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

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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