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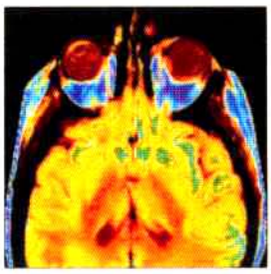

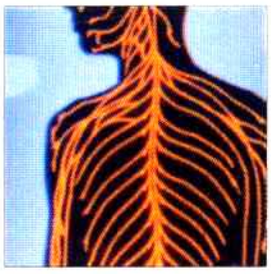
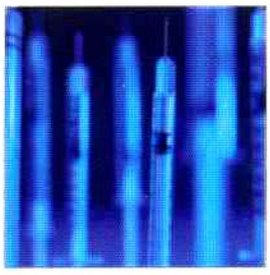

Diagnostic and Treatment Guidelines for Parkinson's Disease

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Dr. Lyons has served as a consultant for St. Jude Medical, Targacept and Teva Neuroscience.

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INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disease. It is estimated that PD affects over 1,000,000 people in the United States, with approximately 50,000 to 60,000 new cases diagnosed each year. The average age of PD onset is 60 years; although onset can be much later. On the other hand, up to 10% of patients are diagnosed with PD prior to the age of 40.[1,2] The cardinal motor symptoms of PD are bradykinesia, rigidity, and resting tremor as well as postural instability in the later stages of the disease.[3] PD patients may also experience a wide range of nonmotor symptoms including autonomic, neuropsychiatric, sensory, and sleep disturbances.[4] The cause of PD is unknown and there is currently no cure. The primary neurochemical change is a loss of dopamine in the substantia nigra; although it is increasingly recognized that additional neurotransmitters and brain areas are involved.[5,6]

There are numerous challenges in the diagnosis and management of PD. Early symptoms may be subtle and may be attributed to aging, other health issues, or misdiagnosed as another movement disorder. Determining the appropriate treatment(s) can also be a challenge. It is important to consider the specific needs, presentation, and disability of each individual. Current treatment options include levodopa, dopamine agonists, monoamine oxidase type B (MAO-B) inhibitors, catechol-O-methyltransferase (COMT) inhibitors, amantadine, and anticholinergics as well as deep brain stimulation (DBS) surgery of the subthalamic nucleus (STN), globus pallidus interna (GPi), or ventral intermediate nucleus of the thalamus (Vim). The treatment goal is to reduce symptoms without causing side effects, and the ultimate goal is to stop or slow the progression of PD.

There have been several guidelines developed throughout the world to aid physicians in the diagnosis and treatment of PD. Although the majority of the guidelines are similar, there are also some differences. We will review the recommendations of six different guidelines for the diagnosis, potential neuroprotection, early treatment, advanced treatment, and treatment of nonmotor symptoms of PD.

EPIDEMIOLOGY

- Cause of PD
  - Exposure to environmental toxins[7]
    - Herbicide and pesticide exposure
    - Rural living, farming, well water consumption
    - Industrial chemical exposure
  - Genetic factors[8]
    - Multiple genes and several additional loci identified
    - Genetics account for only about 10–15% of cases
  - Hypothesized that PD results from a combination of environmental and genetic factors
- Prevalence of PD (number of persons currently diagnosed)
  - Estimates range from 76 to 329 per 100,000[1]
    - Prevalence rates increase with age
    - Approximately 60% of PD patients are male
- Incidence of PD (number of new cases each year)
  - Estimates range from 16 to 19 per 100,000 per year[2]
- Primary risk factors
  - Age
  - Family history of PD
  - Male gender
- Lifetime risk of PD[9]
  - 2.0% in men
  - 1.3% in women

COST ISSUES

- Estimated US annual costs of PD as high as $25 billion
  - Healthcare costs
  - Medications and other treatments
  - Disability
  - Loss of productivity
  - Long-term care
- Age and gender matched PD versus non-PD control cost study[10]
  - Costs similar for first 5 years
  - Years 5–10 costs doubled for PD patients compared to non-PD controls
    - Increased hospital admissions
    - Longer hospital stays
    - Greater physician costs
    - Greater medication/treatment costs
  - Motor fluctuations are the strongest predictor of healthcare costs for PD patients.

GUIDELINES

The following guidelines were identified as providing recommendations for healthcare professionals on the diagnosis and/or treatment of PD. These guidelines have drawn conclusions and developed recommendations based on the available evidence in the literature and also good practice principles based on expert opinion, experience, and consensus. It should be noted that the guidelines are limited by the availability and quality of the literature and that newer guidelines reflect changes in the literature and practice principles, which may lead to discrepancies with aspects of the earlier guidelines.

Evidence Levels

All of the guidelines provide a review and rating of the literature. Although there are slight differences in how studies are rated, the following levels of evidence are a basis, which is relevant for all of the guidelines[11,12]:

- Level/Class I: High quality, well described, prospective, randomized, controlled trial (RCT). The trial should be powered appropriately and use appropriate statistical analyses, have a masked outcome assessment and include the appropriate population. The study should clearly describe the randomization process, primary outcome, inclusion/exclusion criteria, completers/dropouts, and baseline characteristics.
- Level/Class II: Prospective, high-quality, well described, case-control, or matched-group cohort study in the appropriate population with masked outcome assessment. Alternatively, an RTC that does not contain all of the items to qualify as a Level I study above.

- Level/Class III: All other controlled trials in the appropriate population, wherein outcome assessment is independent of patient treatment
- Level/Class IV: Evidence from uncontrolled studies, case series, case reports, or expert opinion

General Description

- **American Academy of Neurology (AAN)**
  - Diagnosis[13]
  - Neuroprotective strategies[14]
  - Initiation of treatment[12]
  - Treatment of motor fluctuations and dyskinesia[15]
  - Depression, psychosis and dementia[16]
  - Non-motor symptoms[17]

The AAN guidelines are evidence-based with expert opinion and future directions noted where applicable. Recommendations are based on the following criteria:

A – Effective, ineffective or harmful, requiring 2 consistent Class I studies

B – Probably effective, ineffective or harmful, 1 Class I study or at least 2 consistent Class II studies

C – Possibly effective, ineffective or harmful, 1 Class II study or 2 consistent Class III studies

U – Data inadequate or conflicting (treatment unproven)

Canadian Guidelines on Parkinson's Disease[18]

- The Canadian guidelines are relevant to the Canadian Health C5are System and are evidence-based with expert consensus when evidence is not available. These guidelines are based on the findings of the AAN, EFNS, and NICE guidelines, which are referenced as appropriate after each point in the Canadian guideline.

- **European Federation of Neurological Societies (EFNS)**
  - Early (uncomplicated) Parkinson's disease[11]
  - Late (complicated) Parkinson's disease[19]

The EFNS guidelines are evidence-based. The recommendations are based on the following criteria:

A – Effective, ineffective or harmful –a Class I study or 2 consistent Class II studies

B – Probably effective, ineffective or harmful –a Class II study or overwhelming Class III evidence

C – Possibly effective, ineffective, or harmful – at least 2 convincing class III studies

GPP – Good practice point

- **Movement Disorder Society (MDS)**
  - Treatments for motor symptoms[20]
  - Treatments for nonmotor symptoms[21]

The MDS guidelines are evidence-based. The recommendations are based on the following criteria:

- Efficacious/non-efficacious –1 high quality (score >75%) RTC without conflicting Level I data
- Likely efficacious/unlikely efficacious – Any level I study without conflicting level 1 data
- Insufficient evidence – no trials meeting the requirements above

- **National Institute for Health and Clinical Excellence (NICE)**
  - Parkinson's disease: Diagnosis and management in primary and secondary care[22]

The NICE guidelines are published by the Royal College of Physicians of London and are clinical evidence-based guidelines for the National Health Service of England and Wales. Recommendations are based on the following criteria:

A – High quality RCT with low risk of bias
B – High quality case-control or cohort studies or extrapolation from RTCs
C – Well-conducted, case-control or cohort studies or extrapolated from level B studies;
D – Nonanalytic studies or expert opinion (GPP – good practice point)

- **Scottish Intercollegiate Guidelines Network (SIGN)**
  - Diagnosis and pharmacological management of Parkinson's disease[23]

The SIGN guidelines are evidence-based. Recommendations are based on the following criteria:

A – High quality RCT with low risk of bias
B – High quality case-control or cohort studies or extrapolation from RTCs
C – Well-conducted, case-control or cohort studies or extrapolated from level B studies
D – Nonanalytic studies or expert opinion (GPP – good practice point)

DIAGNOSTIC ISSUES

Differential Diagnosis

According to the Canadian, NICE, and SIGN recommendations,[18,22,23] PD should be considered in patients with tremor, rigidity, bradykinesia, and/or gait and balance issues. These guidelines also recommend that because the diagnosis of PD is clinical, patients suspected of having PD should be sent to a movement disorder specialist before being treated in order to obtain confirmation of diagnosis, as other disorders can have similar symptoms, particularly early in the disease course. According to the AAN and Canadian guidelines,[13,18] the most common symptoms used to rule out a diagnosis of PD include falls at disease presentation, poor levodopa response, symmetry at onset, rapid progression, lack of tremor, and dysautonomia.

Diagnostic Criteria

The United Kingdom Parkinson's Disease Society Brain Bank clinical diagnostic criteria are the most commonly used criteria in the diagnosis of PD.[24] These criteria are based on a three step process: (1) identify the primary symptoms of parkinsonism; (2) exclude the diagnosis of PD based on history, signs and symptoms uncharacteristic for idiopathic PD; and (3) identify at least three supporting criteria for the diagnosis of idiopathic PD:

- Step 1: Diagnosis of parkinsonism:
  - Bradykinesia (slow initiation of movement; progressive reduction in speed/amplitude with repetition)
  - And at least one of the following:
    - Muscular rigidity
    - 4–6 HZ rest tremor
    - Postural instability