to evaluate the efficacy of other medications as potential neuroprotective agents in PD.

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?

- This review found no consistent evidence that treatment with DAs plus L-dopa controlled PD symptoms better than treatment with L-dopa alone in patients with advanced PD; however, treatment with DAs was associated with lower L-dopa doses.

- There is no evidence that different DAs vary in treatment effects in patients with advanced PD.

- Treatment with COMT inhibitors combined with L-dopa showed significantly greater efficacy in treating PD symptoms than than treatment with L-dopa alone in patients with advanced PD. Use of COMT inhibitors was associated with lower L-dopa doses; however, long term (greater than seven months) results are lacking, and hepatotoxicity is a potentially lethal side effect that has been rarely associated with tolcapone. Treatment of medication-induced side effects is addressed in question 6.

- These meta-analysis results should be viewed with caution, as they are based on the small number of RCTs that met the inclusion criteria for this systematic review. Due to the small number of studies within each meta-analysis, these findings are sensitive to possible publication bias in the literature.

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

Dyskinesias and motor fluctuations were rarely reported in a quantifiable manner. Lower L-dopa doses are associated with improvement in dyskinesias. Based on information from a limited

number of studies, use of DAs, selegiline, and COMT inhibitors was associated with lower doses of L-dopa.

Thirteen surgical studies reported dyskinesia scores; almost all reported improvement in mean dyskinesia scores, particularly contralateral scores, after surgery. Studies of DBS of the STN that reported L-dopa dosages showed a significant decrease in L-dopa dose after surgery. Hence, there is evidence that pharmacologic and surgical approaches to managing L-dopa side effects may be effective in reducing dyskinesias.

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

No treatment-related deaths, hospitalizations, cancers, or life-threatening events were reported in any pharmacologic studies.

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

Limited data suggests efficacy and safety of clozapine in the treatment of PD patients with dopamine-induced psychosis. Long-term RCTs (i.e., > 6 months) are needed to confirm these findings. While depression is reported to be a common finding in PD patients, this issue cannot be adequately addressed in this report, as insufficient studies met the inclusion criteria for acceptance into the database.

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

- The overall quality of the surgery literature was lower than the quality of the pharmacologic literature, as very few RCTs were done to evaluate the efficacy and safety of surgical procedures. It must be recognized, however, that it is very difficult to perform RCTs of surgical procedures, and other study designs may have to suffice.

- Surgery studies have generally been performed on young patients with advanced PD who are suffering from intolerable drug-induced dyskinesias or motor fluctuations.

- On average, for pallidotomy and DBS, endpoint PD scale "off" scores were significantly better than baseline scores. Mean L-dopa doses did not change significantly after pallidotomy.

- DBS of the STN and GPi resulted in significant improvement in PD scale "off" scores, but only STN DBS was associated with a decrease in L-dopa doses.

- There were insufficient studies of thalamotomy to draw any conclusions regarding efficacy.

- Across all fetal brain cell transplant studies, endpoint PD scale scores were significantly better than baseline scores; however, the small sample size limits interpretation, and a

recent RCT comparing tissue transplantation to sham surgery raised important questions regarding the efficacy and long-term safety of the procedure.

- These meta-analysis results should be viewed with caution, as they are based on results of the small number of studies that met the inclusion criteria for this systematic review. Due to the small number of studies within each meta-analysis, these findings are sensitive to possible publication bias in the literature.

10. What are the outcomes of rehabilitation in PD?

Short-term (≤ one month) studies of physical therapy, music therapy, speech therapy, and multidisciplinary rehabilitation programs demonstrated improvements in strength, flexibility, speech, and quality of life, but their short duration precludes any conclusions regarding their long-term efficacy. Intensive speech therapy has been shown to improve vocal intensity up to twelve months after treatment; however, these long–term results are from only one study of 22 patients.

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

Recent studies have identified specific genetic mutations that are associated with familial PD, but the evidence suggests that genetics do not play a major role in most PD patients with age of disease onset > 50 years. Although current evidence is sparse, this is an area of active research, and updates of this review may be able to address genetic issues more fully.

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?

Most of the studies in the database excluded patients with significant comorbidities; therefore, no conclusions may be drawn regarding treatment of patients with multiple disease processes. Very few studies addressed race, ethnicity, and income level. In the few studies that identified the race of their subjects, the vast majority of patients were Caucasians. No distinctions were made between outcomes in males and females. Studies in the database did not address patients at age extremes. When age of disease onset was reported, there was minimal variation, and patients with young age of onset were not well represented in the database. Very few studies reported presentation of symptoms. Therefore, evidence-based conclusions regarding differences in treatment or outcome based on differences in age, presentation of symptoms, cognitive status, duration of illness, comorbidities, gender, race, ethnicity, and income level are not possible.

Chapter 5. Strengths and Limitations of the Evidence Base

The strengths of this review include the clear definition of the research questions, adherence to an explicit research protocol developed prior to the analysis, the comprehensive nature of the data search (employing both electronic databases and manual bibliography searches, resulting in the inclusion of all relevant published materials), and the requirement that consensus be reached by two reviewers on all data elements prior to entry into the database.

Another primary strength of this evidence base is the collaboration of multidisciplinary researchers who participated in its development. It was compiled by investigators who are skilled in employing highly systematic and unbiased methods to collect, review and synthesize data from published clinical literature. Throughout the course of this project, there was frequent input from the co-investigator (a clinical content expert) and the TEP. In addition, the final report has benefited from input from the TEP and peer reviewers.

The major limitations of this review are related to weaknesses inherent in the available published literature on the management of PD. While the prevalence of PD is reportedly almost equal in males and females, the studies were composed predominantly of males. This was particularly true for studies in which patients with advanced disease were evaluated. Patients with age of disease onset prior to 50 years, an important subset of PD patients, were largely absent from the database. The exclusion criteria for most studies were extensive, excluding most patients with comorbidities. This brings the generalizability of results into question.

While most studies reported PD scale results, these results were reported in a wide variety of formats. Reliance on figures to show data and trends in the data was common. While these methods may be useful for the purposes of explaining data in primary studies, they interfere with the ability to statistically amass a body of evidence over time. "On-off" time, which is an important measure of treatment efficacy, particularly in patients with advanced PD, was described with such wide variation that the results from different studies could not be combined in a meaningful way.

Many studies were excluded from this Evidence Report due to insufficient study duration or cross-over design. While we recognize that strict application of inclusion and exclusion criteria caused some pertinent and potentially useful studies to be excluded, an essential element of a systematic review is to apply uniform criteria that were established *a priori*. The investigators believe that even with these restrictions, a sufficient number of studies met inclusion criteria to address all of the questions posed in this Task Order. Studies that did not meet inclusion criteria but were deemed important for discussion in this evidence report were addressed in Appendix J, although formal data extraction and statistical analyses were not performed on these studies.

Another limitation of this Evidence Report is that it was limited to published studies only. As studies with unfavorable results are often not published, the efficacy of a particular treatment, such as surgery, may appear falsely elevated.

Chapter 6. Recommendations for Future Research

The following recommendations would enable researchers to generate useful data to support answers to the questions posed in this report.

Standardize methods of reporting results.

Standardization of reporting results facilitates inter-study comparisons. Given the unlikely probability that any one study will conclusively demonstrate the efficacy of a given treatment, it becomes very important for authors to make sure that their results are both clear and complete enough to allow future synthesis with other important studies in the field.

The reliability and validity of the UPDRS has been widely documented, and it is currently the most common instrument used to measure the progression of PD. Investigators should report baseline, endpoint, and change in UPDRS scores, along with their respective standard deviations. While some researchers only report the motor subscore, and it is important that the ADL score be reported as well. Many researchers reported much of this data in figures, making estimates of means imprecise, and estimation of standard deviations almost impossible. Unless researchers report change score standard deviations, the added certainty those researchers achieve by controlling for an individual's pre-test data will not be directly available to future researchers.

The CAPIT committee recommended that surgical studies report UPDRS scores ("off" and "on"), H&Y stages ("off" and "on"), Dyskinesia Rating Scale ("on"), timed tests of motor function ("off" and "on)," and self-reporting diary. We enthusiastically endorse these recommendations, for studies of pharmacological and ancillary as well as surgical treatments, because standardized reporting of baseline and outcome data can only enhance the ability to build an evidence base regarding the optimal treatment of PD.

Duration and severity of "on" and "off" periods are useful parameters to follow, particularly in patients with advanced PD. These could not be meta-analyzed, due to the widely divergent methods used in reporting. "On" and "off" time should be consistently reported, using a standardized method.

Patient withdrawal should preferably be modeled using the sophisticated statistical methods currently published and in development for the problem;[306] when these methods cannot be employed, researchers should use ITT/LOCF and record whether they do so. When researchers deem LOCF findings inappropriate, they should explain how they are accounting for patient withdrawal and whether their findings are sensitive to how patient withdrawal is handled.

Adequately power studies.

Many of the studies meta-analyzed had very small sample sizes. While one of the benefits of meta-analysis is that a synthesis of inadequately powered studies can yield interesting findings, such meta-analyses require large numbers of studies in order to make conclusive findings. Researchers should make sure to power their efficacy studies appropriately.

Report L-dopa usage.

The number of patients who receive L-dopa, and their doses, should be clearly stated. Many studies mentioned whether L-dopa treatment was allowed, and failed to report how many patients needed such treatment, or what their average dose was. Given that most treatments incorporate L-dopa into the regimen, and given that an important treatment outcome is whether an additional drug allows for a decrease in L-dopa dose, data regarding actual L-dopa usage are quite important in evaluation.

Include patients with comorbidities in clinical trials.

In clinical practice, clinicians see patients with numerous comorbidities in addition to PD. As nearly all of the studies excluded patients with serious illnesses, the generalizability of study results is limited.

Include more elderly patients and members of different racial and ethnic groups in clinical trials.

As the body of evidence increases in size, the power to detect difference in efficacy of treatment based on certain characteristics increases. More detailed description of patients enrolled in studies could help researchers to identify which treatments may be more efficacious in patients of different age, gender, or ethnic background.

Perform studies that include patients with younger onset of disease.

Only three of the 356 treatment arms in the database reported mean age of disease onset as less than 50. While PD is mainly a disease of the elderly, it does occur in young patients as well, and it would be inappropriate to assume that patients with early onset of PD should necessarily be treated the same as patients with older onset of PD. More studies of younger patients are needed to determine whether different treatment is appropriate in this population.

Evaluate use of combinations of tests in diagnosing PD.

Preliminary evidence suggests that the PD test battery may be helpful in diagnosing PD. More research should be done looking at combinations of tests for diagnosing PD.

Improve quality and duration of studies of ancillary treatments for PD.

Further studies of PT, OT, speech therapy, and other nonpharmacologic and nonsurgical modalities should be of longer duration and should measure standardized, clinically meaningful outcomes.

Report family perceptions relating to patient care.

Families are one of the most important resources for managing patients. They play an important role in the results of an intervention by their participation as well as their interpretation

of the success. Family caregiver perceptions should be included in research as an independent variable and should be included systematically as an important endpoint.

Continue research on genetic components of PD risk.

Important new developments in genetic susceptibility for PD are likely to have a major impact on the diagnosis and management of PD. Information on these topics should be collected and included in an update of this systematic review. Studies of genetic abnormalities in PD patients should continue, to help identify which patients are appropriate for genetic testing.

Perform long-term studies on efficacy of surgical procedures.

The literature indicates that research is needed on the efficacy of surgical outcomes in patients 65 years of age and over. The literature also indicates that research is needed to evaluate long-term efficacy and safety in the areas of DBS and tissue transplantation.

Chapter 7. Harnessing the Available Evidence

This systematic review has led to an evidence base that contains a wealth of data regarding diagnosis and management of PD. The relational database could be provided with a navigational software interface that permits easy filtering and exporting for analysis. The evidence base provides a valuable opportunity to develop clinical practice guidelines or evaluate current guidelines against the weight of the best available evidence. Given the large volume of information continuing to be published regarding PD, semi-annual updates are recommended to keep this evidence base current.

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Evidence Table 1. Summary of Rejected Studies

Rejected	Reason for Rejection [1]
96	Studies published prior to 1990
81	Studies with less than 24 weeks of follow-up (other than diagnosis)
72	Studies that are not RCTs (pharmacological treatment only)
52	Abstracts, letters, comments, reviews, editorials, case reports, or meta-analyses
49	Studies not including tests to establish or support diagnosis of PD
29	Studies with less than 10 patients
17	Outcomes not extractable
24	Studies not including treatment or diagnosis
13	No outcome of interest
6	Cross-over studies
6	Mixed populations where results for PD patients cannot be separately extracted
10	Studies not including an objective clinical outcome measure of PD activity
2	Duplicate studies
2	In vitro studies
2	Languages other than English
2	Pharmacodynamic or pharmacokinetic study
2	Study populations not including Parkinson's Disease
465	**TOTAL**

[1] Based on

Evidence Table 2. Study Level Characteristics

	Total			Diagnosis			Pharmacological			Surgical			Psychiatric			Ancillary		
	k	t	n	k	t	n	k	t	n	k	t	n	k	t	n	k	t	n
Totals	180	353	16,158	59	141	3,369	49	111	9,968	42	52	1,380	10	12	392	20	37	1,049
Location																		
Europe	90	186	6,327	40	94	1,948	25	52	3,478	14	20	393	2	3	73	9	17	435
North America	66	118	6,819	12	27	1,226	14	38	3,902	25	29	831	7	8	292	8	16	568
Other	15	29	888	5	13	94	5	10	708	1	1	13	1	1	27	3	4	46
Multi-National	9	20	2,124	2	7	101	5	11	1,880	2	2	143	0	0	0	0	0	0
Study Design																		
RCT	68	151	10,996	0	0	0	49	111	9,968	4	8	105	2	4	57	13	28	866
nRCT	6	16	273	2	5	83	-	-	-	2	7	117	0	0	0	2	4	73
UCS	49	49	1,627	5	5	278	-	-	-	35	35	1,145	6	6	114	3	3	90
XS	48	119	2,075	46	117	2,055	-	-	-	0	0	0	0	0	0	2	2	20
Other	9	18	1,187	6	14	953	-	-	-	1	2	13	2	2	221	0	0	0
Level of Evidence																		
I	28	70	8,945	0	0	0	26	65	8,454	0	0	0	0	0	0	2	5	491
II	40	79	2,051	0	0	0	23	46	1,514	4	8	105	2	2	57	11	23	375
III	112	204	5,162	59	141	3,369	0	0	0	38	44	1,275	8	10	335	7	9	183
Quality Score																		
1	7	15	180	0	0	0	1	2	20	0	0	0	0	0	0	6	13	160
2	17	35	2,241	0	0	0	8	16	1,502	1	2	13	1	2	20	7	15	706
3	13	28	2,014	0	0	0	11	24	1,959	2	4	55	0	0	0	0	0	0
4	22	51	4,147	0	0	0	20	47	4,073	1	2	37	1	2	37	0	0	0
5	9	22	2,414	0	0	0	9	22	2,414	0	0	0	0	0	0	0	0	0
Industry Sponsorship	42	90	7,355	1	1	30	29	72	6,612	4	4	134	4	5	116	4	8	463

k - number of studies
t - number of treatment arms
n - number of patients
Multi-National - on more than one continent

RCT - randomized controlled trial
nRCT - non-randomized controlled trial
UCS - uncontrolled case series
XS - cross-sectional

Evidence Table 3. Overall Treatment Level Characteristics

	Total		Pharmacological		Surgical		Psychiatric		Ancillary	
	t	n	t	n	t	n	t	n	t	n
Patients Randomized/Enrolled	212	12,789	111	9,968	52	1,380	12	392	37	1,049
Male (n = %)	164	60%	82	60%	40	64%	10	59%	32	62%
Female (n = %)	164	40%	82	40%	40	36%	10	41%	32	38%
Mean Age > 65	64	2,743	17	1,225	10	270	11	373	26	875
Mean Age < 65	130	8,613	80	7,380	41	1,066	1	19	8	148
Disease Stage										
Early*	80	7,505	74	7,405	2	28	NR	NR	4	72
Advanced**	114	4,758	37	2,563	41	1,030	9	344	27	821
Mean Age of Onset > 50	22	1,118	15	928	3	102	1	49	3	39
Mean Age of Onset < 50	3	49	NR	NR	3	49	NR	NR	NR	NR
Race	11	567	8	506	NR	NR	1	11	2	50
Socioeconomic status	10	890	6	820	NR	NR	2	20	2	50

*Early = author defined as "early" or "de novo" or disease duration < 5 years
**Advanced = author defined as "advanced" or disease duration > 5 years

t - number of treatment arms
n - number of patients
NR - not reported

Evidence Table 4. Treatment Level Characteristics of Diagnostic Studies

Test Category	Diagnosis Studies		
	k	t	n
Apomorphine challenge	5	6	229
Autopsy	6	15	253
Clinical or laboratory	10	26	1,412
Color vision test	2	3	35
MRI	3	8	140
Olfactory testing	7	21	355
PD Test battery	3	7	180
PET scans	8	21	185
SPECT scans*	13	29	460
Other scans	2	5	120
Total	59	141	3,369

SPECT - single photon emission computed tomography
PET - positron emission tomography
MRI - magnetic resonance imaging
k - number of studies
t - number of treatment arms
n - number of patients

* includes 5 studies that reported SPECT results before and after administration of apomorphine and one study that compared SPECT and PET results

Evidence Table 5. Treatment Level Characteristics of Pharmacological Studies

Treatment class	Total		Early		Advanced	
	t	n	t	n	t	n
Monotherapy						
LD	41	3,927	25	2,835	16	1,092
Dopamine Agonist	6	508	6	508	0	0
MAO-B inhibitor	5	336	5	336	0	0
Combination therapy						
LD/DA	33	2,935	18	1,907	15	1,028
LD/COMT inhibitor	8	639	2	196	6	443
LD/DA/MAO-B inhibitor	2	68	2	68	0	0
LD/MAO-B inhibitor	7	700	7	700	0	0
DA/MAO-B inhibitor	1	10	1	10	0	0
Other Combinations	4	471	4	471	0	0
Placebo	4	374	4	374	0	0
Total	111	9,968	74	7,405	37	2,563

LD - levodopa (always given with peripheral decarboxylase inhibitor)
DA - dopamine agonist
MAO-B - monoamine oxidase-B
COMT - catechol O-methyl transferase
Other Combinations included 2 studies with LD/Selegiline/Tocopherol and LD/ Tocopherol
k - number of studies
t - number of treatment arms
n - number of patients

Evidence Table 6. Statistical Analysis: Dopamine Agonists with L-Dopa vs. L-Dopa alone

First Author	Year	Dopamine Agonist Tested	Patients on L-dopa	Patients on DA and L-Dopa	Disease Stage	Time of Evaluation (months)	Mean Age (years)	Change-score Effect Sizes
Alarcon	1998	Bromocriptine	38	40	Early	36	63.8	0.137
Allain	2000	Lisuride	41	41	Early	12	59.0	0.411
Gimenez-Roldan	1997	Bromocriptine	23	27	Early	8	60.3	1.463
Hutton	1996	Cabergoline	65	123	Advanced	6	63.1	0.299
Kulisevsky	2000	Pergolide	10	10	Early	24	65.5	-0.057
Lieberman	1997	Pramipexole	172	179	Advanced	8	63.4	0.264
Nakanishi	1992	Bromocriptine	124	117	Early	60	61.4	0.257
Olanow	1994	Pergolide	187	189	Advanced	6	63.0	0.203
Olanow	1995	Bromocriptine	21	19	Early	14	66.2	-0.239
Olsson	1990	Bromocriptine	140	137	Early	12	58.5	0.230
Parkinson Study Group	2000	Pramipexole	150	151	Early	24	61.2	-0.398
Przuntek	1996	Bromocriptine	302	285	Early	48	65.0	0.240
Rabey	1990	Lisuride	13	15	Advanced	48	65.4	0.329
Rascol	2000	Ropinirole	89	179	Early	60	63.0	-0.418
Rinne	1998	Cabergoline	205	208	Early	18	61.6	-0.288
Sethi	1998	Ropinirole	77	70	Early	12	61.9	0.521
Steiger	1996	Cabergoline	11	6	Advanced	6	62.1	-0.102
Inzelberg*	1996	Cabergoline vs. Bromocriptine	22 (Caber.)	22 (Bromo.)	Advanced	12	-	0.167
Korczyn*	1999	Ropinirole vs. Bromocriptine	102 (Ropin.)	112(Bromo.)	Early	36	62.9	-0.164

L-dopa = Levodopa
DA = Dopamine Agonisr
Caber = Cabergoline
Bromo = Bromocriptine
Ropin = Ropinirole

*Both groups were on both DA and L-dopa. The names in parentheses indicate which DA was used to treat a particular group.

Evidence Table 7. Statistical Analysis: Selegiline with L-Dopa vs. L-Dopa alone

First Author	Year	Patients on L-dopa	Patients on Selegiline and L-Dopa	Disease Duration (years)	Time of Evaluation (months)	Mean Age (years)	Change-score Effect Sizes
Larsen	1999	81	73	Early	60	64.3	0.593
Lees	1995	213	233	Early	12	63.2	0.810
Myllyla	1992	25	27	Early	12	61.1	-0.277
Olanow	1995	21	20	Early	14	NR	0.931
Palhagen	1998	81	76	Early	12	63.8	-0.343

L-dopa = Levodopa

Evidence Table 8. Statistical Analysis: COMT Inhibitors with L-Dopa vs. L-Dopa alone

First Author	Year	COMT Inhibitor Tested	Patients on L-dopa	Patients on COMT Inhibitors and L-Dopa	Disease Duration (years)	Time of Evaluation (months)	Mean Age (years)	Change-score Effect Sizes
Baas*	1997	Tolcapone	58	60	9.75	3	63.0	0.263
Baas*	1997	Tolcapone	58	59	10.25	3	63.5	0.553
Parkinson Study Group	1997	Entacapone	102	103	11.05	7	63.3	0.278
Rajput*	1997	Tolcapone	66	69	10.75	3	64.0	0.180
Rajput*	1997	Tolcapone	66	67	10.80	3	64.5	0.103
Rinne	1998	Entacapone	86	85	10.75	6	62.7	0.310
Waters*	1997	Tolcapone	102	98	4.15	6	67.0	0.397
Waters*	1997	Tolcapone	102	98	3.75	6	65.0	0.471

LD - Levodopa
COMT - Catechol O-Methyl Transferase

* Separate treatment groups (different doses) of the same study

Evidence Table 9. Pharmacological Studies: Adverse Events

Adverse Events	Total		LD		DAs		MAO-B		LD/DA		LD/COMT		LD/DA/MAO-B		LD/MAO-B		Other		Placebo	
	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n
Deaths	4.8	5,635	5.0	2,342	14.0	64	0.9	336	3.3	1,708	-	0	-	0	13.1	634	0.0	409	0.7	142
Treatment Related Deaths	0.0	1,232	0.0	317	-	0	0.0	255	0.0	557	-	0	-	0	0.0	27	0.0	10	0.0	66
Withdrawals	29.2	8,961	30.4	3,605	48.4	508	12.8	336	28.8	2,505	39.1	384	32.4	68	32.6	700	9.8	481	17.4	374
Efficacy Withdrawals	5.1	5,840	6.1	2,597	10.0	468	-	0	3.4	2,077	1.9	103	0.0	41	3.8	373	0.0	10	4.1	171
Safety Withdrawals	11.2	7,444	8.3	3,268	20.6	490	-	0	12.8	2,256	15.5	639	9.8	41	13.0	446	5.6	72	4.7	232
Adverse Events																				
Cardiac	12.2	4,332	10.8	1,637	9.6	228	0.4	255	16.9	1,712	4.2	119	-	0	3.7	134	0.0	10	4.6	237
Cerebrovascular	0.6	345	1.2	81	-	0	0.5	191	-	0	-	0	-	0	0.0	73	-	0	-	0
GI	23.8	6,019	22.0	2,326	30.3	228	0.8	255	28.2	2,067	29.3	639	-	0	22.4	134	16.7	72	13.4	298
Infections	9.8	1,641	8.2	451	-	0	-	0	11.4	797	9.9	332	-	0	0.0	61	-	0	-	0
Musculoskeletal	8.2	1,796	5.5	990	-	0	-	0	10.9	614	19.3	119	-	0	5.5	73	-	0	-	0
Pulmonary	2.8	689	1.6	255	-	0	-	0	3.5	315	3.4	119	-	0	-	0	-	0	-	0
Urinary system	7.8	903	0.5	366	-	0	-	0	5.9	17	12.9	520	-	0	-	0	-	0	-	0
Other*	8.6	3,308	5.3	1,524	14.6	164	-	0	11.4	1,376	-	0	-	0	8.2	73	-	0	8.8	171

n - number of patients
LD - levodopa
DA - dopamine agonist
MAO-B - monoamine oxidase-B
COMT - catechol O-methyl transferase
GI - gastro-intenstinal

*Other includes: asthenia, fatigue, pain, peripheral edema, pruritis, sweating increased, syncope, weight increased.

Evidence Table 10. Pharmacological Studies: Neurological and Psychiatric Adverse Events

Adverse Events	Total		LD		DAs		LD/DA		LD/COMT		LD/DA/MAO-B		LD/MAO-B		Other		Placebo	
	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n
Neurological																		
Akinesia	20.6	413	23.9	205	-	0	17.3	208	-	0	-	0	-	0	-	0	-	0
Ataxia	10.8	622	6.5	245	-	0	16.1	274	6.8	103	-	0	-	0	-	0	-	0
Dizziness	18.9	4,076	15.5	1,975	-	0	26.3	1,511	14.6	384	-	0	9.6	73	2.8	72	1.6	61
Dyskinesias	23.1	5,828	20.2	2,522	1.9	262	24.7	2,052	35.8	639	4.9	41	30.1	312	-	0	-	0
Dystonia	12.0	2,640	11.4	1,303	7.4	270	10.2	714	-	0	12.2	41	22.4	312	-	0	-	0
Headache	9.9	3,297	7.6	1,657	-	0	13.8	1,192	8.9	315	-	0	-	0	8.3	72	0.0	61
PD Aggravated	24.5	1,203	31.4	328	-	0	20.2	772	35.0	103	-	0	-	0	-	0	-	0
Tremor	11.1	934	10.7	476	-	0	11.6	458	-	0	-	0	-	0	-	0	-	0
Other	5.7	724	4.1	539	62.5	8	13.0	92	2.4	85	-	0	-	0	-	0	-	0
Psychiatric																		
Confusion	6.5	1,548	3.7	804	4.7	64	10.0	680	-	0	-	0	-	0	-	0	-	0
Depression	9.6	2,576	7.8	1,351	-	0	12.0	1,152	-	0	-	0	5.4	73	-	0	-	0
Hallucinations	7.6	4,052	5.1	1,790	9.9	172	10.2	1,595	10.2	324	-	0	-	0	-	0	2.3	171
Sleeping Disorders	25.4	5,009	19.2	2,238	43.9	164	30.4	1,697	31.6	639	-	0	15.0	100	-	0	21.6	171
Other	12.2	2,048	9.9	817	-	0	10.4	769	20.2	435	-	0	3.7	27	-	0	-	0

Neurological Other: Chorea, freezing, hemiparesis, hyperkinesia, paresthesia, vertigo
Psychiatric Other: Agitation, amnesia, anorexia, anxiety, appetite increase, dementia, psychosis

n - number of patients
LD - levodopa
DA - dopamine agonist
MAO-B - monoamine oxidase-B
COMT - catechol O-methyl transferase
GI - gastro-intenstinal

ence Table 11. Treatment Level Characteristics of Surgical Studies

Type of Surgery	Surgical Studies	
	t	n
Pallidotomy	20	764
Thalamotomy	5	134
DBS	16	288
GPi	4*	22*
STN	8*	135*
thalamic	4*	131*
Tissue Transplant	9	165
Adrenal Medulla	3**	91**
Human fetal brain cells	5**	52**
Porcine fetal brain cells	1**	12**
No surgery	2	29
Total	52	1380

DBS - direct brain stimulation
Gpi- globus pallidus
STN- subthalamic nucleus
t- number of treatment arms
n- number of patients

* Subgroups of DBS
** Subgroups of Tissue Transplant

ıidence Table 12. Statistical Analysis: Pallidotomy

First Author	Year	Surgical Intervention	Number of Patients	Time of Evaluation (months)	Mean Age (years)	"Off" score Effect Sizes	"On" score Effect Sizes
Baron	2000	Unilateral	10	48	58.0	0.100	-0.200
Dalvi	1999	Medial	12	12	65.3	0.870	0.140
de Bie	1999	Unilateral	18	6	60.6	0.590	-0.130
Desaloms	1998	Unilateral	35	12	60.0	1.120	-
Dewey	2000	Unilateral	32	12	61.1	0.660	0.590
Dogali	1996	Unilateral	33	12	60.3	1.660	-
Eskandar	2000	Mixed	68	24	61.0	0.200	-0.100
Herrera	2000	Unilateral	13	16	60.0	0.930	-
Kondziolka	1999	Unilateral	58	9	67.0	0.750	0.280
Lang	1997	Unilateral	39	6	58.8	1.360	0.310
Masterman	1998	Unilateral	32	6	65.0	0.420	0.430
Melnick	1999	Medial	29	6	66.4	0.580	-
Samii	1999	Unilateral	20	12	61.0	1.430	-0.170
Samuel	1998	Unilateral	22	3	55.9	0.480	0.000
Shannon	1998	Unilateral	22	6	59.3	0.520	-0.200
Young	1998	Mixed	17	6	69.2	-	0.200

Evidence Table 13. Statistical Analysis: Deep Brain Stimulation

First Author	Year	Surgical Intervention	Number of Patients	Time of Evaluation (months)	Mean Age (years)	"Off" score Effect Sizes	"On" score Effect Sizes
Ardouin	1999	GPi	8	3	52.0	1.550	-
Ardouin	1999	GPi	5	6	55.0	0.990	-
Burchiel	1999	GPi	4	12	46.5	0.940	0.662
Krack	1998	GPi	5	6	51.0	1.665	-0.552
Ardouin	1999	STN	41	3	54.9	2.753	-
Ardouin	1999	STN	8	6	53.4	1.317	-
Bejjani	2000	STN	10	6	54.0	3.712	2.472
Burchiel	1999	STN	5	12	62.8	0.903	1.442
Houeto	2000	STN	23	6	53.0	1.644	0.795
Krack	1998	STN	8	6	51.0	3.243	0.335
Limousin	1998	STN	20	12	56.0	2.945	0.077
Molinuevo	2000	STN	15	6	60.9	-0.094	0.424
Kumar	1999	Thal	11	16	71.0	0.131	-
Limousin	1999	Thal	73	12	61.5	-0.108	-

GPi = globus pallidus
STN = subthalamic nucleus
Thal = thalamic

dence Table 14. Statistical Analysis: Tissue Transplantation

First Author	Year	Number of Patients	Time of Evaluation (months)	Mean Age (years)	"Off" score Effect Sizes	"On" score Effect Sizes
Fink	2000	12	12	61.0	0.740	-
Henderson	1991	9	12	56.0	0.480	-0.030
Kopyov	1996	22	24	55.0	0.830	0.830
Kopyov	1997	6	6	53.0	-	1.040
Kopyov	1997	7	6	60.0	-	2.380
Lopez-Lozano	1997	10	60	61.0	1.670	1.640

/idence Table 15. Surgical Studies: Adverse Events*

	Total		Pallidotomy		Thalamotomy		DBS		Transplant	
	%	n	%	n	%	n	%	n	%	n
Deaths	5.4	672	3.0	398	1.5	65	4.8	84	15.2	125
Treatment Related Deaths	1.9	567	1.3	307	0	23	1.2	82	8.2**	73
Adverse Events										
Infections	7.4	122	3.6	56	-	NR	4.2	24	14.3	42
Cardiac	4.0	75	5.6	18	0	23	4.5	22	8.3	12
Neurological	6.7	668	5.3	488	15.3	59	8.1	111	10.0	10
Gastrointestinal	5.0	80	4.3	70	-	NR	-	NR	10.0	10
Musculoskeletal	6.3	96	6.3	96	-	NR	-	NR	-	NR
Neoplasm	4.1	48	4.1	48	-	NR	-	NR	-	NR
Psychiatric	6.9	404	6.0	250	8.7	23	8.3	60	8.5	71
Cerebrovascular	6.4	342	7.1	237	0	23	4.3	46	8.3	36

*Does not include studies in which adverse events were reported in terms of # of events, rather than # of patients

*Does not include short-term, transient, postoperative adverse events.

** All transplant-related deaths occurred in adrenal medulla transplant patients.

n - number of patients in treatment groups reporting event

% - % of patients with event in studies reporting the event

NR - Not Reported

0 - no events were reported and one or more studies reported 0 events

DBS - deep brain stimulation

Infections include pneumonia, sepsis, and nonspecific infections.

Cerebrovascular includes hemorrhage and stroke

Evidence Table 16. Treatment Level Characteristics of Ancillary Studies

Author	Year	Study design	Level of Evidence	Quality Score	n	Duration	Intervention
Adams	1992	XS	III	NA	10	NA	Speech Therapy
Comella	1996	XO-RCT	II	2	18	1 month	PT
Dam	1996	nRCT	III	NA	40	12 months	PT
DeAngelis	1997	UCS	III	NA	20	1 month	Speech Therapy
Formisano	1992	nRCT	III	NA	33	4 months	PT
Jahanshahi	1994	RCT	II	1	40	6 months	NP
Katsikitis	1996	RCT	II	1	16	1 month	OPT
Mally	1999	UCS	III	NA	10	10 days	TMS
Mercer	1996	RCT	II	2	50	12 months	PROPATH
Montgomery	1994	RCT	I	2	400	6 months	PROPATH
Nagaya	2000	XS	III	NA	10	NA	Swallowing Therapy
Pacchetti	2000	RCT	II	1	32	3 months	PT vs MT
Patti	1996	RCT	II	1	20	6 months	In-patient Rehab
Platz	1998	RCT	II	1	15	< 1 month	PT
Ramig	1995	RCT	II	2	45	1 month	LSVT
Ramig	1996	RCT	II	2	35	12 months	LSVT
Reynolds	2000	RCT	I	2	185	12 months	NP
Schenkman	1998	RCT	II	2	51	2.5 months	PT
Sitzia	1998	nRCT	III	NA	60	1-2 months	In-patient Rehab
Thaut	1996	RCT	II	1	37	< 1 month	PT (RAS)

Level of Evidence - I-V, I is best
Quality Score - 1-5, 5 is best

n = number of patients

PT = physical therapy
RAS = rhythmic auditory stimulation
LSVT = Lee Silverman Voice Treatment
NP = nurse practitioner
PROPATH = a patient education and health promotion program
OPT = orofacial physiotherapeutic treatment
TMS = transcranial magnetic stimulation
MT = music therapy

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Appendix A. Major Parkinson's Disease Rating Scales

Numerous rating scales and diagnostic criteria are used to evaluate the severity of PD. While the most common scale in current use is the UPDRS, many of the studies in the database reported other scales. This section provides a brief description of the major scales and diagnostic criteria that are used to evaluate clinical severity of PD.

List of Scales Used:

1. Unified Parkinson Disease Rating Scale (UPDRS)
2. Abnormal Involuntary Movements Scale (AIMS Score)
3. Activities of Daily Living (ADL)
4. Barthel Index
5. Beck Depression Inventory
6. Brief Psychiatric Rating Scale (BPRS)
7. Columbia University Rating Scale (CURS)
8. Dyskinesia rating scale
9. Hamilton Depression Scale (HAM-D)
10. Hoehn and Yahr Clinical Staging Scale
11. Levodopa Equivalent Units (LEU)
12. Mini-Mental Status Exam (MMSE)
13. Northwestern University Disability Scale (NUDS or NWUDS)
14. Phenyl Ethyl Alcohol or Detection Threshold (PEA)
15. Parkinson Psychosis Rating Scale (PPRS)
16. Proposed Diagnostic Criteria for Parkinson Disease
17. Schwab & England Activities of Daily Living Scale (S&E) and (SEADL)
18. Sickness Impact Profile (SIP)
19. UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria
20. University of Pennsylvania Smell Identification Test (UPSIT)
21. Webster's Parkinson's Disease Rating Scale (WPDRS)

Unified Parkinson Disease Rating Scale (UPDRS)[1]

The UPDRS is a rating tool to follow the longitudinal course of Parkinson's Disease. A total of 199 points are possible. 199 represents the worst (total) disability, 0 indicates no disability.

UPDRS is made up of three distinct subscales:

I. Mentation, behavior, and mood
II. Activities of daily living (ADL) during "off" and "on" periods
III. Motor function during "on" periods

A fourth subscale is also sometimes used:

IV. Complications of therapy (In the past week)

Sections composing each subscale are usually 0-4 points.

These scores are calculated by interviewing the patient. Some sections require multiple grades assigned to each extremity.

I. MENTATION, BEHAVIOR, AND MOOD

1. Intellectual Impairment

0 = None.

1 = Mild. Consistent forgetfulness with partial recollection of events and no other difficulties.

2 = Moderate memory loss, with disorientation and moderate difficulty handling complex problems. Mild but definite impairment of function at home with need of occasional prompting.

3 = Severe memory loss with disorientation for time and often to place. Severe impairment in handling problems.

4 = Severe memory loss with orientation preserved to person only. Unable to make judgements or solve problems. Requires much help with personal care. Cannot be left alone at all.

2. Thought Disorder (Due to dementia or drug intoxication)

0 = None.

1 = Vivid dreaming.

2 = "Benign" hallucinations with insight retained.

3 = Occasional to frequent hallucinations or delusions; without insight; could interfere with daily activities.

4 = Persistent hallucinations, delusions, or florid psychosis. Not able to care for self.

3. Depression

0 = None

1 = Periods of sadness or guilt greater than normal, never sustained for days or weeks.

2 = Sustained depression (1 week or more).

3 = Sustained depression with vegetative symptoms (insomnia, anorexia, weight loss, loss of interest).

4 = Sustained depression with vegetative symptoms and suicidal thoughts or intent.

4. Motivation/Initiative

0 = Normal.

1 = Less assertive than usual; more passive.

2 = Loss of initiative or disinterest in elective (nonroutine) activities.

3 = Loss of initiative or disinterest in day to day (routine) activities.

4 = Withdrawn, complete loss of motivation.

II. ACTIVITIES OF DAILY LIVING (ADL) for both "off" and "on"

5. Speech

0 = Normal.

1 = Mildly affected. No difficulty being understood.

2 = Moderately affected. Sometimes asked to repeat statements.

3 = Severely affected. Frequently asked to repeat statements.

4 = Unintelligible most of the time.

6. Salivation

0 = Normal.

1 = Slight but definite excess of saliva in mouth; may have nighttime drooling.

2 = Moderately excessive saliva; may have minimal drooling.

3 = Marked excess of saliva with some drooling.

4 = Marked drooling, requires constant tissue or handkerchief.

7. Swallowing

0 = Normal.

1 = Rare choking.

2 = Occasional choking.

3 = Requires soft food.

4 = Requires NG tube or gastrotomy feeding.

8. Handwriting

0 = Normal.

1 = Slightly slow or small.

2 = Moderately slow or small; all words are legible.

3 = Severely affected; not all words are legible.

4 = The majority of words are not legible.

9. Cutting food and handling utensils

0 = Normal.

1 = Somewhat slow and clumsy, but no help needed.

2 = Can cut most foods, although clumsy and slow; some help needed.

3 = Food must be cut by someone, but can still feed slowly.

4 = Needs to be fed.

10. Dressing

0 = Normal.

1 = Somewhat slow, but no help needed.

2 = Occasional assistance with buttoning, getting arms in sleeves.

3 = Considerable help required, but can do some things alone.

4 = Helpless.

11. Hygiene

0 = Normal.

1 = Somewhat slow, but no help needed.

2 = Needs help to shower or bathe; or very slow in hygienic care.

3 = Requires assistance for washing, brushing teeth, combing hair, going to bathroom.

4 = Foley catheter or other mechanical aids.

12. Turning in bed and adjusting bed clothes

0 = Normal.

1 = Somewhat slow and clumsy, but no help needed.

2 = Can turn alone or adjust sheets, but with great difficulty.

3 = Can initiate, but not turn or adjust sheets alone.

4 = Helpless.

13. Falling (unrelated to freezing)

0 = None.

1 = Rare falling.

2 = Occasionally falls, less than once per day.

3 = Falls an average of once daily.

4 = Falls more than once daily.

14. Freezing when walking

0 = None.

1 = Rare freezing when walking; may have start hesitation.

2 = Occasional freezing when walking.

3 = Frequent freezing. Occasionally falls from freezing.

4 = Frequent falls from freezing.

15. Walking

0 = Normal.

1 = Mild difficulty. May not swing arms or may tend to drag leg.

2 = Moderate difficulty, but requires little or no assistance.

3 = Severe disturbance of walking, requiring assistance.

4 = Cannot walk at all, even with assistance.

16. Tremor (Symptomatic complaint of tremor in any part of body.)

0 = Absent.

1 = Slight and infrequently present.

2 = Moderate; bothersome to patient.

3 = Severe; interferes with many activities.

4 = Marked; interferes with most activities.

17. Sensory complaints related to parkinsonism

0 = None.

1 = Occasionally has numbness, tingling, or mild aching.

2 = Frequently has numbness, tingling, or aching; not distressing.

3 = Frequent painful sensations.

4 = Excruciating pain.

III. MOTOR EXAMINATION

18. Speech

0 = Normal.

1 = Slight loss of expression, diction and/or volume.

2 = Monotone, slurred but understandable; moderately impaired.

3 = Marked impairment, difficult to understand.

4 = Unintelligible.

19. Facial Expression

0 = Normal.

1 = Minimal hypomimia, could be normal "Poker Face".

2 = Slight but definitely abnormal diminution of facial expression

3 = Moderate hypomimia; lips parted some of the time.

4 = Masked or fixed facies with severe or complete loss of facial expression; lips parted 1/4 inch or more.

20. Tremor at rest (head, upper and lower extremities)

0 = Absent.

1 = Slight and infrequently present.

2 = Mild in amplitude and persistent. Or moderate in amplitude, but only intermittently present.

3 = Moderate in amplitude and present most of the time.

4 = Marked in amplitude and present most of the time.

21. Action or Postural Tremor of hands

0 = Absent.

1 = Slight; present with action.

2 = Moderate in amplitude, present with action.

3 = Moderate in amplitude with posture holding as well as action.

4 = Marked in amplitude; interferes with feeding.

22. Rigidity (Judged on passive movement of major joints with patient relaxed in sitting position. Cogwheeling to be ignored.)

0 = Absent.

1 = Slight or detectable only when activated by mirror or other movements.

2 = Mild to moderate.

3 = Marked, but full range of motion easily achieved.

4 = Severe, range of motion achieved with difficulty.

23. Finger Taps (Patient taps thumb with index finger in rapid succession.)

0 = Normal.

1 = Mild slowing and/or reduction in amplitude.

2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.

3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.

4 = Can barely perform the task.

24. Hand Movements (Patient opens and closes hands in rapid succesion.)

0 = Normal.

1 = Mild slowing and/or reduction in amplitude.

2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.

3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.

4 = Can barely perform the task.

25. Rapid Alternating Movements of Hands (Pronation-supination movements of hands, vertically and horizontally, with as large an amplitude as possible, both hands simultaneously.)

0 = Normal.

1 = Mild slowing and/or reduction in amplitude.

2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.

3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.

4 = Can barely perform the task.

26. Leg Agility (Patient taps heel on the ground in rapid succession picking up entire leg. Amplitude should be at least 3 inches.)

0 = Normal.

1 = Mild slowing and/or reduction in amplitude.

2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.

3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.

4 = Can barely perform the task.

27. Arising from Chair (Patient attempts to rise from a straightbacked chair, with arms folded across chest.)

0 = Normal.

1 = Slow; or may need more than one attempt.

2 = Pushes self up from arms of seat.

3 = Tends to fall back and may have to try more than one time, but can get up without help.

4 = Unable to arise without help.

28. Posture

0 = Normal erect.

1 = Not quite erect, slightly stooped posture; could be normal for older person.

2 = Moderately stooped posture, definitely abnormal; can be slightly leaning to one side.

3 = Severely stooped posture with kyphosis; can be moderately leaning to one side.

4 = Marked flexion with extreme abnormality of posture.

29. Gait

0 = Normal.

1 = Walks slowly, may shuffle with short steps, but no festination (hastening steps) or propulsion.

2 = Walks with difficulty, but requires little or no assistance; may have some festination, short steps, or propulsion.

3 = Severe disturbance of gait, requiring assistance.

4 = Cannot walk at all, even with assistance.

30. Postural Stability (Response to sudden, strong posterior displacement produced by pull on shoulders while patient erect with eyes open and feet slightly apart. Patient is prepared.)

0 = Normal.

1 = Retropulsion, but recovers unaided.

2 = Absence of postural response; would fall if not caught by examiner.

3 = Very unstable, tends to lose balance spontaneously.

4 = Unable to stand without assistance.

31. Body Bradykinesia and Hypokinesia (Combining slowness, hesitancy, decreased armswing, small amplitude, and poverty of movement in general.)

0 = None.

1 = Minimal slowness, giving movement a deliberate character; could be normal for some persons. Possibly reduced amplitude.

2 = Mild degree of slowness and poverty of movement which is definitely abnormal. Alternatively, some reduced amplitude.

3 = Moderate slowness, poverty or small amplitude of movement.

4 = Marked slowness, poverty or small amplitude of movement.

IV. COMPLICATIONS OF THERAPY (In the past week)

A. DYSKINESIAS

32. Duration: What proportion of the waking day are dyskinesias present? (Historical information.)

0 = None

1 = 1-25% of day.

2 = 26-50% of day.

3 = 51-75% of day.

4 = 76-100% of day.

33. Disability: How disabling are the dyskinesias? (Historical information; may be modified by office examination.)

0 = Not disabling.

1 = Mildly disabling.

2 = Moderately disabling.

3 = Severely disabling.

4 = Completely disabling.

34. Painful Dyskinesias: How painful are the dyskinesias?

0 = No painful dyskinesias.

1 = Slight.

2 = Moderate.

3 = Severe.

4 = Marked.

35. Presence of Early Morning Dystonia (Historical information.)

0 = No

1 = Yes

B. CLINICAL FLUCTUATIONS

36. Are "off" periods predictable?

0 = No

1 = Yes

37. Are "off" periods unpredictable?

0 = No

1 = Yes

38. Do "off" periods come on suddenly, within a few seconds?

0 = No

1 = Yes

39. What proportion of the waking day is the patient "off" on average?

0 = None

1 = 1-25% of day.

2 = 26-50% of day.

3 = 51-75% of day.

4 = 76-100% of day.

C. OTHER COMPLICATIONS

40. Does the patient have anorexia, nausea, or vomiting?

0 = No

1 = Yes

41. Any sleep disturbances, such as insomnia or hypersomnolence?

0 = No

1 = Yes

42. Does the patient have symptomatic orthostasis?

(Record the patient's blood pressure, height and weight on the scoring form)

0 = No

1 = Yes

AIMS Score (Abnormal Involuntary Movements Scale)[2]

This scale requires the examiner to observe the patient sitting quietly at rest and again while the patient carries out selected motor tasks (mouth opening, tongue protrusion, finger taps, and walking, among others). Seven body areas are rated: muscles of facial expression, lips and perioral area, jaw, tongue, upper and lower extremities, and trunk. A five-point scheme ranging from 0 (normal) to 4 (severe) is used to assess each body part. The worst dyskinesias seen in each body part are rated for the intensity of the movement and the chosen rating score is reduced by one point if that body region has dyskinesias during the quiet rest phase of the observation. There are also three global rating scales to complete: overall severity, incapacitation for the patient, and the patient's awareness of the dyskinesias. Finally, two interview questions for the patient concentrate on dental hygiene and the wearing of dentures.

Activities of Daily Living (ADL)[3]

The ADL scale measures the impact of PD on 14 categories, including:

- Speech
- Salivation
- Swallowing

- Handwriting
- Cutting food and handling utensils
- Dressing
- Hygiene
- Turning in bed and adjusting bedclothes
- Falling
- Freezing when walking
- Walking
- Left-sided tremor
- Right-sided tremor
- Sensory complaints.

Each category is scored on a 0-4 scale, with 0 indicating normal or unaffected functioning, and 4 signifying a patient who is helpless or non-ambulatory. For example, the response scale for cutting food and handling utensils is as follows:

0 = Normal

1 = Somewhat slow and clumsy, but no help needed

2 = Can cut most foods, although clumsy and slow; some help needed

3 = Food must be cut by someone, but can still feed slowly

4 = Needs to be fed

The scores for the 14 categories are summed to give an overall ADL score. The overall score ranges from 0 to 56, with higher scores reflecting greater disability and the need for assistance.

Barthel Index[4]

Full credit is not given for an activity if the patient needs even minimal help/supervision. A score of 0 is given when patient cannot meet criteria as defined.

1. Feeding

A(10 pts). Independent; feeds self from tray or table; can put on assistive device if needed; accomplishes feeding in reasonable time.

B(5 pts). Assistance necessary with cutting food, etc.

C(0 pts). Cannot meet criteria

2. Moving (from wheelchair to bed and return)

A(15 pts). Independent in all phases of this activity.

B(10 pts). Minimal help needed or patient needs to be reminded or supervised for safety of 1 or more parts of this activity.

C(5 pts). Patient can come to sitting position without help of second person but needs to be lifted out of bed and assisted with transfers.

D(0 pts). Cannot meet criteria

3. Personal Toilet

A(5pts). Can wash hands, face; combs hair, cleans teeth. Can shave (males) or apply makeup (females) without assistance; females need not brain or style hair.

B(0 pts). Cannot meet criteria

4. Getting On and Off Toilet

A(10 pts). Able to get on and off toilet, fastens/unfastens clothes, can use toilet paper without assistance. May use wall bar or other support if needed; if bedpan necessary patient can place it on chair, empty, and clean it.

B(5 pts). Needs help because of imbalance or other problems with clothes or toilet paper.

C(0 pts). Cannot meet criteria

5. Bathing Self

A(5 pts). May use bath tub, shower or sponge bath. Patient must be able to perform all functions without another person being present.

B(0 pts). Cannot meet criteria

6. Walking on Level Surface

A(15 pts). Patient can walk at least 50 yards without assistance or supervision; may use braces, prostheses, crutches, canes, or walkerette but not a rolling walker. Must be able to lock/unlock braces, assume standing or seated position, get mechanical aids into position for use and dispose of them when seated (putting on and off braces should be scored under dressing). 15

B(10pts). Assistance needed to perform above activities, but can walk 50 yards with little help.

C(0 pts). Cannot meet criteria

7. Propelling a Wheelchair

Do not score this item if patient gets score for walking.

A(5 pts). Patient cannot ambulate but can propel wheelchair independently; can go around corners, turn around maneuver chair to table, bed toilet, etc. Must be able to push chair 50 yards.

B(0 pts). Cannot meet criteria

8. Ascending and Descending Stairs

A(10 pts). Able to go up and down flight of stairs safely without supervision using canes, handrails, or crutches when needed and can carry these items as ascending/descending.

B(5 pts). Needs help with or supervision of any of the above items.

C(0 pts). Cannot meet criteria

9. Dressing/Undressing

A(10 pts). Able to put on, fasten and remove all clothing; ties shoelaces unless necessary adaptions used. Activity includes fastening braces and corsets when prescribed; suspenders, loafer shoes and dresses opening in the front may be used when necessary.

B(5 pts). Needs help putting on, fastening, or removing clothing; must accomplish at least half of task alone within reasonable time; women need not be scored on use of brassiere or girdle unless prescribed.

C(0 pts). Cannot meet criteria

10. Continence of Bowels

A(10 pts). Able to control bowels and have no accidents. Can use a suppository or take an enema when necessary (as for spinal cord injury patients who have had bowel training)

B(5 pts). Needs help in using a suppository or taking an enema or has occasional accidents.

C(0 pts). Cannot meet criteria

11. Controlling Bladder

A(10 pts). Able to control bladder day and night. Spinal injury patients must be able to put on external devices and leg bags independently, clean and empty bag, and must stay dry day and night.

B(5 pts). Occasional accidents occur, cannot wait for bed pan, does not get to toilet in time or needs help with external device.

C(0 pts). Cannot meet criteria.

Beck Depression Inventory[5]

This is a twenty question survey to be completed by the patient. Answers are scored on 0 to 3 scale, 0 = minimal, and 3 = severe.

1. Sadness
2. Hopelessness
3. Past failure
4. Anhedonia
5. Guilt
6. Punishment
7. Self-dislike
8. Self-blame
9. Suicidal thoughts
10. Crying

11. Agitation
12. Loss of interest in activities
13. Indecisiveness
14. Worthlessness
15. Loss of energy
16. Insomnia
17. Irritability
18. Decreased appetite
19. Diminished concentration
20. Fatigue
21. Lack of interest in sex

<15 = Mild Depression
15-30 = Moderate Depression
>30 = Severe Depression

Brief Psychiatric Rating Scale (BPRS)[6]

This scale consists of 24 symptom constructs, each to be rated in a 7-point scale of severity ranging from 1 (not present) to 7 (extremely severe). Total score ranges from 24-168, with higher scores indicating more severe psychosis.

1. Somatic concern
2. Anxiety
3. Depression
4. Suicidality
5. Guilt
6. Elated
7. Grandiosity

8. Suspiciousness
9. Hallucinations
10. Unusual thought content
11. Bizarre behavior
12. Self-neglect
13. Disorientation
14. Conceptual disorganization
15. Blunted affect
16. Emotional withdrawal
17. Motor retardation
18. Tension
19. Uncooperativeness
20. Excitement
21. Distractibility
22. Motor hyperactivity
23. Mannerisms and posturing

Columbia University Rating Scale (CURS)[7]

This scale was presented in 1970 by researchers from Columbia University who used it in their initial L-dopa trials. Total scores range from 0-65, 0 is normal and 65 is maximum disability. This scale was a modification of the Webster scale (see page C22), which was published in 1968. In addition to the activities measured in the Webster scale, this scale also measures salivation, arising from a chair, postural stability and rapid movements of fingers, hands and feet. Subsequent modifications of this scale include NYU Scale and Kings College Hospital Scale.

1. Facial Expression

0 = Normal

1 = Minimal hypomimia, could be normal ‘poker face’

2 = Slight but definitely abnormal dimunition of facial expression

3 = Moderate hypomimia

4 = Masked or fixed facies with severe or complete loss of facial expression

2. Seborrhea

0 = Normal

1 = Greasy forehead, no dermatitis

2 = Mild dermatitis, erythema, and scaling

3 = Moderate dermatitis

4 = Severe dermatitis

3. Sialorrhea

0 = None

1 = Slight but definite excess of saliva in pharynx (patients may be unaware of it); no drooling

2 = Moderately excessive saliva with minimal drooling, if any

3 = Marked excess of saliva with some drooling

4 = Marked drooling, requiring special measures

4. Speech Disorder

0 = Normal

1 = Slight loss of expression, diction, and/or volume

2 = Monotone, slurred but understandable

3 = Marked impairment, difficult to understand

4 = Unintelligible

5. **Arising from chair** (with straight back)

   0 = Normal

   1 = Slow

   2 = Pushes self up from arms or seat

   3 = Tends to fall back and may have to try several times but can get up without help

   4 = Unable to arise without help

6. **Posture**

   0 = Normal erect

   1 = Not quiet erect, slightly stooped, could be normal for older people

   2 = Moderate simian posture, definitely abnormal

   3 = Marked simian posture with kyphosis

   4 = Severe flexion with extreme abnormality of posture

7. **Postural Stability** (If Romberg is normal, judge response to sudden posterior displacement produced by push of sternum)

   0 = Normal

   1 = Retropulsion, but recovers unaided

   2 = Absence of postural response; would fall if not caught

   3 = Very unstable, tends to fall

   4 = Unable to stand without assistance

8. **Gait Disturbance**

   0 = Freely ambulatory, good stepping, turns readily

   1 = Walks slowly, may shuffle with short steps; no festination or propulsion

   2 = Walks with great difficulty, with festination, short steps; shows freezing and pulsing but requires little or no assistance

3 = Severe disturbance, requires frequent assistance

4 = Cannot walk, even with help

9. **Tremor** (Head and four limbs are scored separately; maximum score = 20.)

   0 = Absent

   1 = Slight and infrequently present

   2 = Moderate in amplitude but only intermittently present

   3 = Moderate and present most of the time

   4 = Marked in amplitude and present most of the time

10. **Finger Dexterity** (Tested in both hands; maximum score = 8; patients taps thumb with forefinger, then with each finger in rapid succession.)

    0 = No dysfunction

    1 = Slightly slow, may be normal

    2 = Definite dysfunction

    3 = Very slow with frequent errors

    4 = Unable to perform test

11. **Succession Movements** (Tested in both hands; maximum score = 8; patient taps knees alternatively with palm and dorsum of hands.)

    0 = No dysfunction

    1 = Slightly slow; may be normal

    2 = Definite dysfunction

    3 = Very slow with frequent errors

    4 = Unable to perform test

12. **Foot Tapping** (Tested in both feet; maximum sore = 8; using heel as fulcrum, patients taps floor with ball of foot.)

    0 = Normal

1 = Slightly slow

2 = Slow

3 = Markedly slow

4 = Unable to perform test

13. Bradykinesia (Combining both slowness and poverty of movement in general.)

0 = None

1 = Minimal slowness giving movement a deliberate character

2 = Mild degree of slowness and poverty of movements; definitely abnormal

3 = Moderate slowness; occasional hesitation on initiating movements and arrests of ongoing movements

4 = Marked slowness and poverty of movement; frequent freezing and long delays in initiating movements

Dyskinesia Rating Scale[8]

Several variations of the rating scale for dyskinesia are used. This Dyskinesia Scale Score is the arithmetic mean of the intensity and duration scores, and is only assessed in the "on" state.

The intensity score is given as score and definition:

0 = absent

1 = minimal severity: patient is not aware of dyskinesias

2 = patient is conscious of the presence of dyskinesias but there is no interference with voluntary motor acts

3 = dyskinesias may impair voluntary movements but patient is normally capable of undertaking most motor tasks

4 = intense interference with movement control, and daily life activities are greatly limited

5 = violent dyskinesias, incompatible with any normal motor task

The duration score is given as score and definition:

0 = absent

1 = only present when carrying out motor tasks

2 = present between 25-50% of waking hours

3 = present between 51-75% of waking hours

4 = present between 76-99% of waking hours

5 = continuous throughout the day, 100%

Hamilton Depression Scale (HAM-D)[9]

This is a twenty one question survey to be completed by a physician. The range is 0-64 points, higher score = more severe depression.

1. Depressed mood (0 to 4)
2. Feelings of guilt (0 to 4)
3. Suicide (0 to 4)
4. Insomnia
    5. Early (0 to 2)
    6. Middle (0 to 2)
    7. Late (0 to 2)
8. Work activities (0 to 4)
9. Retardation to stupor (0 to 4)
10. Agitation (0 to 2)
11. Fear (0 to 4)
12. Anxiety (0 to 4)
13. Gastrointestinal symptoms (0 to 2)
14. Systemic somatic symptoms (0 to 2)

15. Decreased libido or menstrual disturbance (0 to 2)

16. Hypochondiasis (0 to 4)

17. Weight loss (0 to 2)

18. Diminished insight (0 to 2)

19. Symptom diurnal variation (1 to 2)

20. Feelings of unreality (0 to 4)

21. Paranoid symptoms (0 to 3)

22. Obsessive Compulsive Symptoms (0 to 2)

10-13: Mild depression
14-17: Moderate depression
>17: Severe depression

Hoehn and Yahr Clinical Staging Scale[10]

Stages I-V, lower stage indicates better function.

Stage I.
Unilateral involvement only, usually with minimal or no functional impairment.

Stage II.
Bilateral or midline involvement, without impairment of balance.

Stage III.
First sign of impaired righting reflexes. This is evident by unsteadiness as the patient turns or is demonstrated when he is pushed from standing equilibrium with the feet together and eyed closed. Functionally the patient is somewhat restricted in his activities but may have some work potential depending upon the type of employment. Patients are physically capable of leading independent lives, and their disability is mild to moderate.

Stage IV.
Fully developed, severely disabling disease; the patient is still able to walk and stand unassisted but is markedly incapacitated.

Stage V.
Confinement to bed or wheelchair unless aided.

Modified Hoehn and Yahr Staging

Stage 0 = No signs of disease.

Stage 1 = Unilateral disease.

Stage 1.5 = Unilateral plus axial involvement.

Stage 2 = Bilateral disease, without impairment of balance.

Stage 2.5 = Mild bilateral disease, with recovery on pull test.

Stage 3 = Mild to moderate bilateral disease; some postural instability; physically independent.

Stage 4 = Severe disability; still able to walk or stand unassisted.

Stage 5 = Wheelchair bound or bedridden unless aided.

This rating system has been largely replaced by the Unified Parkinson's Disease Rating Scale (UPDRS).

Levodopa Equivalent Units (LEU)[11]

Conversion formula:

100 LEU = 100 mg regular L-dopa, given with a peripheral decarboxylase inhibitor = 133 mg L-dopa plus DCI in controlled-release tablets = 10 mg bromocriptine = 1 mg pergolide mesylate.

Mini-Mental Status Exam (MMSE)[12]

Range 0-30, lower scores indicate more severe impairment.

This scale is widely used for assessing cognitive mental status. As a clinical instrument, the MMSE has been used to detect impairment, follow the course of an illness, and monitor response to treatment. While the MMSE has limited specificity with respect to individual clinical syndromes, it represents a brief, standardized method by which to grade cognitive mental status. It assesses orientation, attention, immediate and short-term recall, language, and the ability to follow simple verbal and written commands. Furthermore, it provides a total score that places the individual on a scale of cognitive function.

Northwestern University Disability Scale (NUDS or NWUDS)[13]

Clinical experience suggested that the symptoms of Parkinson's Disease make themselves felt most frequently in the areas of walking, personal hygiene, dressing, eating and feeding, and

speaking. These five areas constitute the range of this scale. It was decided to assign a maximum of 20 points to each of the five sub-scales, in this way a total of 100 points is possible, so that the degree of disability may be expressed as a percentage. Lower score represents greater disability.

Scale A: Walking

Never Walks Alone

0 Cannot walk at all, even with maximum assistance.

1 Needs considerable help even for short distances; cannot walk outdoors with help.

2 Requires moderate help indoors; walks outdoors with considerable help.

3 Requires potential help indoors and active help outdoors.

Sometimes Walks Alone

4 Walks from room to room without assistance, but moves slowly and uses external support; never walks alone outdoors.

5 Walks from room to room with only moderate difficulty; may occasionally walk outdoors without assistance.

6 Walks short distances with ease; walking outdoors is difficult but often accomplished without help; rarely walks longer distances alone.

Always Walks Alone

7 Gait is extremely abnormal; very slow and shuffling; posture grossly affected; there may be propulsion.

8 Quality of gait is poor and rate is slow; posture moderately affected; there may be a tendency toward mild propulsion; turning is difficult.

9 Gait only slightly deviant from normal in quality and speed; turning is the most difficult task; posture essentially normal.

10 Normal.

Scale B: Dressing

Requires Complete Assistance

0 Patient is a hindrance rather than a help to assistant.

1 Movements of patient neither help nor hinder assistant.

2 Can give some help through bodily movements.

3 Gives considerable help through bodily movements.

Requires Partial Assistance

4 Performs only gross dressing activities alone (hat, coat).

5 Performs about half of dressing activities independently.

6 Performs more than half of dressing activities alone, with considerable effort and slowness.

7 Handles all dressing alone with the exception of fine activities (tie, buttons).

Complete Self-Help

8 Dresses self completely with slowness and great effort

9 Dresses self completely with only slightly more time and effort than normal

10 Normal

Scale C: Hygiene

Requires Complete Assistance

0 Unable to maintain proper hygiene even with maximum help.

1 Reasonably good hygiene with assistance, but does not provide assistant with significant help.

2 Hygiene maintained well; gives aid to assistant

Requires Partial Assistance

3 Performs a few tasks alone with assistant nearby.

4 Requires assistance for half of toilet needs.

5 Requires assistance for some tasks not difficult in terms of co-ordination.

6 Manages most of personal needs alone; has substituted methods for accomplishing difficult tasks (electric razor).

Complete Self-Help

7 Hygiene maintained independently, but with effort and slowness; accidents are not infrequent; may employ substitute methods.

8 Hygiene activities are moderately time-consuming; no substitute methods; few accidents.

9 Hygiene maintained normally, with exception of slight slowness.

10 Normal.

Scale D: Eating and Feeding

Eating

0 Eating is so impaired that a hospital setting is required to get adequate nutrition.

1 Eats only liquids and soft food; these are consumed very slowly.

2 Liquids and soft food handled with ease; hard foods occasionally eaten, but require great effort and much time.

3 Eats some hard food routinely, but these require time and effort.

4 Follows a normal diet, but chewing and swallowing are labored.

5 Normal

Feeding

0 Requires complete assistance.

1 Performs only a few feeding tasks independently.

2 Performs most feeding activities alone, slowly and with effort; requires help with specific tasks (cutting meat, filling cup).

3 Handles all feeding alone with moderate slowness; still may get assistance in specific situations (cutting meat in restaurant); accidents not infrequent.

4 Fully feeds self with rare accidents; slower than normal.

5 Normal

Scale E: Speech

0 Does not vocalize at all.

1 Vocalizes but rarely for communicative purposes.

2 Vocalizes to call attention to self.

3 Attempts to use speech for communication, but has difficulty in initiating vocalization; may stop speaking in middle of phrase and be unable to continue.

4 Uses speech for most of communication, but articulation is highly unintelligible; may have occasional difficulty in initiating speech; usually speaks in single words or short phrases.

5 Speech always employed for communication, but articulation is still very poor; usually uses complete sentences.

6 Speech can always be understood if listener pays close attention; both articulation and voice may be defective.

7 Communication accomplished with ease, although speech impairment detracts from content.

8 Speech easily understood, but voice or speech rhythm may be disturbed.

9 Speech entirely adequate; minor voice disturbances present.

10 Normal.

Phenyl Ethyl Alcohol or Detection Threshold (PEA)[14]

Detection threshold is a measure of the lowest concentration of a particular olfactory stimulus required to activate peripheral receptors and trigger the perception of the stimulus. To assess olfactory threshold, ascending (10^{-7} –1 mol) dilutions of phenyl-ethyl-alcohol are administered; the threshold value is defined as the lowest concentration that is perceived.

Parkinson Psychosis Rating Scale (PPRS)[15]

This scale was designed to assess the severity of specific symptoms of levodopa-induced psychosis in patients with Parkinson's disease.

Visual Hallucinations

1. Absent
2. Mild: Occasional; complete or partial insight; nonthreatening
3. Moderate: Frequent; absence of full insight; can be convinced; may be threatening
4. Severe: Persisitent hallucinations; no insight; associated with heightened emotional tone, agitation, agression

Illusions and Misidentification of Persons

1. Absent
2. Mild: Occurring infrequently
3. Moderate: Occurring very often
4. Severe: Occurring persistently

Paranoid Ideation (persecutory and/or jealous type)

1. Absent
2. Mild: Associated with suspiciousness
3. Moderate: Associated with tension and excitement
4. Severe: Accusations of family members, aggression and/or lack of cooperation (i.e., refusal to eat and/or take medication)

Sleep Disturbances

1. Absent
2. Mild: Associated with anxiety
3. Moderate: Night terrors with recurrent awakening and feeling of danger
4. Severe: Nightmares with recurrent awakenings, associated with agitation and confusion

Confusion

1. Absent
2. Mild: Disorientation in time/place/person

3. Moderate: Confusion combined with impaired attention/concentration/ registration/recall/interruption of goal-directed actions

4. Severe: Very confused with or without delirium

Sexual Preoccupation

1. Absent

2. Mild: Thoughts, dreams, worry about sexual competence

3. Moderate: Increased demand for sexual activity

4. Severe: Violent sexual impulsiveness

8-12: Mild disease
13-18: Moderate disease
19-24: Severe disease

Proposed Diagnostic Criteria for Parkinson's Disease[16]

Criteria for POSSIBLE diagnosis of Parkinson disease:

At least 2 of the 4 features in Group A* are present; at least 1 of these is tremor or bradykinesia
AND
EITHER None of the features in Group B** is present
OR Symptoms have been present for less than 3 years, and none of the features in Group B is present to date
AND
EITHER Substantial and sustained response to levodopa or a dopamine agonist has been documented
OR Patient has not had an adequate trial of levodopa or dopamine agonist

Criteria for PROBABLE diagnosis of Parkinson disease:

At least 3 of the 4 features in Group A are present
AND
None of the features in Group B is present (note: symptom duration of at least 3 years is necessary to meet this requirement)
AND
Substantial and sustained response to levodopa or a dopamine agonist has been documented

Criteria for DEFINITE diagnosis of Parkinson disease:

All criteria for POSSIBLE Parkinson disease are met

AND

Histopathologic confirmation of the diagnosis is obtained at autopsy***

*Group A features: Characteristic of Parkinson disease

1. Resting tremor

2. Bradykinesia

3. Rigidity

4. Asymmetric onset

**Group B features: Suggestive of alternative diagnoses

1. Prominent postural instability in the first 3 years after symptom onset

2. Freezing phenomena in the first 3 years

3. Hallucinations unrelated to medications in the first 3 years

4. Dementia preceding motor symptoms or in the first year

5. Supranuclear gaze palsy (other than restriction of upward gaze) or slowing of vertical saccades

6. Severe, symptomatic dysautonomia unrelated to medications

7. Documentation of a condition known to produce parkinsonism and plausibly connected to the patient's symptoms (such as suitably located focal brain lesions or neuroleptic use within the past 6 months)

***Proposed criteria for histopathologic confirmation of Parkinson disease:

A. Substantial nerve cell depletion with accompanying gliosis in the substantia nigra

B. At least 1 Lewy body in the substantia nigra or in the locus ceruleus
(note: it may be necessary to examine up to 4 nonoverlapping sections in each of these areas before concluding that Lewy bodies are absent)

C. No pathologic evidence for other diseases that produce parkinsonism
(eg, progressive supranuclear palsy, multiple system atrophy, cortical-basal ganglionic degenration)

Schwab & England Activities of Daily Living Scale (S&E) or (SEADL)[17]

Range 0-100%, with higher % meaning less severe disease

The rating can be assigned by the rater or by the patient.

- **100%**-Completely independent. Able to do all chores without slowness, difficulty, or impairment.
- **90%**-Completely independent. Able to do all chores with some slowness, difficulty, or impairment. May take twice as long.
- **80%**-Independent in most chores. Takes twice as long. Conscious of difficulty and slowing.
- **70%**-Not completely independent. More difficulty with chores. 3 to 4X along on chores for some. May take large part of day for chores.
- **60%**-Some dependency. Can do most chores, but very slowly and with much effort. Errors, some impossible.
- **50%**-More dependant. Help with 1/2 of chores. Difficulty with everything.
- **40%**-Very dependant. Can assist with all chores but few alone.
- **30%**-With effort, now and then does a few chores alone of begins alone. Much help needed.
- **20%**-Nothing alone. Can do some slight help with some chores. Severe invalid.
- **10%**-Totally dependant, helpless.
- **0%**-Vegetative functions such as swallowing, bladder and bowel function are not functioning. Bedridden.

Sickness Impact Profile (SIP)[18]

The Sickness Impact Profile (SIP) is a general quality of life scale. It consists of 136 items (statements) which measure 12 distinct domains of quality of life:

- Ambulation

- Movement and mobility
- Body care
- Social interaction
- Communication
- Alertness
- Emotional behavior
- Sleep
- Eating
- Work
- Household management
- Recreation

The SIP can be administered by an interviewer or by the patients themselves. Although it is easy to administer and score, it is relatively time-consuming, taking approximately 30 minutes to complete.

Patients identify those statements which describe their experience. Each item is weighted depending on the severity of dysfunction. For each category, the scores are summed and expressed as a percentage of the maximum score possible. Higher scores represent greater dysfunction. Although scores can be calculated for each of the 12 individual domains, three summary scores are typically calculated and reported: total score (includes all domains), a physical score (ambulation, body care, and movement and mobility), and a psychosocial score (emotional behavior, social interaction, alertness, and communication).

UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria[19]

1. Diagnosis of PARKINSONIAN SYMPTOMS:

BRADYKINESIA (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions).
And at least one of the following:

a. muscular rigidity

b. 4-6 Hz rest tremor

c. postural instability not caused by primary visual, vestibular, cerebellar or proprioceptive dysfunction.

2. Exclusion criteria for Parkinson's disease:

a. history of repeated strokes with stepwise progression of Parkinsonian features

b. history of repeated head injury

c. history of definite encephalitis

d. oculogyric crises

e. neuroleptic treatment at onset of symptoms

f. more than one affected relative

g. sustained remission

h. strictly unilateral features after three years

i. supranuclear gaze palsy

j. cerebellar signs

k. early severe autonomic involvement

l. early severe dementia with disturbances of memory, language and praxis

m. Babinski sign

n. presence of a cerebral tumor or communicating hydrocephalus on CT scan

o. negative response to large doses of levodopa (if malabsorption excluded)

p. MPTP exposure

3. Supportive prospective criteria for PARKINSON'S DISEASE. Three or more required for diagnosis of definite Parkinson's Disease.

a. unilateral onset

b. rest tremor present

c. progressive disorder

d. persistent asymmetry affecting the site of onset most

e. excellent response (70-100%) to levodopa

f. severe levodopa-induced chorea

g. levodopa response for 5 years or more

h. clinical course of 10 years or more

University of Pennsylvania Smell Identification Test (UPSIT)[14]

This is a standardized tool that has been widely used in the evaluation of patients affected by neurodegenerative disorders. This “scratch and sniff” test consists of 40 multiple-choice items. The range of scores is 0-40, 40 being the best score. The patient is required to mark one of the four alternatives even if no smell is perceived. To establish the meaning of a given individual’s test score, it is compared to scores from normal persons of equivalent age and gender using tables providing an easy-to-interpret measure of an individual’s performance. In this classification scheme, anosmia is defined as total inability to perceive qualitative odor sensations, whereas microsmia is defined operationally as decreased ability to smell. Microsmia can be further subdivided into “severe,” “moderate,” and “mild” classes. The 40-item UPSIT can be used in both clinical and experimental settings to test patients affected by PD and related disorders.

Webster's Parkinson’s Disease Rating Scale (WPDRS)[20]

This scale was developed as a simple rating scale that can be used to evaluate the degree of total parkinsonian disabilities. It applies a gross clinical rating to each of the 10 listed items, assigning value rating of 0-3 for each item, where 0 = no involvement and 1, 2, and 3 are equated to early, moderate, and severe disease, respectively. Scores range from 0 to 30, and decline represents decrease in severity of PD signs. Values of 1 to 10 indicate early illness; 11 to 20, moderate disability; and 21 to 30, severe or advanced disease.

Bradykinesia of Hands – Including Handwriting

0 = No involvement.

1 = Detectable slowing of the supination-pronation rate, evidenced by beginning difficulty in handling tools, buttoning clothes, and with handwriting.

2 = Moderate slowing of supination-pronation rate, one or both sides, evidenced by moderate impairment of hand function. Handwriting is greatly impaired, micrographia present.
3 = Severe slowing of supination-pronation rate. Unable to write or button clothes. Marked difficulty in handling utensils.

Rigidity

0 = Non-detectable.

1 = Detectable rigidity in neck and shoulders. Activation phenomenon is present. One or both arms show mild, negative, resting rigidity.

2 = Moderate rigidity in neck and shoulders. Resting rigidity is positive when patient not on medication.

3 = Severe rigidity in neck and shoulders. Resting rigidity cannot be reversed by medication.

Posture

0 = Normal posture. Head flexed forward less than 4 inches.

1 = Beginning poker spine. Head flexed forward up to 5 inches.

2 = Beginning arm flexion. Head flexed forward up to 6 inches. One or both arms raised but still below waist.

3 = Onset of simian posture. Head flexed forward more than 6 inches. One or both hands elevated above the waist. Sharp flexion of hand, beginning interphalangeal extension. Beginning flexion of knees.

Upper Extremity Swing

0 = Swings both arms well.

1 = One arm definitely decreased in amount of swing.

2 = One arm fails to swing.

3 = Both arms fail to swing.

Gait

0 = Steps out well with 18-30 inch stride. Turns about effortlessly.

1 = Gait shortened to 12-18 inch stride. Beginning to strike one heel. Turn around time slowing. Requires several steps.

2 = Stride moderately shortened – now 6-12 inches. Both heels beginning to strike floor.

3 = Onset of shuffling gait, steps less than 3 inches. Occasional stuttering-type or blocking gait. Walks on toes-turns around very slowly.

Tremor

0 = No detectable tremor found.

1 = Less than one inch of peak-to-peak tremor movement observed in limbs or head at rest or in either hand while walking or during finger to nose testing.

2 = Maximum tremor envelope fails to exceed 4 inches. Tremor is severe but not constant and patient retains some control of hands.

3 = Tremor envelope exceeds 4 inches. Tremor is constant and severe. Patient cannot get free of tremor while awake unless it is a pure cerebellar type. Writing and feeding himself is impossible.

Facies

0 = Normal. Full animation. No stare

1 = Detectable immobility. Mouth remains closed. Beginning features of anxiety or depression.

2 = Moderate immobility. Emotion breaks through at markedly increased threshold. Lips parted some of the time. Moderate appearance of anxiety or depression. Drooling may be present.

3 = Frozen facies. Mouth open ¼ inches or more. Drooling may be severe.

Seborrhea

0 = None.

1 = Increased perspiration, secretion remaining thin.

2 = Obvious oiliness present. Secretion much thicker.

3 = Marked seborrhea, entire face and head covered by thick secretion.

Speech

0 = Clear, loud, resonant, easily understood.

1 = Beginning of hoarseness with loss of inflection and resonance. Good volume and still easily understood.

2 = Moderate hoarseness and weakness. Constant monotone, unvaried pitch. Beginning of dysarthria, hesitancy, stuttering, difficult to understand.

3 = Marked harshness and weakness. Very difficult to hear and to understand.

Self-Care

0 = No impairment.

1 = Still provides full self-care but rate of dressing definitely impeded. Able to live alone and often still employable.

2 = Requires help in certain critical areas, such as turning in bed, rising from chairs, etc. Very slow in performing most activities but manages by taking much time.

3 = Continuously disabled. Unable to dress, feed himself, or walk alone.

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Appendix B. Work Plan

Objective

To conduct a systematic review of the literature to assess the quantity and quality of available evidence regarding diagnosis and treatment of Parkinson's disease (PD).

The following 12 specific questions will be addressed in the systematic review:

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 diagnosis and 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?

Background

The topic "Parkinson's Disease" was nominated by the American Academy of Neurology (AAN) to assist in answering several key questions of diagnosis and management of patients with this disease.

PD is a progressive disorder of the central nervous system characterized clinically by tremor, rigidity, and bradykinesia. PD affects 1% of the population over age 60, and up to 2.5% over age 70.[1] Mayo Clinic researchers have estimated the lifetime risk of developing PD at 7.5%.[2] This could have serious health and economic implications as the baby boom generation ages. Annual societal costs related to PD were estimated in 1994 to be $20 billion,[1] and are likely to be much higher now and in the future.

The design and interpretation of all prevention and treatment studies are made more difficult by the fact that PD has a variable and unpredictable clinical course. Furthermore, numerous outcome measures and formats have been developed, which complicate efforts to pool results across studies.[3]

The twelve key questions can be broken down into 4 basic categories: diagnosis, pharmacological treatment, (early and late), surgical treatment, and other modalities.

Not all "parkinsonism" is PD. The incidence of misdiagnosis has been estimated at up to 24% of patients.[4] The goal of this portion of the task order is to establish the evidence base of clinical trials that present sensitivity and specificity data pertaining to clinical and neuroimaging tests that are used to diagnose PD.

Treatment may be subdivided into early, overall, and late treatment, although there is significant overlap between the categories.

The standard treatment for PD has been levodopa (L-DOPA), which, once it reaches the brain, is converted to dopamine to correct the deficiency which characterizes PD. L-DOPA has been a mainstay of therapy since its introduction 40 years ago. However, questions of when to initiate therapy, and long term neurotoxicity, remain chief concerns to patients and practitioners. Several other drugs are often used, either in combination with L-DOPA to enhance its effects, or instead of L-DOPA, when its efficacy wanes or when response fluctuations or toxicity become unmanageable. These can be categorized chiefly as anticholinergics or dopamine agonists. Although there were very few new agents introduced for nearly 3 decades after the introduction of L-DOPA, several new agents, such as new dopamine agonists and the catechol-O-methyl transferase (COMT) inhibitors, with different mechanisms of action have recently been approved by the FDA. None, however, including L-DOPA, have been shown to impact the natural history of PD. They are useful for symptom control only, primarily motor dysfunction.

Research into agents capable of preventing or slowing progression of the disease is currently underway. These include antioxidants such as Vitamin E and coenzyme Q-10, the monoamine oxidase inhibitors selegiline and rasagiline, and glutamate antagonists such as riluzole.

The role of invasive methods such as pallidotomy and deep brain stimulation as additional treatment options require expert assessment. Neural growth factors

and neural cell implants (fetal cells from humans or animals, and genetically engineered stem cells) are the focus of increasingly intense research efforts.

The safe and effective use of co-medications to treat depression, psychosis, and cognitive changes of PD is also the subject of considerable new research.

The role of non-pharmacologic interventions, such as physical rehabilitation therapy, remains uncertain.

The goal of this portion of the task order is to review the evidence base of clinical trials pertaining to the treatment of PD. Given that PD is a chronic condition, and that patients stay on medications for years, the most clinically relevant data will come from long-term trials. For this reason, only trials of greater than or equal to 24 weeks duration will be accepted. Furthermore, the most useful data for analysis concerning pharmacological treatment of PD will be in randomized controlled trials (RCTs); therefore, only RCTs will be accepted for studies pertaining to pharmacological treatment. Studies pertaining to surgery and rehabilitation will not be limited to RCTs.

Genetic testing of relatives of patients with early onset PD is another area of current controversy. This is an area where there would be limited information to be derived from RCTs or even clinical trials; therefore, review articles pertaining to Genetics and PD will be reviewed and summarized for the Final Report.

Methods

MetaWorks will apply the latest and established best methods in the evolving science of review research.[5-9]

A flow diagram outlining the systematic review process is located in Attachment A.

The following tasks will proceed sequentially, and a project timeline has previously been submitted.

Topic Assessment & Refinement

A technical expert panel (TEP) will be assembled, in consultation with the Task Order Officer (TOO), through networking with our nominating partner, our academic collaborator, professional organizations, purchasers of health care, and relevant consumer groups.

After a preliminary assessment of the state of the literature, the TEP, in conjunction with the nominating partner (AAN), the TOO and our co-principal investigator at the Leonard Davis Institute of Health Economics (LDI), will assist in determining all primary and secondary objectives of this task order.

After a preliminary review of the literature, MetaWorks will develop two causal pathways that identify the critical diagnostic and treatment interventions in PD:

a) work-up of Parkinson's symptoms (diagnostic testing, treatment initiation, neuroimaging, genetic testing and neuroprotection)

b) pharmacologic and nonpharmacologic (including surgery and rehabilitation) management of patients with PD.

These causal pathways will serve as guides during this systematic review, and may be updated during the review process. They are not intended to be clinical practice guidelines or algorithms for decisions in patient care.

A report will be developed in consultation with the TOO which will identify which questions, if any, have insufficient evidence to pursue using literature sources, and will suggest specific areas for future research to fill these gaps. The report will clearly state whether or what evidence exists for diagnosis and management of PD in the adult population and, within that population, evidence related to age, gender, race/ethnicity, and income level.

Literature Screening

This task involves identifying and retrieving all potentially relevant literature on the diagnosis and treatment of PD, categorizing by study design, test, results and other key study, patient, and treatment level details for each of the thirteen key questions. Studies which meet the eligibility criteria (see below) will undergo data extraction and data entry.

The published literature will be searched from 1990 to 2000, with the following exceptions:

- Literature pertaining to pharmacological treatment of PD will be searched from 1985 to 2000, in an attempt to identify studies pertaining to anticholinergic medications.

- Literature pertaining to genetic testing will be searched from 1997-2000.

The search cut-off date will be November 9, 2000, and the retrieval cut-off date will be determined after all abstracts have been screened. The search will begin with a Medline screening search using the following search strategies:

I. Diagnosis:

1. (PD OR parkinsonism OR Parkinson) AND [diagnosis OR medical errors OR accuracy OR sensitivity OR specificity OR (diagnosis AND antiparkinson agents)]

II. Treatment:

2. (PD OR parkinsonism OR Parkinson) AND (treatment OR Levodopa OR carbidopa OR amantadine OR anticholinergic OR selegiline OR deprenyl OR dopamine agonist OR tolcapone OR entacapone)

3. (PD OR parkinsonism OR Parkinson) AND (selegiline OR Vitamin E OR Vitamin C OR neuroprotective agents)

4. (PD OR parkinsonism OR Parkinson) AND (psychological OR psychotic OR mental disorder) AND (drug therapy OR drug interactions)

5. (PD OR parkinsonism OR Parkinson) AND (surgery OR pallidotomy OR brain tissue transplant OR deep brain stimulation)

6. (PD OR parkinsonism OR Parkinson) AND rehabilitation

7. #1 OR #2 OR #3 OR #4 OR #5 OR #6 AND limit to clinical trials.

III. Genetics:

(PD OR parkinsonism OR Parkinson) AND genetics AND limit to review articles January 1, 1997-August 1, 2000.

In addition to the MedLine search described above, MetaWorks will search other suitable electronic databases, including Current Contents®, Cochrane Controlled Trials Register (CCTR) as well as a manual search of accepted study references and recent review articles. The Cochrane Library and the National Guidelines Clearinghouse will also be searched for additional information on these topics. In addition, pertinent Internet sites will be checked for potential leads to additional studies.

All citations and abstracts will be printed and screened at MetaWorks for any mention of diagnosis and/or treatment of PD (Level 1 screening) and reviewed for the following exclusion criteria:

Exclusion criteria

Abstracts demonstrating any of the following characteristics will be rejected:

- Reviews (except those regarding diagnosis and genetics), meta-analyses, letters, case reports, editorials, and commentaries.

- Crossover studies.

- Unpublished study reports and abstracts.

- Pharmacokinetic and pharmacodynamic studies.

- Animal or *in vitro* studies.

- Studies where results for PD population cannot be separated from results from other populations.

- Studies not pertaining to diagnosis or treatment of PD.

- Studies written in languages other than English.

- Studies containing < 10 patients as total sample size.

- Pharmacological treatment studies with < 24 weeks of treatment and followup.

While screening for eligibility, abstracts will be sorted and categorized. In some cases, it may not be possible from the abstract alone to determine the relevance of the study. All abstracts lacking obvious exclusion criteria will be included even if the categorization is unclear. Full papers for all studies passing Level 1 screening will be retrieved for second screening (Level 2), where inclusion and exclusion criteria will be applied.

Inclusion Criteria

Diagnosis:

- The following study designs will be accepted: observational [prospective, retrospective, and cross sectional (XS)], or interventional [RCTs, non-randomized controlled trials (nRCTs), and uncontrolled case series (UCSs), XS].

- Adult patients with potential diagnosis of PD.

- Studies addressing any diagnostic test to establish or support a diagnosis of PD.

Pharmacological Treatment:

- RCTs only

- $\geq$ 24 weeks treatment and follow-up duration

- Studies reporting at least one clinical objective outcome measure (efficacy or safety) on at least one of the following drugs or category of drugs:

    - L-DOPA/Carbidopa (Sinemet) – L-DOPA/decarboxylase inhibitor

    - Amantadine (Symmetrel)

- Dopamine agonists:
    - Bromocriptine (Parlodel)
    - Pergolide (Permax)
    - Ropinirole (Requip)
    - Pramipexole (Mirapex)
    - Andropinole
    - Cabergoline (Dostinex)
    - Apomorphine
    - Lisuride (Dopergin)
- Monoamine oxidase B (MAO-B) inhibitors:
    - Selegeline (Deprenyl)
    - Rasagiline (TVP-1012)
- Catechol-O-methyltransferase (COMT) inhibitors:
    - Tolcapone (Tasmar)
    - Entacapone (Comtan)
- Anticholinergic agents:
    - Trihexylphenidyl (Artane)
    - Benztropine (Cogentin)
    - Procyclidine
    - Other

- Studies involving neuroprotection with selegiline, Vitamine E (tocopherol), or Vitamin C.

- Studies addressing use of antipsychotic medications in conjunction with antiparkinsonian agents.

- Studies addressing the use of atypical antipsychotic medications in management of adult patients with PD.
    - Clozapine (Clozaril)
    - Olanzapine (Zyprexa)
    - Quetiapine (Seroquel)

Nonpharmacological Treatment:

- The following study designs will be accepted: observational [prospective, retrospective, and cross sectional], or interventional (RCTs, nRCTs, and UCSs).
- $\geq$ 24 weeks study and followup duration
- Must report at least one clinical objective outcome measure.
- Studies addressing surgery in adult patients with PD including:
    - Ablative or destructive surgery (thalmotomy, pallidotomy)
    - Stimulation surgery or Deep Brain Stimulation (DBS)
    - Transplantation or restorative Surgery (cell transplants)
- Studies addressing treatment of non-psychotic behavioral and psychological dysfunction in adult patients with PD.
- Studies addressing treatment of psychotic symptoms in adult patients with PD.
- Studies reporting at least one of the following specific interventions:
    - Allied health interventions
        - Occupational therapy (OT)
        - Physical therapy (PT)
        - Psychotherapy (counseling)
        - Speech therapy

- Studies reporting at least one of the following specific outcomes:
    - Acute hospitalization
    - Rehabilitation hospitalization
    - Nursing home admission
    - Work absenteeism
    - Quality of Life (QoL)
    - Activities of Daily Life (ADL) assessment

Genetics:

- The study design will be limited to review articles only.
- Adult patients undergoing genetic testing to establish or support a diagnosis of PD.

Upon completion of Level 2 screening, all accepted articles will be eligible for data extraction.

Assessment of Quality in the Primary Studies

All studies will be appraised according to a previously published Level of Evidence (Attachment B). Each accepted RCT will also be scored for quality (features of randomization method used, blinding of treatments, and accounting for all patients entered and withdrawn) by the Jadad Quality Score Assessment (Attachment C).

Data Extraction

Data extraction forms (DEFs) will be created specifically for this project. Data will be extracted onto the DEF independently by one reviewer and the completed DEF will be 100% checked against the original articles by a second reviewer. Any differences will be resolved by consensus; thus, two reviewers must agree on all data. In all cases, at least one physician reviews all data points. The data will then be entered in MetaWorks' relational database, MetaHub™. At this time, it is anticipated that the following data elements will be extracted.

These preliminary selections may change prior to finalization of the DEF as a result of input from the TEP and/or subsequent revisions to this Work Plan.

Study level characteristics

- Publication year
- Geographical location of study
- Study design (observational - retrospective or prospective interventional – RCT, nRCT, UCS, XS)
- Methodological assessment
    - Level of Evidence (I-V) – all studies
    - Jadad Quality Score – RCT's
- Total number of patients enrolled
- If RCT, number of patients randomized
- Primary study objective
- Funding source/industry sponsorship (name if yes or no/NR)
- Diagnostic test or treatment intervention studied
- Study duration
- Follow-up period
- Study type
    - Diagnostic
    - Treatment: pharmacologic or nonpharmacologic
        - Early
        - Late
        - General

Patient characteristics (by group)

- Age: years (mean, median, and range)
- Gender distribution
- Race and/or ethnicity
- Socioeconomic status
- Age at diagnosis
- Family history of PD
- Presenting symptoms (resting tremor, gait disturbance, rigidity, bradykinesia, motor dysfunction, etc.)
- Criteria used for Diagnosis of PD
- Patient exclusion criteria
- Stage of PD (early, moderate, advanced)
- Prior treatments received for PD
- Treatment resistance (# and type of antiparkinsonian agents tried previously)
- Criteria for establishing dementia diagnosis and for documenting presence of psychosis
    - Type of dementia diagnosed
    - Measures of cognitive impairment
- Other co-morbid conditions

Intervention Characteristics (by group)

- Diagnostic interventions
    - History and physical examination
    - Neuroimaging:
        - Computed tomography (CT)

        - Magnetic resonance imaging (MRI)
        - Fluorodopa positron emission tomography (PET) scans
        - Single proton emission computed tomography (SPECT) scans using dopamine transporter ligands
    - Other
        - Blood (serum ceruloplasmin concentration)
        - Urine (24 hour copper excretion)
        - Slit lamp examination
        - Liver biopsy (to rule out Wilson's disease)
    - Genetic testing
    - Other tests to rule out coexisting organic disease
    - Response to L-DOPA

Treatment interventions (by group)

- **Pharmacological interventions**
    - Treatment type, dose, frequency and duration
        - L-DOPA/Carbidopa
        - Dopamine agonists
        - MAO-B inhibitors
        - COMT-inhibitors
        - Anticholinergic Agents
        - Neuroprotective Agents
        - Antipsychotic medications
        - Other

- Comparison group, if any (placebo or active controls)
    - Concomitant medication (protocol prescribed or allowed)

- **Nonpharmacological interventions**
    - **Surgical**
        - Indications for surgery
        - Type of surgery performed
    - **Other**
        - OT
        - PT
        - Psychotherapy
        - Speech Therapy

Outcomes (by group)

Diagnostic tests

- Sensitivity
- Specificity
- Accuracy
- Negative Predictive Value (NPV)
- Positive Predictive Value (PPV)

Treatment Outcomes

Efficacy

- Hospitalizations or admissions to chronic care facilities
- Symptomatic improvement or worsening (documented motor improvement and other manifestations of disease severity)

- Work absenteeism
- Clinical, objective outcome measures
- QoL
- ADL assessment
- Other

Safety

- Adverse Events (related to treatment)
    - Grade 3 and 4
- Deaths (related to treatment)
- Patient withdrawals due to adverse events or lack of efficacy

Database Development

All consensed data will be entered into the MetaWorks MetaHub™ database. 100% of entered data is checked back to the DEFs after each form is completely entered. In addition, a 20% random sampling of data in the completed database will be checked by the QC group at MetaWorks against the data extraction forms. All discrepancies in data are reconciled by referring back to the original papers. Error rates in excess of 2% of checked data will trigger a 100% check of all data elements in the data base.

Once the accuracy of the database has been verified as described above, it is locked. No further changes are allowed after the data is locked. This is the dataset that will be used by the statisticians for analysis and to create raw data tables displaying key data elements of interest, by study.

All data are maintained in the MetaHub database, in a manner suitable to allow outputs to: a) spreadsheet programs for customized evidence table displays; b) to statistical programs for analysis.

Statistical Analyses

Statistical analyses will be performed as the data permit. The search criteria for the 12 questions have been restricted to allow us to select only those studies most likely to contribute data that could be analyzable. Further details of analysis will be developed later in an analysis plan.

However, we also note that several questions are related to management of patients with PD. Studies in the literature addressing clinical practice or medical

management are typically very limited, and will probably only allow for descriptive analysis.

Synthesis & Reporting

This task involves bringing together all of the evidence into a coherent report and presenting the raw data in a tabular format as well as performing both qualitative and quantitative data syntheses as data permit and as protocol objectives require.

MetaWorks will prepare and submit to the TOO evidence tables for each step in the causal pathways, as data permits.

Technical Experts

MetaWorks will identify a TEP through networking with our nominating partner, our academic collaborators, professional organizations and relevant consumer groups. The TEP will be composed of six to eight individuals with specific expertise in general neurology, PD, neurosurgery, internal medicine, and at least one consumer representative. The TEP will review and provide timely feedback to all draft Work Plans and deliverables on an ongoing basis. MetaWorks will consult with these individuals as appropriate in carrying out the tasks required under this task order.

Peer Review

In addition to the TEP described above, MetaWorks will identify up to 12 additional individuals who are experts in the topic area, to serve as peer reviewers of the draft evidence report. These individuals will be chosen from the fields of neurology, general practice and internal medicine, as well as consumers who have experienced PD. These individuals will be sought from professional organizations which have been instrumental in developing guidelines in aspects of PD treatment or diagnosis, such as the American Academy of Neurology. Consumers will be sought from consumer groups such as the National Parkinson Foundation Inc., the Parkinson's Disease Foundation, Inc., the Parkinson's Institute and others active in PD initiatives.

Names of potential reviewers will come from our technical expert panel, the nominating partner, LDI, AHRQ, and from the literature being reviewed by the project team. The profile of the peer review group will be similar to that of the TEP, and may also include representatives from manufacturers of the medications and diagnostics included in the evidence report.

A copy of the draft evidence report will be sent to each peer reviewer, along with a reviewer's form to be completed and returned to MetaWorks. This form will contain a checklist of items to be assessed as well as provide room for free-

form text comments. The form will be pre-screened by the TEP and the TOO prior to being sent to the peer reviewers. Reviewers will be given 3 weeks to respond, after which they will be contacted. All feedback will be stored in a project folder at MetaWorks. A statement of response to each reviewer's comments will be prepared and stored with each reviewer's comments. This response will also be returned to the reviewer.

A summary of the main comments and responses will be prepared and shared with the TOO. Reviewer comments and additional analyses and text resulting from the response to reviewer critique will be incorporated into the final iteration of the evidence report.

Implementation and Dissemination

An implementation plan will be prepared with the nominator, the American Academy of Neurology. Dissemination will occur via AHRQ. MetaWorks/LDI will prepare a manuscript describing key aspects of the work for publication in peer reviewed journals. Abstracts of same may also be submitted for presentation at professional meetings.

References

1. Marsh L. Neuropsychiatric aspects of Parkinson's disease. Psychosomatics 2000; 41:15-23.

2. Research Digest: Parkinsonism more common than previously thought. Aug. 24, 1999. Mediconsult.com

3. Clarke CE, Speller JM. Pergolide versus bromocriptine for levodopa-induced motor complications in Parkinson's disease. and Hilten JJ van, Ramaker C, Beek WJT van de, Finken MJJ. Bromocriptine for levodopa-induced motor complications in Parkinson's disease. (Cochrane Review). In: The Cochrane Library, Issue 1, 1999. Oxford: Update Software).

4. Clarke CE. Managing early Parkinson's disease. The Practitioner 1999; 243: 41-46.

5. Chalmers TC, Lau J. Meta-analytic stimulus for changes in clinical trials. Statistical Methods in Medical Research 1993; 2: 161-72.

6. Sacks HS, Berrier J, Reitman D, Pagano D, Chalmers T. Meta-analyses of randomized controlled trials. N Engl J Med 1987; 316: 450-5.

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8. Cook DJ, Mulrow CD, Haynes RB. Systematic reviews: synthesis of best evidence for clinical decisions. Ann Intern Med 1997; 126: 376-80.

9. Mulrow CD, Oxman AD (eds). Cochrane Collaboration Handbook. The Cochrane Library. The Cochrane Collaboration; Issue 1. Oxford: Update Software; 1997. Updated quarterly.

Work Plan Acceptance

AHRQ

By: _____
Name: _____
Title: _Task Order Officer_____

American Academy of Neurology:

By: _____
Name: _____
Title: AAN Representative_____

MetaWorks Inc.

By: _____
Name: _____
Title: Principal Investigator, MetaWorks

LDI

By: _____
Name: _____
Title: Co-Principal Investigator, LDI

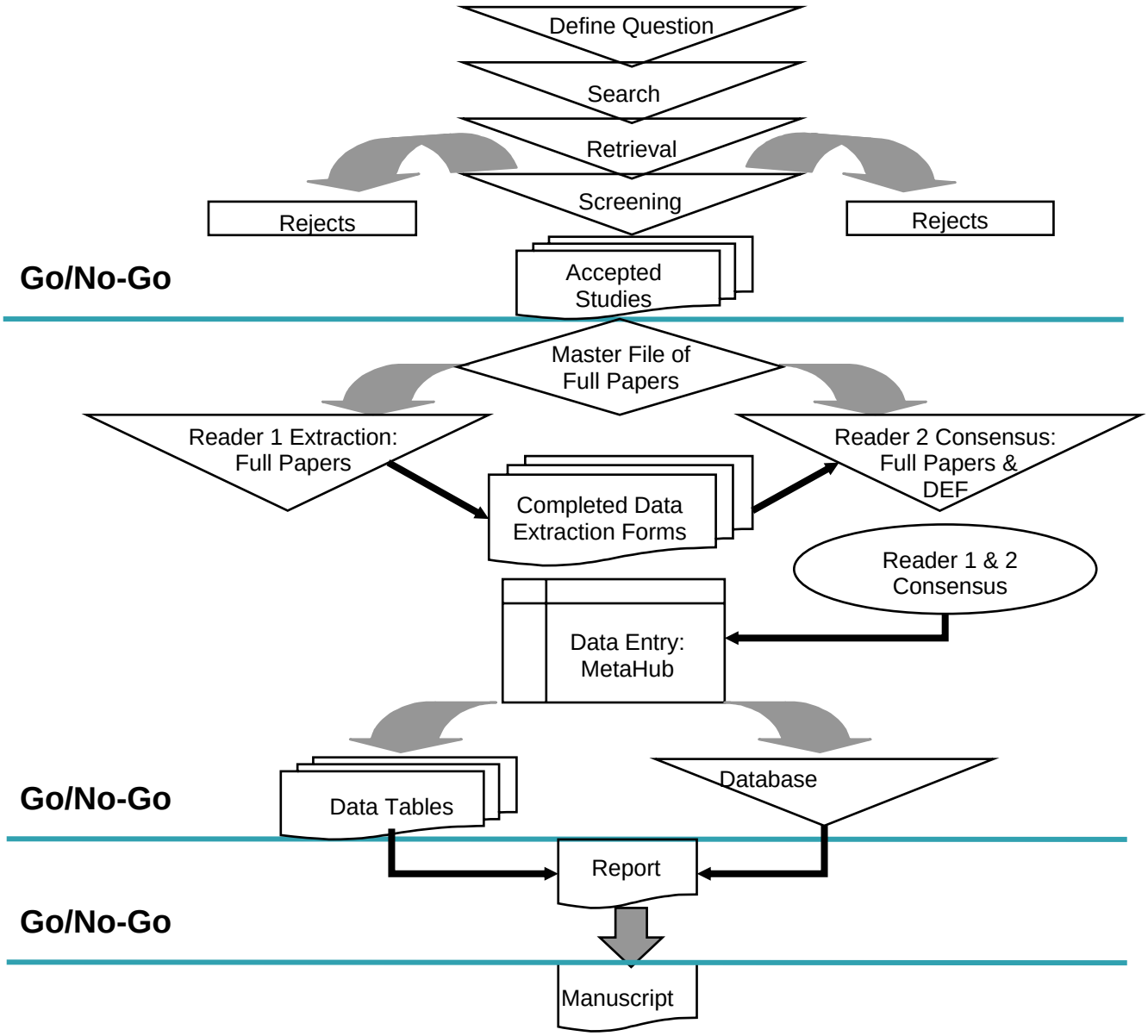
Attachments:

Attachment A: Flow Diagram Systematic Review

Attachment B: Levels of Evidence

Attachment C: Jadad Quality Score Assessment

Attachment A: MetaWorks Flow Diagram



Attachment B: Levels of Evidence

I. Evidence based on randomized controlled clinical trials (or meta-analysis of such trials) of adequate size to ensure a low risk of incorporating false-positive or false-negative results.

II. Evidence based on randomized controlled trials that are too small to provide level I evidence. These may show either positive trends that are not statistically significant or no trends and are associated with a high risk of false-negative results.

III. Evidence based on nonrandomized, controlled or cohort studies, case series, case-controlled studies or cross-sectional studies.

IV. Evidence based on the opinion of respected authorities or that of expert committees as indicated in published consensus conferences or guidelines.

V. Evidence which expresses the opinion of those individuals who have written and reviewed these guidelines, based on their experience, knowledge of the relevant literature and discussion with their peers.

These 5 levels of evidence do not directly describe the quality or credibility of evidence. Rather, they indicate the nature of the evidence being used. In general, a randomized, controlled trial has the greatest credibility (level I); however, it may have defects that diminish its value, and these should be noted. Evidence that is based on too few observations to give a statistically significant result is classified as level II. In general, level III studies carry less credibility than level I or II studies, but credibility is increased when consistent results are obtained from several level III studies carried out at different times and in different places.

Decisions must often be made in the absence of published evidence. In these situations it is necessary to use the opinion of experts based on their knowledge and clinical experience. All such evidence is classified as "opinion" (levels IV and V). Distinction is made between the published opinion of authorities (level IV) and the opinion of those who have contributed to these guidelines (level V). However, it should be noted that by the time level V evidence has gone through the exhaustive consensus-building process used in the preparation of these guidelines, it has achieved a level of credibility that is at least equivalent to level IV evidence.

from: The Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer. CMAJ 1998:158

Attachment C: Jadad Quality Score Assessment

Please read the articles and try to answer the following questions (see attached instructions):

1. Was the study described as randomized (this includes the use of words such as randomly, random, and randomization)?

2. Was the study described as double-blind?

3. Was there a description of withdrawals and drop outs?

Scoring the items:

Either give a score of 1 point for each 'yes' or 0 for each 'no'. There are no in-between marks.

Give an additional point if:	For question 1, the method to generate the sequence of randomization was described and it was appropriate (table of random numbers, computer generated, coin tossing, etc.)
and/or:	If for question 2 the method of double-blinding was described and it was appropriate (identical placebo, active placebo, dummy, etc.)
Deduct 1 point if:	For question 1, the method to generate the sequence of randomization was described and it was inappropriate (patients were allocated alternately, or according to date of birth, hospital number, etc.)
and/or:	For question 2 the study was described as double-blind but the method was inappropriate (e.g., comparison of tablet vs.injection with no double dummy)

Guidelines for assessment

1. Randomization:

A method to generate the sequence of randomization will be regarded as appropriate if it allowed each study participant to have the same chance of receiving each intervention and the investigators could not predict which treatment was next. Methods of allocation using date of birth, date of admission, hospital numbers or alternation should not be regarded as appropriate.

2. Double-blinding:

A study must be regarded as double-blind if the word double-blind is used. The method will be regarded as appropriate if it is stated that neither the person doing the assessments nor the study participant could identify the intervention being assessed, or if the absence of such a statement the use of active placebos, identical placebos or dummies is mentioned.

3. Withdrawals and drop outs:

Participants who were included in the study but did not complete the observation period or who were not included in the analysis must be described. The number and the reasons for withdrawal in each group must be stated. If there were no withdrawals, it should be stated in the article. If there is no statement on withdrawals, this item must be given no points.

from: Jadad AR, Moore A, Carroll D, et al: Assessing the Quality of Reports of Randomized Clinical Trials: Is Blinding Necessary? Controlled Clinical Trials 1996; 17:1-12.

Appendix C. Topic Assessment and Refinement

Objective

The objective of this Task Order is to conduct a systematic review of the literature to assess the quantity and quality of available evidence regarding diagnosis and treatment of Parkinson's Disease (PD).

Project Status to Date

Thirteen key questions were posed by the Agency for Healthcare Research and Quality (AHRQ) and the American Academy of Neurology (AAN). After a preliminary review of the literature, MetaWorks and the Leonard Davis Institute (LDI) worked collaboratively to modify the original key questions, making them more amenable to answers by systematic literature review. The content of the revised questions is unchanged; however, they are now worded differently. 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 ask "what are the results," or "what is the evidence."

Causal pathways relevant to the key objectives of this project were developed to help guide the literature review. Many of the elements included in the causal pathways are controversial, particularly the use of MAO-B inhibitors for neuroprotection, and the question of when L-Dopa should be started. One of the goals of this Task Order is to identify the weight of the available evidence regarding these and other issues.

After numerous discussions with representatives from AHRQ, AAN, and LDI, final decisions were made regarding the composition of the Technical Expert Panel (TEP) for this project. The TEP is composed of four neurologists/PD experts, one neurosurgeon/PD expert, one general neurologist, one general internist, and one PD patient, who is a cardiologist. This multidisciplinary approach will provide valuable feedback from a variety of perspectives.

The Work Plan and Causal Pathways were sent to all members of the TEP for review on September 19, 2000. Feedback was requested by October 16, 2000, and has been received from 7 of the 8 members of the TEP.

Based on preliminary assessment of the literature, relevant databases, input from collaborating partners, and feedback received from the TEP, the Work Plan and the Causal Pathways have been modified accordingly.

Twenty people have been invited to participate in the project as Peer Reviewers of our draft evidence report. To date, seven have accepted. More potential peer reviewers are being contacted, with an ultimate goal of at least twelve peer reviewers, from multiple disciplines.

To date, 957 abstracts have been identified from the Medline search, 397 from the Current Contents search, and 590 from the Cochrane Library search, yielding a total of 1,944 citations. After 614 duplicates were identified, a total of 1,330 abstracts were downloaded into Reference Manager at MetaWorks.

Level I screening of all abstracts for exclusion criteria has been completed, and resulted in 560 potential accepted studies. Full papers are being retrieved for all accepted abstracts.

Level 2 screening of the full articles for inclusion and exclusion criteria is nearly complete. All studies that are rejected at Level 2 are required to be reviewed by a second researcher, to insure that there is 100% consensus regarding which studies are to be rejected. Manual bibliography checks of all accepted studies are currently underway, in search of potential accepts that may not have been identified by electronic searches.

After Level 2 screening is complete, data extraction of the accepted articles will commence. The Revised Work Plan describes, in great detail, the remaining steps in the systematic review process. The draft Evidence Report will be submitted to AHRQ by July 2, 2001.

Appendix D. Causal Pathways: Diagnosis and Treatment of Parkinson's Disease

Please Note:
The causal pathways are **not** clinical practice guidelines, nor are they algorithms for decisions in patient care. They have been constructed solely for use as guides during this systematic review of the literature.

Causal Pathway: Diagnosis of Parkinson's Disease Legends

[1]Principal Symptoms Present:

*Two or more present, one of which is resting tremor or bradykinesia

1**. Rigidity** affecting one or more limbs, cogwheel in nature

2. Resting, postural **tremor** most often asymmetrical, 3-7 Hz, hands preferentially affected

3. **Bradykinesia** (akinesia, hypokinesia)

4. **Postural/Gait disturbance** often appears late in disease

[2]Principal Symptoms *May Be* Present:

*One or more *may be* present

1. Rigidity affecting one or more limbs, may or may not be cogwheel in nature

2. Tremor may be asymmetrical, but frequently bilateral and higher frequency (5-12 Hz). Head, voice, tongue, palate, leg and/or trunk tremor may occur

3. Bradykinesia

4. Postural/Gait disturbance

[3]Secondary Symptoms *May Be* Present:

1. Psychiatric symptoms (depression, anxiety, psyshosis)

2. Autonomic dysfunction (sexual dysfunction, orthostatic hypotension)

3. Gastrointestinal dysfunction (constipation, weight loss, dysphagia)

4. Urologic dysfunction

5. Speech and swallowing problems

6. Falls

7. Sleep disturbances

8. Visual disturbances

9. Cognitive dysfunction (dementia)

10. Olfactory dysfunction

11. Difficulty writing

[4]Secondary Symptoms *May Be* Present:
(as above)

[5]Radiology/Laboratory Tests not as useful in diagnosis:

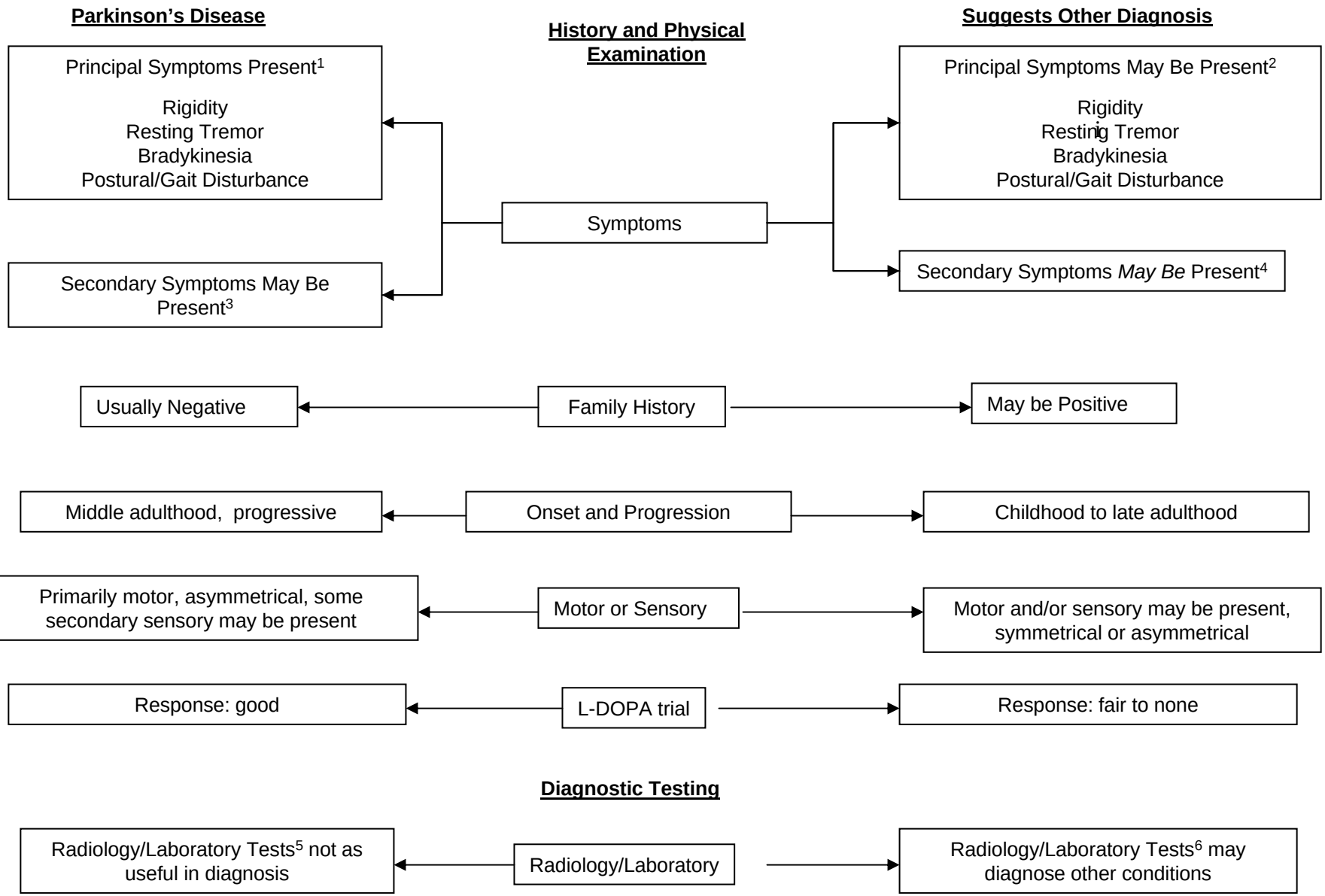
Results of computed tomography (CT), magnetic resonance imaging (MRI), cerebrospinal fluid analysis, and electroencephalography (EEG) are usually normal and of little diagnostic asistance.

Positron-emission tomography (PET scan) using radio-labeled dopa may be helpful in confirming a diagnosis.

[6]Radiology/Laboratory Tests helpful in diagnosis of other conditions:

CT, MRI useful to eliminating other disease processes such as tumors, strokes, hydrocephalus, etc. Laboratory investigation should be performed when atypical symptoms exist, there is a strong family history or early age of onset.

Causal Pathway: Diagnosis of Parkinson's Disease



Causal Pathway: Treatment of Parkinson's Disease Legends

For all medications, start with low dose, increase dose slowly until:

symptoms abate OR
maximum dose is reached OR
intolerable side effects occur.

Only make one medication change at a time.

[1] MAO-B Inhibitors: Monoamine oxidase B inhibitors (for neuroprotection) :

[2] Seligiline, Rasagiline

[3] Dopamine Agonists : Bromocriptine, Pergolide, Pramipexole, Andropinrole,

[4] Cabergoline, Ropinirole, Apomorphine (activate dopamine receptors)

[5] Other Modalities: Rehabilitation, Physical Therapy, Occupational Therapy, Speech Therapy, Counseling, Dietary Changes.

[6] L-DOPA/PDI: Levodopa/Carbidopa (peripheral decarboxylase inhibitor)

[7] Disabling tremor: may occur any time during the course of the disease.

[8] COMT inhibitors: Catechol-O-methylransferase inhibitor: Tolcapone, Entacapone

[9] Anticholinergic agents: Trihexylphenidyl, Benztropine, Procyclidine

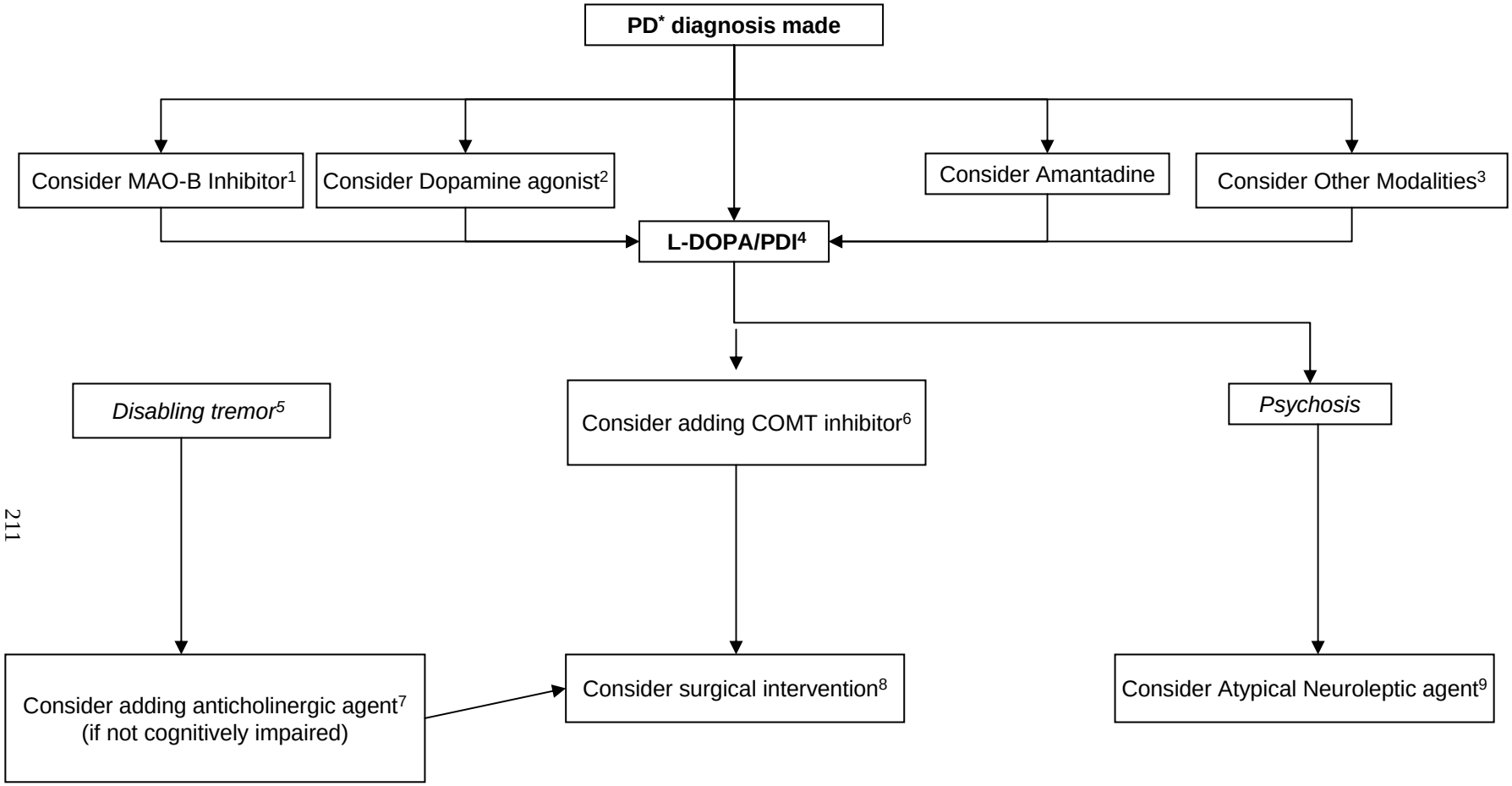
[10] Surgical interventions: pallidotomy, thalamotomy, deep brain stimulation, fetal nigral implants.

[11] Atypical Neuroleptic agents: Clozapine, Olanzapine, Quietipine

Many aspects of this causal pathway are controversial, including when to initiate therapy with L-DOPA, and when to use other agents. Monitoring for toxicities should be done throughout treatment, and is not specifically mentioned in this pathway. Similarly, physical therapy, counseling, speech therapy, and rehabilitation should start as soon as PD is diagnosed, and continue indefinitely.

The causal pathways are **not** clinical practice guidelines, nor are they algorithms for decisions in patient care. They have been constructed solely for use as guides during this systematic review of the literature.

Causal Pathway: Treatment of Parkinson's Disease



* PD = Parkinson's Disease

Appendix E. Screening Sheets and Data Extraction Forms

Extracted by _____
Date _____

Data Extraction Form
Diagnosis of Parkinson's Disease

Consensed by _____
Date _____

Study Characteristics

Study ID: _____ **First Author:**_____ **Pub. Date:** _____

Study Location: ___ North America _____ **Institution** _____

____ Europe _____ **Kin(s)**:_____

____ Other _____ _____

Study Design: _ __ RCT ___nRCT ___UCS ___XS ___Other _____

Level of Evidence: _____ (I) _____ (II) _____(III) _____(IV) _____(V)

Industry Sponsorship: Yes _____
NR

Diagnostic Criteria Category:

_____Apomorphine/L-Dopa Test
_____Autopsy Data
_____Blood/CSF Tests - Levels
_____Evoked Potentials
_____H&P/Clinical Exam
_____ Misc. Tests_____
_____MRI
_____PET
_____SPECT
_____Ultrasound
_____Visual Testing
_____Other _____
_____

Patients Enrolled: _____Total #
_____PD
_____Controls
_____Other _____
_____
_____

Primary Study Objective

Study Conclusion

AHRQ – PARKINSON DISEASE
Level II Screening
DIAGNOSIS

Reviewed by_____ **MetaHub Study ID**_____
First Author_____ **Year Published**_____

Status: Accept Reject

If REJECT, Specify Reason:

Animal or *in vitro* studies

Abstracts, letters, comments, reviews, editorials, case report, meta-analyses

Pharmacodynamic or Pharmacokinetic Study

Study with < 10 patients

Languages other than English

Studies published prior to 1990

Study populations not including Parkinson Disease

Studies not including tests to establish or support diagnosis of Parkinson Disease

Cross-over studies

Mixed populations where results for Parkinson patients not separately extractable

Other _____

If ACCEPT, then record:

Study Design:

____Observational
_____Prospective
_____Retrospective
_____Cross-sectional

_____ Interventional
____RCT
____nRCT
____UCS
____Cross-sectional

Geographic Location: _____North America
_____Europe
_____Other:_____

Patients Enrolled:_____

Diagnostic Test(s): _____
_____
_____
_____

AHRQ – PARKINSON DISEASE
Level II Screening
NON-PHARMACOLOGICAL TREATMENT

Reviewed by_____ **MetaHub Study ID**_____
First Author_____ **Year Published**_____

Status: Accept Reject

If REJECT, Specify Reason:

Animal or *in vitro* studies

Abstracts, letters, comments, editorials, meta-analyses

Studies not including a clinical objective outcome measure of PD activity

Pharmacodynamic or Pharmacokinetic Study

Languages other than English

Studies with <10 patients

Studies published prior to 1990

Studies < 24 weeks of treatment/follow-up

Study populations not including Parkinson Disease

Studies not including treatment or diagnosis

Cross-over studies

Mixed populations where results for Parkinson patients not separately extractable

Other _____

If ACCEPT, then record:

Surgery:
____ Pallidotomy
____ Thalamotomy
____ Deep Brain Stimulation (DBS)
____ Cell transplants
____ Other _____

Geographic Location: _____North America
_____Europe
_____Other_____

Patients Enrolled:_____

Rehabilitation:
____ Occupational therapy (OT)
____ Physical therapy (PT)
____ Psychotherapy (counseling)
____ Speech therapy
____ Other _____
Other: _____
_____

Study Duration: _____months

Outcome Measures: _____
_____
_____
_____

Study Design:

____Observational
_____Prospective
_____Retrospective
_____Cross-sectional

_____Interventional
____RCT
____nRCT
____UCS

AHRQ – PARKINSON DISEASE
Level II Screening
PHARMACOLOGICAL TREATMENT

Reviewed by_____ **MetaHub Study ID**_____
First Author_____ **Year Published**_____

Status: Accept Reject

If REJECT, Specify Reason:

Animal or *in vitro* studies
Abstracts, letters, comments, reviews, editorials, case report, meta-analyses
Pharmacodynamic or Pharmacokinetic Study
Languages other than English
Study populations not including Parkinson Disease
Studies not including clinical objective outcome measure of Parkinson Disease activity
Mixed populations where results for Parkinson patients not separately extractable
Studies that are not RCTs
Studies with <10 patients
Studies < 24 weeks of treatment/follow-up
Studies published prior to 1985
Cross-over studies
Other _____

If ACCEPT, then record:

____Early
____Advanced
____Other
____ Neuroprotection
____ Psychology

Geographic Location: _____North America
_____Europe
____ Other_____

Patients Enrolled: _____

Study Duration: _____months

Outcome Measures: _____
_____
_____
_____

Medication:
____ L-DOPA/Carbidopa* (Sinemet)
____Amantadine (Symmetrel)
Dopamine Agonist:
_____ Andropinole
_____ Apomorphine
_____ Bromocriptine (Parlodel)
_____ Cabergoline (Dostinex)
_____ Lisuride (Dopergin)
_____ Pergolide (Permax)
_____ Pramipexole (Mirapex)
_____ Ropinirole (Requip)

Antipsychotic medications:
____ Clozapine (Clozaril)
____ Olanzapine (Zyprexa)
____ Quetiapine (Seroquel)

Comparison: Placebo / Active _____
_____

Monoamine oxidase B (MAO-B) inhibitors:
____ Rasagiline (TVP-1012)
____ Selegeline (Deprenyl

Catechol-O-methyltransferase (COMT) inhibitors:
____ Entacapone (Comtan)
____ Tolcapone (Tasmar)

Anticholinergic agents:
____ Benztropine (Cogentin)
____ Procyclidine
____ Trihexylphenidyl (Artane)

Neuroprotective agents:
____ Vitamine E (tocopherol)
____ Vitamin C

___Other_____
_____

Extracted by _____
Date _____

Data Extraction Form
Ancillary Treatment of Parkinson's Disease

Consensed by _____
Date _____

Study Characteristics

Study ID: _____ **First Author:** _____ **Pub. Date:** _____

Study Name _____

Study Location: ___ North America _____ Institution _____

____ Europe _____ Kin(s):_____

____ Other _____ _____

Study Design: ___**RCT** ___**nRCT** ___**UCS** ___**XS** ___**Other**

Quality Score: ___(rand) + ___(blind) + ___(w/drwl) = ___(Total)

Level of Evidence: _____ (I) _____ (II) _____ (III) _____ (IV) ____ (V)

Accrual years _____ _____ **Patients Enrolled**

Industry Sponsorship: Yes _____
NR

Intervention:

Inclusion Criteria:

Exclusion Criteria:

Primary study objective

Study conclusion

Extracted by _____
Date _____

Data Extraction Form
Pharmacological Treatment of Parkinson's Disease

Consensed by _____
Date _____

Study Characteristics

Study ID: _____ **First Author:** _____ **Pub. Date:** _____

Study Location: ___ North America _____ Institution _____
____ Europe _____ Kin(s):_____
____ Other _____ _____

Quality Score: ___(rand) + ___ (blind) + ___(w/drwl) = ___(Total)

Level of Evidence: ____ (I) ___ (II) ____ (III) ___ (IV) ____ (V)

Tx Duration:_____ (mos) **F/U Duration:**_____ _____ **Patients Enrolled**

Accrual years _____

Industry Sponsorship: Yes _____

Treatment: ___Early ____Advanced ____General NR

Medications:

Dopamine Agonist:	**MAO-B Inhibitor:**	**Anticholinergic agent:**	**Psychotropic agent:**
__Andropinole	__Rasagiline (TVP-1012)	___Benztropine (Cogentin)	___Clozapine (Clozaril)
__Apomorphine	__Selegeline (Deprenyl)	___Procyclidine	___Olanzapine (Zyprexa)
__Bromocriptine (Parlodel)	__Tranylcypromine	___Trihexylphenidyl (Artane)	___Quetiapine (Seroquel)
__Cabergoline (Dostinex)	__Other _____	___Other _____	___Other_____
__Lisuride			
__Pergolide (Permax)	**COMT Inhibitor:**		**Other**
__Pramipexole (Mirapex)	__Entacapone (Comtan)	**Neuroprotective agent:**	_____
__Rimantadine	__Tolcapone (Tasmar)	___Vitamin E (Tocopherol)	_____
__Ropinirole (Requip)	__ Other _____	___Vitamin C	
__Other_____		___Other _____	**Comparison group:**
	__**L-DOPA/Carbidopa**		___Placebo
__**Amantadine**	__Other _____		___Active

Inclusion Criteria:

Exclusion Criteria:

Primary study objective

Primary efficacy variable

Extracted by _____
Date _____

Data Extraction Form
Psychiatric Treatment of Parkinson's Disease

Consensed by _____
Date _____

Study Characteristics

Study ID:_____ **First Author:**_____ **Pub. Date:**_____

Study Location: ___ North America _____ Institution _____

____ Europe _____ Kin(s):_____

____ Other _____ _____

Study Design: ___**RCT** ___**nRCT** ___**UCS** ___**XS** ___**Other**

Quality Score: ___(rand) + ___(blind) + ___(w/drwl) = ___(Total)

Level of Evidence: _____ (I) _____ _____ (III) _____ (IV ____ (V)

Accrual years _____ _____ **Patients Enrolled**

Industry Sponsorship: Yes _____

NR

Treatment:

____Clozapine
____Risperidone
____Citalopram
___Piracetam
___Quetiapine
___Other _____

Inclusion Criteria:

Exclusion Criteria:

Primary study objective

Study conclusion

Extracted by _____
Date _____

Data Extraction Form
Surgical Treatment of Parkinson's Disease

Consensed by _____
Date _____

Study Characteristics

Study ID:_____ **First Author:**_____ **Pub. Date:**_____

Study Location: ___ North America _____ Institution _____
____ Europe _____ Kin(s):_____
____ Other _____ Industry: Yes_____
NR

Study Design: _ __ RCT ___nRCT ___UCS ___XS ___Other _____

Quality Score: ___(rand) + ___(blind) + ___(w/drwl) = ___(Total)

Level of Evidence: _____ (I) _____ (II) _____ (III) _____ (IV) ____ (V)

F/U Duration:_____**(mos)** _____ **Patients Enrolled**

Accrual years _____

Surgical Intervention	
Deep Brain Stimulation ___ Pallidotomy ___ Unilateral _____ (# pts) Bilateral _____ (# pts) Type _____ _____	Thalmotomy ___ Tissue Transplant ___ Adrenal Medulla ___ Fetal brain cells ___ Other_____ _____

Inclusion Criteria:

Exclusion Criteria:

Primary study objective

	Group 1:	**SD / SEM**	**Group 2:**	**SD / SEM**
# Enrolled / Randomized				
# Analyzed for Saf/Eff				
Age (Mean, Med, Range)				
# Male / # Female				
# R handed / # L handed				
Race or ethnicity				
Socioeconomic status				
Duration of PD (yrs)				
Age @ onset (yrs)				
Family history of PD				
Prior treatments for PD				
Comorbidities				

Appendix F. Statistical Reference

Interpretation of Standardized Mean Differences

Standardized mean differences (δs) are used to represent the difference between two groups when the groups are measured on differently scaled measures across many studies. For instance, in the pharmacological studies, patients are evaluated on as many as seven different measures. A standardized mean difference between groups is simply the mean difference re-scaled so that all measures have the same variance and standard deviation in scores. If we make the assumption that these scales or subscales measure roughly the same construct (past validity studies make this a safe assumption for the scales in question),[1] meta-analysis of standardized mean differences (also commonly referred to as "effect sizes" in this report) becomes both possible and theoretically meaningful.

The value of the standardized mean difference might be best considered as the degree of overlap between the distributions of treatment and control group scores. Because delta (δ) is the standardized score of the treatment group mean in the control group distribution, we can calculate approximately what proportion of the control group scores are less than the *average* score in the treatment group.[2] The table below summarizes percentages for a range of effect sizes.

Effect Size	0.10	0.20	0.30	0.40	0.50	0.60	0.70	0.80	1.00	1.20	1.50
% of treatment group with scores better than the average person in the control group	54%	58%	62%	66%	69%	73%	76%	79%	84%	88%	93%

Thus, someone undergoing a treatment (e.g., bromocriptine) that has an expected effect size of .50 would expect that his symptoms afterwards would be better than 70 percent of those who underwent the "control" procedure (e.g., L-dopa alone).

Even small effects can be important, depending on the importance of the outcome. In past medical studies, small but statistically significant effect sizes have been deemed important enough to prematurely end double-blinding: the 1987 study of the effect of aspirin on reducing the risk of heart attacks found an effect size for aspirin over placebo equivalent to a standardized mean difference of .07.[3]

Calculation of Change Score Standard Deviations

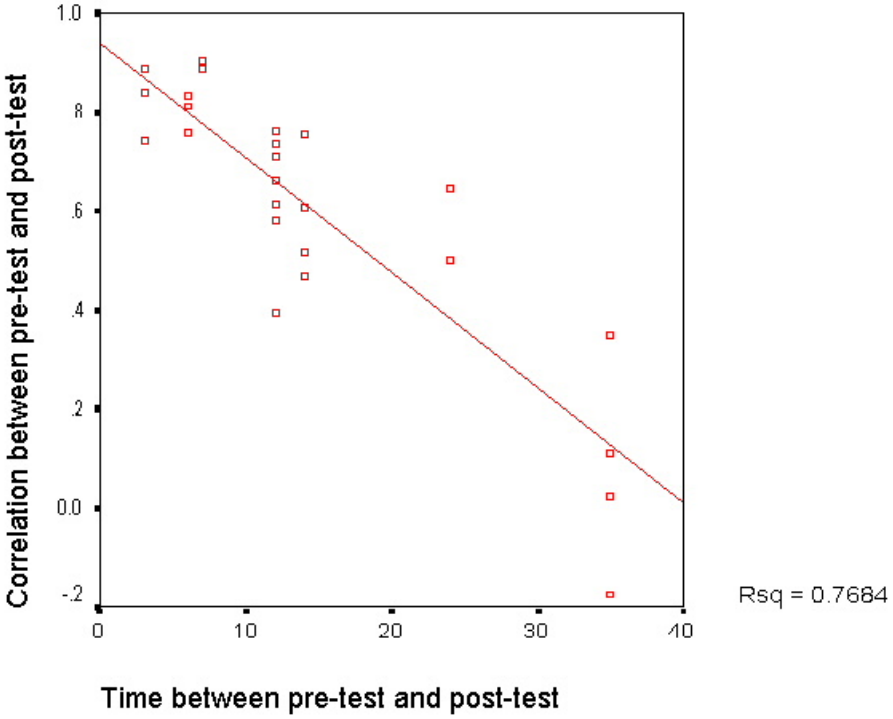
While many studies reported both baseline and outcome data (from which change score means can be calculated), only a few studies (most from the Parkinson's Study Group) reported change score standard deviations. Because controlling for pre-test differences was desired, and the "change score" standardized mean difference was desirable as a meta-analytic outcome, we estimated change score standard deviations when the data was not directly available.

This estimation was possible due to the studies that reported pre-test means and standard deviations, post-test means and standard deviations, and change score means and standard deviations. This data was available for 25 treatment arms, and it allowed for the calculation of 25

pre/post-test correlations. Figure 1 demonstrates that the time between pre-test and post-test scores was strongly related to the correlation between pre-test and post-test scores. In fact, the relationship was strong enough (R^2=.77) to make imputation of the pre/post-test correlation possible. The method used gave slightly more conservative (i.e., lower) correlations than those implied by the figure. For studies with a treatment duration of 10 months or less, a correlation of .8 was used to estimate the change-score standard deviation; .6 was used for those between 10.1 months and 20 months; .4 for those between 20.1 months and 30 months; .2 for those between 30.1 months and 40 months; and .1 for those studies of longer duration. The formula used was

$$s_{CHANGE\_SCORE} = \sqrt{s^2_{BASELINE} + s^2_{OUTCOME} - 2 * r_{PRE-POST} * s_{BASELINE} * s_{OUTCOME}}.$$

Figure 1. Time of evaluation versus pre-test post-test correlation



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Appendix G. Technical Experts and Peer Reviewers

Appendix G. Technical Experts and Peer Reviewers

AHRQ Diagnosis and Treatment of Parkinson's Disease Peer Reviewer Panel

Name	Specialty	Affiliation
Bressman, Susan - MD	PD Expert	Beth Israel Medical Center New York, NY
Brooks, Deborah W.	Consumer Advocate	Executive Director, The Michael J. Fox Foundation New York, NY
Brown, Janet - MA CCC-SLP	Speech-Language Pathology	Associate Director Health Care Services in Speech-Language Pathology American Speech-Language-Hearing Association Rockville, MD
Cohen, Perry - MD	Consumer Advocate	Director, Health Services Research Parkinson's Disease Foundation Washington, DC
Cosgrove, G. Rees - MD, FRCS (C.)	Neurosurgeon	Director, Movement Disorders Center Wang Ambulatory Care Center Massachusetts General Hospital Boston, MA
Langston, J William - MD	PD Expert	Founder, The Parkinson's Institute Sunnyvale, CA
Leurgans, Sue - PhD	Statistician	Department of Preventive Medicine & Neurological Sciences Rush-Presbyterian - St. Lukes Medical Center Chicago, IL
Marder, Karen - MD, MPH	PD Expert	Associate Professor of Clinical Neurology Sergievsky Center, Columbia University New York, NY
Neuman, William "Richey" - MD	Internist	Assistant Professor of General Internal Medicine Presbyterian Medical Center Philadelphia, PA
Nutt, John G. - MD	PD Expert	Oregon Health Sciences University Department of Neurology Portland, OR
Oertel, Wolfgang H. - MD	PD Expert	Philipps University Department of Neurology Director, Center for Nervous Diseases Marburg D 35033 Germany
Pfeiffer, Ron - MD	PD Expert	University of Tennessee, Memphis Department of Neurology Memphis, TN

AHRQ Diagnosis and Treatment of Parkinson's Disease Technical Expert Panel (TEP)

Name	Specialty	Affiliation
Baime, Michael - MD	Internist	Chief of Internal Medicine PENNCare at Rittenhouse Square Philadelphia, PA
Carter, Julie - RN, PhD	PD Expert	Oregon Health Sciences University Department of Neurology Portland, OR
Factor, Stewart A. - MD	PD Expert	Albany Medical Center Department of Neurology Albany, NY
Kieburtz, Karl D. - MD	PD Expert	Chief, Movement and Inherited Neurological Disorders Unit University of Rochester Medical School Rochester, NY
Levy, Sanford - MD	Neurologist	Department of Neurology North Shore Medical Center Salem, MA
Turner, Dennis - MD	PD Expert	Duke University Medical Center Division of Neurosurgery Durham, NC
Wistran, Daniel - MD	Consumer Advocate	Cardiology Physicians Inc. North Shore Medical Center Salem, MA
Zesiewicz, Theresa A. - MD	PD Expert	University of South Florida Parkinson's Disease Movement Disorders Center Tampa, FL

Peer Reviewer Form

AHRQ Task Order: Diagnosis and Treatment of Parkinson's Disease: A Systematic Review of the Literature

Please indicate your level of agreement with each of the following Statements, by placing an "X" in the appropriate column.				
Statements	**Very much agree**	**Moderately agree**	**Not very much in agreement**	**Do not agree at all**
1. This topic is relevant to healthcare decision-making (clinical practice and policy making) in 2001.				
2. The criteria used to select articles for inclusion were appropriate.				
3. Based on selection criteria used, it is not likely that relevant studies were missed.				
4. The validity of the studies was appraised appropriately.				
5. The methods are presented in such a way as to be reproducible.				
6. The statistical analytic methods are appropriate to the material and the objectives.				
7. The results are stated clearly.				
8. Given the nature of the topic and the data, all clinically important outcomes were considered.				
9. I agree with the conclusions presented in the report.				

On the following page, please provide:
a) A brief explanation of both positive and negative answers;
b) Suggestions for improvement of the content or format of this review;
c) Suggestions for additional analyses of this dataset worth including in this report, or in future reports.

**We would prefer that you complete and return this form electronically. However, you may also fax the form back to us, or fax back an annotated version of the draft report if you prefer. Contact information is provided below.

Thank you in advance for your time in completing this form and giving us your feedback. We value your input and greatly appreciate your efforts. Please send the completed form and comments to MetaWorks by **July 30, 2001.**

Contact: Rhonda P. Estok, RN, BSN, CNOR
Metaworks Inc.
E-mail: restok@metawork.com
Phone: (781) 395-0700 x254
Fax: (781) 395-7336

Peer Reviewer Form

AHRQ Task Order: Diagnosis and Treatment of Parkinson's Disease: A Systematic Review of the Literature (continued)

Please print legibly or type comments here:

(signature) (date)

(print name)

Appendix H. Accepted Studies Log

Citation

Study Category:Ancillary Treatment

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Appendix I. Rejected Studies Log

Citation

Rejection Reason: Abstract, letter comment, review, case report, or meta-analysis

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Rejection Reason: Duplicate Study

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Rejection Reason: Mixed populations where results for PD patients can not be separately extracted

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Rejection Reason: No outcome of interest

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Rejection Reason: Outcomes not extractable

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Rejection Reason: Pharmacodynamic or pharmacokinetic study

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Rejection Reason: Studies not including an objective clinical outcome measure of PD activity

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Rejection Reason: Studies not including tests to establish or support diagnosis of PD

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Rejection Reason: Study populations not including Parkinson Disease

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Appendix J. Studies of Interest Excluded from Database

A few studies did not meet inclusion criteria, but the consulting PD experts recommended that they be mentioned in this review. These studies are discussed below, but were not extracted, entered into the database, or included in the statistical analyses.

Pharmacological Treatment

The Parkinson Study Group conducted a 10-week, multicenter, double-blind RCT comparing placebo with various doses of pramipexole as monotherapy in 264 patients with early PD.[1] The trial did not meet the inclusion criteria for this review, due to its short duration; however, only two studies of pramipexole in early PD are included in the database, and this study is mentioned here for comparison. Pramipexole was well tolerated, and resulted in total UPDRS scores that were significantly improved compared with placebo. Studies of longer duration are necessary to confirm these favorable results.

A French, multicenter, open-label RCT compared tolcapone with bromocriptine in 146 PD patients who experienced "wearing-off" or "on/off" fluctuations on L-dopa/PDI.[2] As the trial lasted only eight weeks, it did not meet the inclusion criteria for this review, but it is the only direct comparison of tolcapone and bromocriptine, and therefore deserves mention. After eight weeks, patients in both groups had similar degrees of motor disability and "on/off" time. Patients in the tolcapone group were able to reduce their daily L-dopa dose more than were patients in the bromocriptine group. The side effect profile varied between the two groups. Studies of longer duration are necessary before conclusions can be made regarding a comparison of the efficacy and safety of bromocriptine and tolcapone.

Three double-blinded, placebo-controlled RCTs that were rejected because of insufficient study duration were readdressed upon the recommendation of a TEP member. One was the French selegiline multicenter trial (FSMT), a three-month study which showed that selegiline was statistically superior to placebo in improving symptoms in patients with early PD.[3] One study reported that pergolide monotherapy had superior efficacy to placebo in a three-month study of patients with early PD.[4] One six-week study of patients with "wearing-off" phenomenon on L-dopa assessed different doses of tolcapone in addition to L-dopa.[5] The addition of tolcapone reduced the "wearing-off" phenomenon. While all of these studies are important, their short duration precludes our ability to statistically compare the results of these studies to other studies in the database, and they remained in the "unaccepted studies" log.

A few studies have been performed using GM1 ganglioside, a normal constituent of nerve cell membranes, in human PD patients.[6,7,8] None of the studies met the criteria for acceptance for this review; only one was an RCT, and the study duration was less than 24 weeks. The study is, nevertheless, mentioned in this review, as GM1 represents a new category of pharmacologic treatment for PD that may receive further attention among researchers, although no studies published after 1998 were found.

After an initial intravenous test dose of GM1 1000 mg or placebo, 48 patients with mild to moderate PD were randomized to self-administered GM1 100 mg or placebo subcutaneously twice a day for 16 weeks.[8] Forty-five patients completed the study, and no withdrawals were

related to the safety or efficacy of GM1. The main adverse events were injection site reaction, including rash, erythema, or swelling, in ten GM1 patients and one placebo patient, and insomnia in five GM1 patients and two placebo patients. Twelve placebo patients and three GM1 patients complained of fatigue. The UPDRS motor scores improved a mean of 7.5 points after 16 weeks of GM1, while remaining essentially unchanged in the placebo patients. Twenty-one patients elected to continue to take GM1 in an open-label extension of the RCT.[7] Eighteen of these 21 patients continued to have UPDRS motor scores better than baseline, while three had worse scores. Patients who took GM1 continuously for two years showed the greatest improvement from their baseline UPDRS motor scores. Three patients who were followed after they discontinued GM1 at the end of the double blind trial all developed worsening of their UPDRS motor scores.

Anticholinergic Drugs

No trials of anticholinergic drugs met the inclusion criteria for this systematic review. In order to present the available information on this category of drugs, eight studies that were rejected for inclusion into the database but are pertinent to anticholinergic drugs in PD are mentioned here. The most recent studies are discussed first.

A cross-sectional study of the prevalence of dementia in PD was performed on 70 consecutive PD outpatients at a clinic of a university hospital.[9] Patients with dementia had received anticholinergic drugs for significantly longer than patients who were not mentally impaired, leading the authors to conclude that anticholinergic drugs should be avoided in PD patients with cognitive decline.

One study tested the cognitive function of 13 patients with newly diagnosed PD, before and after two weeks of treatment with trihexyphenidyl.[10] No patients were demented at baseline, and no significant change was seen in neuropsychological testing before and after the trihexylphenidyl. Given the short duration of the trial and the lack of cognitive impairment at baseline, it is difficult to draw any conclusions from this study.

In a retrospective analysis of 113 PD patients at a movement disorder clinic, the memory performance of patients taking anticholinergics was not significantly different from that of patients on dopaminergic medications alone.[11] This observation held true for patients with early, middle, or advanced disease. The presence of dementia at baseline was not reported, and may confound these findings, as other studies have suggested that anticholinergics impair cognitive function in patients who are already impaired at baseline.[12]

A study of 78 PD patients showed that patients with PD for > 3 years had memory performance that was worse than controls, and patients on benzhexol had dosage-dependent memory impairment compared to patients on L-dopa alone.[13] The authors concluded that memory is impaired in PD, and benzhexol contributes to the memory decline.

Most studies of anticholinergics were published prior to 1990. In a placebo-controlled, double-blind cross-over study published in 1981, 29 men with PD for one year, on stable doses of L-dopa/PDI, were treated with 10 weeks of benztropine or placebo, followed by a five-week washout period, then 10 weeks of the opposite treatment.[14] The authors reported that qualitative and quantitative evaluations showed small but statistically significant improvements for rigidity, finger tapping speed, and ADL for patients on benztropine, compared with patients on placebo. No patients had dementia at baseline. Patients on benztropine had a ten percent decrease in one of the five cognitive measures tested, two patients complained of memory problems, poor

concentration, irritability and confusion, and two patients experienced hallucinations. All adverse effects were reportedly mild and reversible with decreasing the medication dose. Interpretation of this study is limited by its short duration, the absence of results prior to cross-over, and the difficulty in comparing their evaluations with today's UPDRS scores.

A study published in 1978 evaluated 20 patients with early PD who were taking trihexyphenidyl.[15] L-dopa/PDI was openly added for eight weeks. All patients improved in bradykinesia, tremor, rigidity, and disability scale. The authors concluded that adding L-dopa/PDI to anticholinergics improves the therapeutic response in PD. This study is mainly of historic interest, as practitioners at that time were hesitant to use L-dopa, and were often treating PD patients with anticholinergics alone.

A double-blinded RCT comparing L-dopa plus trihexyphenidyl to L-dopa plus placebo was published in 1974.[16] There was no significant difference between the two groups, indicating that L-dopa alone was equivalent to L-dopa plus trihexyphenidyl.

The literature contains limited data regarding the efficacy and safety of anticholinergics in PD. Anticholinergics played an important role in the treatment of PD prior to the development of L-dopa, but their current role is limited to young, cognitively intact PD patients who have resting tremor as the predominant symptom.[17]

Surgery

One study compared overall effects of unilateral vs. bilateral STN in patients with advanced PD.[18] The study was not accepted into the database because no baseline data was reported on the ten patients in the study. They all underwent bilateral STN electrode implants, and the UPDRS scores of nine patients were assessed six months postoperatively, off medication, with stimulation off, on unilaterally, and on bilaterally. For all parameters measured, bilateral stimulation resulted in the greatest improvement, although unilateral STN DBS also led to moderate improvement in all PD symptoms.

One study that was published too late to meet the inclusion criteria for this systematic review was an RCT comparing the outcomes of embryonic tissue transplantation to sham surgery.[19] The active group consisted of 20 patients who underwent transplantation of human embryonic mesencephalic tissue containing dopamine neurons into their putamens. A control group of equal size underwent sham surgery, in which burr holes were drilled into their skulls, without penetration of the dura. The mean subjective global rating scores reported by patients one year after surgery were not significantly different between the two groups. The mean total UPDRS "off" scores one year postoperatively improved in the transplantation group compared to the control group, but the difference was not statistically significant ($p=0.11$). Patients ≤ 60 in the active group had significantly better UPDRS total, motor, rigidity, and bradykinesia scores than patients in the sham surgery group. Patients > 60 in the active group showed mild, not statistically significant improvement in UPDRS total scores, but no improvement in bradykinesia. Tremor did not improve in either age group.

The transplanted embryonic dopamine neurons survived well, as evidenced by 18F-fluorodopa PET scans in 19 transplant recipients, and autopsies in two transplant recipients who died of causes unrelated to their surgeries. Five of the younger patients who initially responded well to transplants developed severe, refractory dystonia and dyskinesia after the first year after transplantation. The researchers postulated that the transplanted embryonic dopamine neurons were producing too much dopamine in these patients.

While the initial results of embryonic tissue transplantation appeared promising in the younger patients, the development of late dystonia and dyskinesia clearly showed that this procedure is not a panacea for PD patients.

Psychological

The **PSY**chosis and **CLO**zapine in **P**arkinson'**S** Disease (PSYCLOPS) trial examined the effects of clozapine on dopaminergic-induced psychosis.[20] As the trial lasted only four weeks, it did not meet the criteria for acceptance into our database, however, the study is worthy of mention due to the paucity of information on treatment of patients with antiparkinsonian drug-induced psychosis. Sixty PD patients with hallucinations or delusions induced by antiparkinsonian drugs were randomized to receive low-dose clozapine (n=30) or placebo (n=30). Dosage was titrated between 6.25 and 50 mg daily, depending on clinical response. In the treatment of schizophrenia, clozapine is generally prescribed at a much higher dosage of 300 to 900 mg daily. Patients in the clozapine group showed improvement in all measures of psychosis, and had no worsening of motor symptoms. There was a statistically significant improvement in tremor in the patients in the clozapine group. During the four weeks of the trial, one patient on clozapine developed leukopenia, and one discontinued clozapine due to sedation. In an open-label extension of the trial, another patient developed leukopenia, and six patients died. The investigators did not believe that any of the deaths were related to clozapine use. While these results are promising, RCTs of longer duration are needed, particularly to evaluate adverse events.

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Appendix K. Acronyms in This Report

AAN = American Academy of Neurology

ACTH = adrenocorticotropic hormone

AD = Alzheimer's Dementia

ADL = activities of daily living

AEs = adverse events

AHRQ = Agency for Healthcare Research and Quality

ASHA = American Speech-Language-Hearing Association

BDI = Beck Depression Inventory

CAPIT = core assessment program for intracerebral transplantations

CAPSIT-PD = core assessment program for surgical interventional therapies in Parkinson's Disease

CBD = corticobasal degeneration

CBF = cerebral blood flow

COMT = catechol O-methyl transferase

CR = controlled release

CSF = cerebrospinal fluid

CT = computerized tomography

DA = dopamine agonist

DATATOP = deprenyl and tocopherol antioxidative therapy for Parkinson's Disease

DBS = deep brain stimulation

DEF = data extraction form

DLBD = diffuse Lewy body disease

EMG = electromyogram

FSMT = French selegiline multicenter trial

GH = growth hormone

GPi = globus pallidus

H&Y = Hoehn & Yahr Disability Scale

HVA = homovanillic acid

IBZM = ^{123}I-iodobenzamide

IPD = idiopathic Parkinson's Disease

ITT = intention to treat

L-dopa = levodopa

LFT = liver function tests

LDI = Leonard Davis Institute

LID = L-dopa-induced dyskinesia

LSVT = Lee Silverman Voice Treatment

MAOB = monoamine oxidase B

MRI = magnetic resonance imaging

MSA = multiple system atrophy

MT = music therapy

NHP = Nottingham Health Profile

NMR = nuclear magnetic resonance

NPV = negative predictive value

nRCT = non-randomized controlled trial

NUDS = Northwestern University Disability Score

ODT = odor discrimination test

OIT = odor identification test

OPT = orofacial physiotherapeutic treatment

OT = occupational therapy

PBL - peripheral blood lymphocyte

PD = Parkinson's Disease

PDI = peripheral decarboxylase inhibitor

PET = positron emission tomography

PIGD = postural instability and gait disturbance

PMT = premotor time

PPV = positive predictive value

PRL = prolactin

PROPATH = a patient education and health promotion program

PSP = progressive supranuclear palsy

PSYCLOPS = **psy**chosis and **clo**zapine in **P**arkinson'**s** Disease

PT = physical therapy

QC = quality control

QoL = quality of life

RAS = rhythmic auditory stimulation

RCT = randomized controlled trial

ROC = receiver operating characteristic

ROI = region of interest

S&E = Schwab and England scale

SLI = somatostatin-like immunoreactivity

SPECT = single photon emission computed tomography

SPM = statistical parametric mapping

SSRI = selectove serotonin reuptake inhibitor

STN = subthalamic nucleus

TCCS = transcranial color-coded real-time sonography

TEP = technical expert panel

TMS = transcranial magnetic stimulation

TOO = task order officer

UCS = uncontrolled case series

UPDRS = Unified Parkinson Disease Rating Scale

UPSIT = University of Pennsylvania Smell Identification Test

VEP = visual evoked potentials

WRS = Webster Rating Scale

XS = cross sectional