Protocol for proposed practice guideline project: Initiation of treatment for Parkinson’s Disease

Proposal of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology

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Approved by the Guideline Development, Dissemination, and Implementation Subcommittee on October 21, 2017. All comments submitted during the 30-day public comment period in which this protocol is posted will be reviewed and addressed by the author panel members. Although all comments will be considered, author panel members will not specifically respond to individual comments online.

STUDY FUNDING
This practice guideline protocol was developed with financial support from the American Academy of Neurology. Authors who serve as AAN subcommittee members or methodologists (TP), or who are AAN staff members, were reimbursed by the AAN for expenses related to travel to subcommittee meetings where drafts of manuscripts were reviewed.

DISCLOSURES
Tamara Pringsheim has reported no conflicts of interest.
Robertus de Bie has reported no conflicts of interest.
Alberto Espay serves as a member of the advisory boards for Abbvie and US WorldMeds; serves on the speakers bureau for Abbvie and US WorldMeds; has received awards from Novartis and US WorldMeds.
Deborah Hall has reported no conflicts of interest.
Robert Hauser has received funding for travel from US WorldMeds; has received honoraria from US WorldMeds and Abbvie; has received commercial entities from Abbvie; has attended Abbvie Parkinson’s Advisory Board Meeting in 2013.
Anthony Lang has served on advisory boards for Abbvie, Acorda, Avanir Pharmaceuticals, Biogen, Bristol Myers Squibb, Cipla, Intekrin, Jazz Pharma, Sun Pharma, and Merck; received honoraria from Sun Pharma, Medichem, Medtronic, Teva, UCB, AbbVie and Sunovion; received grants from Brain Canada, Canadian Institutes of Health Research, Edmond J Safra Philanthropic Foundation, Michael J. Fox Foundation, the Ontario Brain Institute, National Parkinson Foundation, Parkinson Society Canada, and W. Garfield Weston Foundation; received publishing royalties from Saunders, Wiley-Blackwell, Johns Hopkins Press, and Cambridge University Press.
Janis Miyasaki receives grant funding from NINDS, PCORI, Allergen, and UHF; receives honoraria from Davis Phinney Foundation, Sunovier; receives publishing royalties from Up to Date: Functional Movement Disorders; does consulting work for GE Consulting and Cynapses Consulting.

Emmanuel Roze has served on scientific advisory boards for Orkyn, Ultragenix, Retrophin, and Merz-Pharma; has received travel funding from Elivie, Sanofi-Genzyme, the Dystonian Coalition, The Dystonia Medical Research Foundation, the Movement Disorders Society, and the European Academy of Neurology; has received speech honorarium from Orkyn, Aguettant, Merz-Pharma, Medday pharma, and Ultragenix; and has received research support from Merz-Pharma, Orkyn, Aguettant, Elivie, Ultragenix, and INSERM.

Lori Billinghurst has reported no conflicts of interest.

Gregory Day has reported no conflicts of interest.

Nicole Licking has reported no conflicts of interest.

Justin Martello has reported no conflicts of interest.

Kelly Sullivan has reported no conflicts of interest.

Melissa Armstrong has reported no conflicts of interest.

Lauren McLaughlin has reported no conflicts of interest.

Michael Fitts has reported no conflicts of interest.

Lynn Hagerbrant has reported no conflicts of interest.

DESCRIPTION OF AAN DOCUMENT TYPES

This protocol is the planning document for one of four AAN document types: focused systematic review, comprehensive systematic review, practice advisory (based on a systematic review), or practice guideline (based on a systematic review). The term Guideline is the general term that refers to all AAN evidence-based documents. Because it is for planning purposes only, this protocol document is not a substitute for the complete Systematic Review or Guideline.
GUIDELINE PROJECT PROTOCOL

Guideline project development plan

This proposed project will be developed in accordance with the processes described in the 2017 edition of the AAN clinical practice guideline development process manual. The developers of this Guideline project intend to develop a practice guideline based on a systematic review. This protocol will be posted for public comment.

Guideline project timeline

Following is the tentative timeline for development of this practice guideline based on a systematic review:

Panel formation: July 2017

Drafting of protocol: September 2017

Approval of protocol by the AAN Guideline Development, Dissemination, and Implementation Subcommittee (GDDI): October 2017

Protocol posted for public comment: November 2017

Literature search: January 2018

Panel review of abstracts: January-March 2018

Review of full articles, data extraction, and development of evidence tables: April-October 2018

Develop recommendations based on systematic review and other pillars (principles, strong related evidence from other conditions, inferences): November-December 2018

Submit draft guideline to AAN GDDI for review and approval for public comment: January 2019

Post guideline for public comment: March 2019

Submit to AAN GDDI for review and approval of final document (Neurology will do preliminary review concurrently; when approved by GDDI, the AAN Practice Committee also will review): July 2019

Submission to Neurology: September 2019

Composition of the author panel

In August 2017, the AAN GDDI recruited a multidisciplinary panel consisting of 13 AAN clinician members to develop this Guideline project protocol. The panel included content experts (TP, RDB, AE, DH, JMM, AL, RH, ER, JPM, MA), a methodology expert (TP), AAN Quality and Safety Subcommittee (QSS) member (JPM), AAN GDDI members (GD, NL, KS, LB, MA), patient representatives (MF, LH), and a staff representative from the Michael J Fox Foundation (LM). The members were required to submit online conflict of interest
(COI) forms and copies of their curriculum vitae (CV). The panel leadership, consisting of the lead developer (TP), the AAN methodologist (TP), and AAN staff persons (MDOB), reviewed the COI forms and CVs for financial and intellectual COI. These documents were screened specifically to exclude both those individuals with a clear financial conflict and those whose profession and intellectual bias would diminish the credibility of the review in the eyes of the intended users. In accordance with AAN policy, the lead developer (TP) has no COI. Five of the [Guideline] developers was determined to have COI, but the COI were judged to be not significant enough to preclude this developer from authorship (AE, JMM, AL, RH, ER). The developers determined to have COI (AE, JMM, AL, RH) will not be permitted to review or rate the evidence. These individuals will be consulted in an advisory capacity to help with the validation of the key questions, the scope of the literature search, and the identification of seminal articles to validate the literature search. The panel members with COI will be allowed to participate in the recommendation development process. The lead developer recommended the final panel membership to the AAN GDDI leadership, who reviewed the list of members and the panel leaders’ COI forms, and provided final approval. This panel will be solely responsible for the final decisions about the design, analysis, and reporting of the proposed systematic review and proposed subsequent practice guideline, which will then be submitted for approval to the AAN GDDI.

Introduction to proposed practice guideline project topic

Parkinson’s disease is a common neurodegenerative disorder with increasing prevalence with age, affecting approximately 1% of individuals aged 70 to 79, and 2% of individuals over the age of 80 years (Pringsheim 2014). Individuals with Parkinson’s disease typically present with symptoms of bradykinesia, tremor, and rigidity. Symptoms progress gradually with time, and affected individuals require on-going medical care and consultation with neurologists from disease onset until the end of life. The classification of the severity of PD is often described using the Hoehn and Yahr Scale (Hoehn and Yahr, 1967). According to this classification scheme, in Stage 1, individuals have unilateral disease only, with Stage 1.5 characterized by unilateral plus axial involvement. In Stage 2 disease, there is bilateral involvement without impairment of balance. A total of 5 stages are described, with Stage 5 characterized by a wheelchair bound or bedridden state unless aided. Patients in Stages 1 and 2 are considered to have early stage disease.

Symptomatic therapies for Parkinson’s disease are available and for most patients offer therapeutic benefit. In the early stages of PD, patients receive dopaminergic treatment with monoamine oxidase inhibitors, dopamine agonists and/or levodopa. The choice of initial treatment is variable among clinicians, due to concerns regarding impulse control disorders associated with dopamine agonists, and motor complications associated with levodopa. Clinicians and individuals with Parkinson’s disease are eager to find neuroprotective treatments to halt the progression of this ultimately disabling disease.

Rationale for this practice guideline

In 2002, the AAN published a practice guideline on the initiation of treatment in Parkinson’s disease, to create recommendations on the role of selegiline, a monoamine oxidase inhibitor, in the early treatment of Parkinson’s disease, and the initiation of dopaminergic treatment for symptomatic treatment (Miyasaki 2002). The authors concluded that selegiline has a very mild symptomatic benefit with no evidence for neuroprotective benefit, and that for PD patients requiring initiation of symptomatic therapy, either levodopa or a dopamine agonist can be used. It was determined that levodopa provides superior motor benefit but is associated with a higher risk of dyskinesia. There was no evidence that initiating treatment with sustained release levodopa provided an
advantage over immediate-release levodopa. As fifteen years have passed since the publication of the guideline, many new medications and new formulations of medications are available for the treatment of Parkinson’s disease. We wish to provide guidance to clinicians on the treatment of early stage Parkinson’s disease, addressing the specific clinical questions listed below.

Clinical questions

The systematic review for this practice guideline will address the following questions:

1. In people with early Parkinson’s disease, do MAO-B inhibitors compared to placebo provide symptomatic benefit for motor or non-motor symptoms?

2. In people with early Parkinson’s disease, do pharmacological treatments (including MAO-B inhibitors) compared to placebo delay disease progression?

3. In people with early Parkinson’s disease, what is the comparative efficacy of levodopa versus dopamine agonists versus MAO-B inhibitors for motor symptoms or non-motor symptoms?

4. In people with early Parkinson’s disease, what is the comparative risk of adverse effects (including motor complications) of levodopa versus dopamine agonists versus MAO-B inhibitors?

5. In people with early Parkinson’s disease, what is the comparative efficacy of different formulations of dopamine agonists for motor symptoms or non-motor symptoms?

6. In people with early Parkinson’s disease, what is the comparative risk of adverse effects (including motor complications) of different formulations of dopamine agonists?

7. In people with early Parkinson’s disease what is the comparative efficacy of sustained-release or long-acting levodopa versus immediate release levodopa for motor or non-motor symptoms?

8. In people with early Parkinson’s disease, what is the comparative risk of adverse effects (including motor complications) of sustained-release versus immediate release levodopa?

9. In people with early Parkinson’s disease, do physical therapy or exercise programs compared to control interventions improve motor or non-motor symptoms?

10. In people with early Parkinson’s disease, what is the risk of impulse control disorders with dopamine agonists, levodopa, and other medications used for the treatment of early Parkinson’s disease, and does the risk differ between drug formulations?

11. In people with early Parkinson’s disease initially treated with dopamine agonists versus levodopa, what is the long term risk of disabling dyskinesias?

12. In people with early Parkinson’s disease, what is the efficacy of anticholinergic medications versus placebo or active comparators for resting tremor?

Using related evidence and principles of care, we will address the following questions:

1. When should dopaminergic therapy be started in people with early Parkinson’s disease?
TABLE 1

<table>
<thead>
<tr>
<th>Question (type)*</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcome</th>
<th>Study design</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. In people with early Parkinson’s disease, do MAO-B inhibitors compared to placebo provide symptomatic benefit for motor and non-motor symptoms? (Therapeutic)</td>
<td>people with early Parkinson’s disease</td>
<td>MAO-B inhibitors</td>
<td>Placebo</td>
<td>motor and non-motor symptoms</td>
<td>RCTs</td>
</tr>
<tr>
<td>2. In people with early Parkinson’s disease, do pharmacological treatments (including MAO-B inhibitors) compared to placebo delay disease progression? (Therapeutic)</td>
<td>people with early Parkinson’s disease</td>
<td>pharmacological treatments (including MAO-B inhibitors)</td>
<td>placebo</td>
<td>disease progression</td>
<td>RCTs Prospective cohort studies</td>
</tr>
<tr>
<td>3. In people with early Parkinson’s disease, what is the comparative efficacy of levodopa versus dopamine agonists for motor symptoms and non-motor symptoms? (Therapeutic)</td>
<td>people with early Parkinson’s disease</td>
<td>levodopa</td>
<td>dopamine agonists</td>
<td>motor and non-motor symptoms</td>
<td>RCTs</td>
</tr>
<tr>
<td>4. In people with early Parkinson’s disease, what is the comparative risk of adverse effects (including motor complications) of levodopa versus dopamine agonists? (Therapeutic)</td>
<td>people with early Parkinson’s disease</td>
<td>levodopa</td>
<td>dopamine agonists</td>
<td>adverse effects, including motor complications</td>
<td>RCTs Prospective cohort studies</td>
</tr>
<tr>
<td>5. In people with early Parkinson’s disease, what is the comparative efficacy of different</td>
<td>people with early Parkinson’s disease</td>
<td>dopamine agonists</td>
<td>dopamine agonists</td>
<td>motor and non-motor symptoms</td>
<td>RCTs</td>
</tr>
<tr>
<td>Formulations of dopamine agonists for motor symptoms or non-motor symptoms? (Therapeutic)</td>
<td>People with early Parkinson’s disease</td>
<td>Dopamine agonists</td>
<td>Dopamine agonists</td>
<td>Adverse effects, including motor complications</td>
<td>RCTs Prospective cohort studies</td>
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<td>6. In people with early Parkinson’s disease, what is the comparative risk of adverse effects (including motor complications) of different formulations of dopamine agonists? (Therapeutic)</td>
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<td>Dopamine agonists</td>
<td>Dopamine agonists</td>
<td>Adverse effects, including motor complications</td>
<td>RCTs Prospective cohort studies</td>
</tr>
<tr>
<td>7. In people with early Parkinson’s disease what is the comparative efficacy of sustained-release versus immediate release levodopa for motor and non-motor symptoms? (Therapeutic)</td>
<td>People with early Parkinson’s disease</td>
<td>Sustained release levodopa</td>
<td>Immediate release levodopa</td>
<td>Motor and non-motor symptoms</td>
<td>RCTs</td>
</tr>
<tr>
<td>8. In people with early Parkinson’s disease, what is the comparative risk of adverse effects (including motor complications) of sustained-release versus immediate release levodopa? (Therapeutic)</td>
<td>People with early Parkinson’s disease</td>
<td>Sustained release levodopa</td>
<td>Immediate release levodopa</td>
<td>Adverse effects (including motor complications)</td>
<td>RCTs Prospective cohort studies</td>
</tr>
<tr>
<td>9. In people with early Parkinson’s disease, what is the risk of impulse control disorders with dopamine agonists, levodopa, and other medications used for the treatment of early Parkinson’s disease, and does the risk differ between drug formulations? (Frequency)</td>
<td>People with early Parkinson’s disease</td>
<td>Dopamine agonists levodopa other medications used in early PD</td>
<td>Placebo</td>
<td>Impulse control disorders</td>
<td>Population-based epidemiological studies Prospective cohort studies RCTs</td>
</tr>
</tbody>
</table>
10. In people with early Parkinson’s disease, do physical therapy or exercise programs compared to control interventions improve motor and non-motor symptoms? (Therapeutic)

11. In people with early Parkinson’s disease initially treated with dopamine agonists versus levodopa, what is the long term risk of disabling dyskinesias? (Frequency)

12. In people with early Parkinson’s disease, what is the efficacy of anticholinergic medications versus placebo or active comparators for resting tremor? (Therapeutic)

*Question type refers to one of the following: screening, diagnostic, therapeutic, prognostic, natural history, and frequency.

Rationale for the clinical questions

We have included clinical questions which are relevant to patients and treating physicians when an individual is diagnosed with early stage Parkinson’s disease. Treatments that offer neuroprotection will ultimately change the evolution of the disease and therefore are highly relevant to patients, caregivers and physicians. As there are several formulations of levodopa and dopamine agonists available for patients and physicians to choose from, it is clinically important to make an informed decision regarding which treatments offer the greatest benefit, while minimizing the risk of long term adverse effects.

Consideration of patient preferences

We will attempt to include information on patient preferences regarding the initiation of treatment in Parkinson’s Disease through several methods. We will include two panel members with lived experience with Parkinson’s Disease on our panel, to represent the view and preferences of patients. We will seek comment at
both the protocol and guideline stage from patient advocacy groups for Parkinson’s Disease. We will attempt to
close related literature on patient preferences in Parkinson’s Disease that can be incorporated into the
formulation of our recommendations. Finally, we will include a staff member from the Michael J. Fox
Foundation on the author panel who will be able to add their insight on patients with Parkinson’s Disease.

**Relevant special populations**

Because there is increasing evidence that not everyone responds to therapies in the same way (whether due to
race/ethnicity, sex, concomitant health issues, or other factors), AAN guidelines now specifically identify
special populations for whom recommendations might possibly be different. There may or may not be available
evidence for these special populations, but the literature search will specifically look for evidence for efficacy in
these populations in addition to in the general population. Special populations of relevance to this practice
advisory include women and the elderly (age 65 and older). Women may be under-represented in clinical trials,
and age influences decision making about treatment since some adverse effects are more common in elderly
patients.

**Rationale for special populations**

Sex and age may influence the choice or outcome of treatments.

**Plan to address special populations in the guideline**

Where available, we will include results by sex and age and consider sex and age when making
recommendations if there is evidence to suggest a difference in included outcomes by sex or age.

**Study screening and selection criteria: inclusion and exclusion criteria for article selection**

**For Therapeutic and Frequency Questions**

**Types of participants**

We will include studies of participants with Parkinson’s Disease in the early stages, e.g. Hoehn and Yahr stages
1 or 2.

**Types of intervention**

We will include studies of dopamine agonists, levodopa and monoamine oxidase B inhibitors to delay the
progression of Parkinson’s disease or to treat motor or non-motor symptoms of Parkinson’s disease in the early
stages of the disease. Studies of other medications to delay the progression of Parkinson’s disease will also be
included. We will include studies of anticholinergics for the treatment of resting tremor in the early stages of
the disease. We will not include studies of COMT inhibitors and amantadine since these medications are less
commonly used in the early stages of Parkinson’s disease.

**Comparison group**

For studies of medications to delay the progression of Parkinson’s disease, we will include studies versus
placebo or an active control. For studies of MAO-B inhibitors for early symptomatic treatment of motor and
non-motor studies, we will include studies comparing MAO-B inhibitors to placebo or active comparators. For
studies of dopamine agonists and levodopa for the early symptomatic treatment of motor or non-motor
symptoms of Parkinson’s disease, we will include studies using active comparators only, e.g. levodopa versus a
dopamine agonist, immediate release levodopa versus sustained release levodopa, etc. For studies of
anticholinergics for the treatment of tremor, we will include studies using placebo and active comparators. For studies of physical therapy or exercise programs for the early symptomatic treatment of motor or non-motor symptoms of Parkinson’s disease, we will include randomized studies using a control group that received another type of intervention.

**Types of outcome measures**

While we will include data from any validated scale for the measurement of motor and non-motor symptoms in Parkinson’s Disease, the preferred outcome measure will be the Unified Parkinson’s Disease Rating Scale, when included and reported in studies. For adverse effects, risk differences will be calculated for dichotomous outcomes.

**Literature search strategy**

**Inclusion and exclusion criteria**

**Inclusion:**
- Human studies
- Languages: all languages
- People with early stages of Parkinson (e.g., Hoehn and Yahr stages 1 or 2)
- Study types: RCTs, prospective cohort studies, population-based epidemiological studies
- Outcomes: motor and non-motor symptoms, disease progression, adverse effects (including motor complications), impulse control disorders, disabling dyskinesias
- Date: database inception to present

**Exclusion:**
- Animal studies
- Study types: retrospective cohort studies, case studies, case series, reviews, meta-analyses
- Outcomes not listed above

**Terms and databases to be used in the literature search**

Medline
Central
ClinicalTrials.gov

**Keywords (to be completed by librarian)**

a) Key Text words and Index words for the condition or closely related conditions, if appropriate (linked by the word "OR"): Parkinson* OR Parkinson* disease OR idiopathic Parkinson* disease OR Lewy Body Parkinson* disease OR paralysis agitans OR primary Parkinsonism

b) Key text words for identification of special populations and relevant comorbidities (linked by the word "OR"): 
c) **Key Text words and Index words for the intervention (linked by the word "OR"):** MAO-B inhibitors OR pharmacological treatments OR levodopa OR sustained release levodopa OR dopamine agonists OR anticholinergics OR physical therapy OR exercise programs

**DISCLAIMER**

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**CONFLICT OF INTEREST**

The American Academy of Neurology is committed to producing independent, critical, and truthful clinical practice guidelines (CPGs). Significant efforts are made to minimize the potential for conflicts of interest to influence the recommendations of this CPG. To the extent possible, the AAN keeps separate those who have a financial stake in the success or failure of the products appraised in the CPGs and the developers of the guidelines. Conflict of interest forms were obtained from all authors and reviewed by an oversight committee prior to project initiation. AAN limits the participation of authors with substantial conflicts of interest. The AAN forbids commercial participation in, or funding of, guideline projects. Drafts of the guideline have been reviewed by at least three AAN committees, a network of neurologists, *Neurology* peer reviewers, and representatives from related fields. The AAN Guideline Author Conflict of Interest Policy can be viewed at www.aan.com. For complete information on this process, access the 2017 AAN process manual.¹
REFERENCES

