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Dopaminergic Therapy for Motor Symptoms in Early Parkinson Disease Practice Guideline

Report by:

Guideline Subcommittee of the American Academy of Neurology

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Practice Guideline Endorsement

This practice guideline was endorsed by the Parkinson's Foundation.

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Presentation Objectives

To review the current evidence on the options available for initiating dopaminergic treatment of motor symptoms in early-stage Parkinson disease (PD) and provide recommendations to clinicians.

Overview

- Introduction
- Clinical questions
- AAN guideline development process
- Methods
- Conclusions
- Practice recommendations

Introduction

In 2002, the American Academy of Neurology (AAN) published the “Initiation of Treatment for Parkinson’s Disease” practice guideline, which contains recommendations regarding the use of dopaminergic medications for patients with PD. Since 2002, many new medications and new formulations of older medications have become available for PD treatment. The goal of this guideline is to review the current evidence on initial dopaminergic treatment of motor symptoms in early-stage PD and provide guidance to clinicians.

Clinical Questions

This guideline addresses the following questions:

1. In people with early PD, what is the comparative efficacy of levodopa vs dopamine agonists (DAs) vs monoamine oxidase type B (MAO-B) inhibitors for motor symptoms?
2. In people with early PD, what is the comparative risk of adverse effects (specifically dyskinesia, hallucinations, and adverse event–related discontinuation) of levodopa vs DAs vs MAO-B inhibitors?
3. In people with early PD, what is the comparative efficacy of different formulations of DAs for motor symptoms?
4. In people with early PD, what is the comparative risk of adverse effects (specifically dyskinesia, hallucinations, and adverse event–related discontinuation) of different formulations of DAs?

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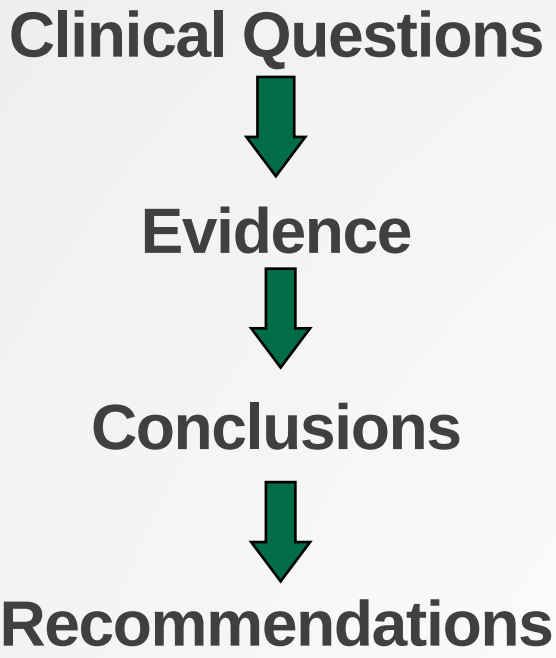
Clinical Questions

This guideline addresses the following questions:

5. In people with early PD, what is the comparative efficacy of long-acting formulations of levodopa (including sustained-release [SR] or controlled-release [CR] formulations of levodopa and levodopa plus entacapone) vs immediate-release (IR) levodopa for motor symptoms?
6. In people with early PD, what is the comparative risk of adverse effects (specifically dyskinesia, wearing-off, hallucinations, and adverse event–related discontinuation) of long-acting formulations of levodopa vs IR levodopa?
7. In people with early PD, what is the risk of impulse control disorders (ICDs) with medications used for the treatment of motor symptoms, and does the risk differ between drug formulations?
8. In people with early PD initially treated with DAs vs levodopa, what is the long-term risk of disabling dyskinesia?

AAN Guideline Development Process*



*Guideline developed using the *AAN 2017 Edition Clinical Practice Guideline Process Manual*.

Literature Search/Review

Rigorous, Comprehensive, Transparent

Cochrane Library, Medline, and ClinicalTrials.gov databases were searched for peer-reviewed articles that met the inclusion criteria published from database inception through March 2018. The search was updated in June 2020 to identify studies published since March 2018.

5,300 abstracts

59 included articles

Inclusion criteria:

- Population—patients in early stages of PD (Hoehn and Yahr stages 1 or 2, or within two years of disease onset)
- Intervention—studies of DAs, levodopa, MAO-B inhibitors, and catechol-o-methyl transferase (COMT) inhibitors to treat motor symptoms
- Outcome—any validated scale for measurement of motor symptoms in PD; preferred measure was the Unified Parkinson's Disease Rating Scale (UPDRS) part III
- Study type—randomized control trials (RCTs) for questions 1–6; RCTs, population-based epidemiologic studies, and prospective cohort studies for questions 7 & 8

Exclusion criteria:

- Studies with participants at Hoehn and Yahr stages above 2, or with disease onset more than two years prior to study onset
- Reviews, meta-analyses, retrospective cohort studies, case control studies, and case series
- Studies with 20 or fewer participants, studies including participants who had diseases other than PD, and articles that were not peer reviewed

Class I

- Randomized controlled clinical trial (RCT) in a representative population
- Triple-masked studies (i.e., the patient, treating provider, and outcome assessors are unaware of treatment assignment)
- Relevant baseline characteristics of treatment groups (or treatment order groups for crossover trials) are presented and substantially equivalent between treatment groups, or there is appropriate statistical adjustment for differences

- Additional Class I criteria:
    a. Concealed allocation
    b. No more than two primary outcomes specified
    c. Exclusion and inclusion criteria clearly defined
    d. Adequate accounting of dropouts (with at least 80 percent of participants completing the study) and crossovers

    e. For noninferiority or equivalence trials claiming to prove efficacy for one or both drugs, the following are also required*:
        i. The authors explicitly state the clinically meaningful difference to be excluded by defining the threshold for equivalence or noninferiority
        ii. The standard treatment used in the study is substantially similar to that used in previous studies establishing efficacy of the standard treatment (e.g., for a drug, the mode of administration, dose, and dosage adjustments are similar to those previously shown to be effective)
        iii. The inclusion and exclusion criteria for participant selection and the outcomes of participants on the standard treatment are comparable with those of previous studies establishing efficacy of the standard treatment
        iv. The interpretation of the study results is based on a per-protocol analysis that accounts for dropouts or crossovers

        v. For crossover trials, both period and carryover effects are examined and statistical adjustments performed, if appropriate

*Numbers i–iii in Class Ie are required for Class II in equivalence trials. If any one of the three is missing, the class is automatically downgraded to Class III.

Class II
- RCT that lacks one or two Class I criteria a–e (see previous slide) - Cohort studies employing methods that successfully match treatment groups on relevant baseline characteristics (e.g., propensity score matching) meeting Class I criteria b–e (see previous slide)
- Randomized crossover trial missing one of the following two criteria: a. Period and carryover effects described b. Baseline characteristics of treatment order groups presented
- All relevant baseline characteristics are presented and substantially equivalent across treatment groups (or treatment order groups for crossover trials), or there is appropriate statistical adjustment for differences
- Masked or objective** outcome assessment

**Objective outcome measurement: an outcome measure that is unlikely to be affected by an observer's (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data)

AAN Classification of Evidence (2017)

Therapeutic Scheme

Class III	Class IV
- Controlled studies (including studies with external controls such as well-defined natural history controls) - Crossover trial missing both of the following two criteria: a. Period and carryover effects b. Presentation of baseline characteristics - A description of major confounding differences between treatment groups that could affect outcome** - Outcome assessment performed by someone who is not a member of the treatment team	- Studies not meeting Class I, II, or III criteria

**Objective outcome measurement: an outcome measure that is unlikely to be affected by an observer's (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data).

Clinical Questions 1 & 2

1. In people with early PD, what is the comparative efficacy of levodopa vs DAs vs MAO-B inhibitors for motor symptoms?
2. In people with early PD, what is the comparative risk of adverse effects (specifically dyskinesia, hallucinations, and AE-related discontinuation) of levodopa vs DAs vs MAO-B inhibitors?

Clinical Questions 1 & 2: Conclusions

Levodopa vs DAs

Change in UPDRS part III score from baseline to endpoint

- Levodopa is possibly no more effective than DAs (with or without levodopa) in improving motor function at 6 months. (Low confidence)
- Levodopa is possibly more effective than DAs (with or without levodopa) in improving motor function at 1 year. (Low confidence)
- Levodopa is likely more effective than DAs (with or without levodopa) in improving motor function at 2 years. (Moderate confidence)
- There is insufficient evidence to support or refute the effectiveness of levodopa compared to DAs (with or without levodopa) in improving motor function at 3 years. (Very low confidence)
- Levodopa is possibly more effective than DAs (with or without levodopa) in improving motor function at 4 years. (Low confidence)
- Levodopa is likely more effective than DAs (with or without levodopa) in improving motor function at 5 years. (Moderate confidence)
- There is insufficient evidence to support or refute the effectiveness of levodopa compared to DAs (with or without levodopa) in improving motor function at 6 years. (Very low confidence)
- There is insufficient evidence to support or refute the effectiveness of levodopa compared to DAs (with or without levodopa) in improving motor function at 10 years. (Very low confidence)

Clinical Questions 1 & 2: Conclusions

Levodopa vs DAs

Risk of dyskinesia

- Levodopa is probably more likely than DAs (with or without levodopa) to induce dyskinesia at 2 years. (Moderate confidence)
- Levodopa is possibly more likely than DAs (with or without levodopa) to induce dyskinesia at 3 years. (Low confidence)
- Levodopa is probably more likely than DAs (with or without levodopa) to induce dyskinesia at 4 years. (Moderate confidence)
- Levodopa is possibly more likely than DAs (with or without levodopa) to induce dyskinesia at 5 years. (Low confidence)
- There is insufficient evidence to determine whether, in early PD, levodopa is more or less likely than DAs (with or without levodopa) to induce dyskinesia at 6 years. (Very low confidence)
- There is insufficient evidence to determine whether, in early PD, levodopa is more or less likely than DAs (with or without levodopa) to induce dyskinesia at 7 years. (Very low confidence)
- There is insufficient evidence to determine whether, in early PD, levodopa is more or less likely than DAs (with or without levodopa) to induce dyskinesia at 10 years. (Very low confidence)
- There is insufficient evidence to determine whether, in early PD, levodopa is more or less likely than DAs (with or without levodopa) to induce dyskinesia at 14 years. (Very low confidence)

Clinical Questions 1 & 2: Conclusions

Levodopa vs DAs

Risk of hallucinations

- DAs (with or without levodopa) are possibly more likely than levodopa to induce hallucinations at 2 years. (Low confidence)
- There is insufficient evidence to determine whether, in early PD, levodopa is more or less likely than DAs (with or without levodopa) to induce hallucinations at 3 years. (Very low confidence)
- DAs (with or without levodopa) are possibly no more likely than levodopa to induce hallucinations at 4 years. (Low confidence)
- DAs (with or without levodopa) are possibly no more likely than levodopa to induce hallucinations at 5 years. (Low confidence)

Clinical Question 1 & 2: Conclusions

Levodopa vs DAs

Risk of adverse event–related discontinuation of treatment

- There is insufficient evidence to determine whether, in early PD, levodopa is more or less likely than DAs (with or without levodopa) to cause medication discontinuation due to adverse effects at 1 year. (Very low confidence)
- DAs (with or without levodopa) are possibly more likely than levodopa to cause medication discontinuation due to adverse effects at 2 years. (Low confidence)
- DAs (with or without levodopa) are possibly no more likely than levodopa to cause medication discontinuation due to adverse effects at 3 years. (Low confidence)
- There is insufficient evidence to determine whether, in early PD, levodopa is more or less likely than DAs (with or without levodopa) to cause medication discontinuation due to adverse effects at 4 years. (Very low confidence)
- DAs (with or without levodopa) are probably no more likely than levodopa to cause medication discontinuation due to adverse effects at 5 years. (Moderate confidence)
- There is insufficient evidence to determine whether, in early PD, levodopa is more or less likely than DAs (with or without levodopa) to cause medication discontinuation due to adverse effects at 10 years. (Very low confidence)

Clinical Questions 1 & 2: Conclusions

Levodopa vs MAO-B Inhibitors

Risk of dyskinesia

- There is insufficient evidence to determine whether, in early PD, levodopa is more or less likely than MAO-B inhibitors to induce dyskinesia at 3 years. (Very low confidence)
- There is insufficient evidence to determine whether, in early PD, levodopa is more or less likely than MAO-B inhibitors to induce dyskinesia at 7 years. (Very low confidence)

Clinical Questions 1 & 2: Conclusions

Levodopa vs MAO-B Inhibitors

Risk of adverse event–related discontinuation of treatment

- There is insufficient evidence to determine whether, in early PD, levodopa is more or less likely than MAO-B inhibitors to cause medication discontinuation due to adverse effects at 3 years. (Very low confidence)
- There is insufficient evidence to determine whether, in early PD, levodopa is more or less likely than MAO-B inhibitors to cause medication discontinuation due to adverse effects at 7 years. (Very low confidence)

Clinical Questions 3 & 4

3. In people with early PD, what is the comparative efficacy of different formulations of DAs for motor symptoms?

4. In people with early PD, what is the comparative risk of adverse effects (specifically dyskinesia, hallucinations, and AE-related discontinuation) of different formulations of DAs?

Clinical Question 3 & 4: Conclusions

Efficacy of different formulations of DAs

Change in UPDRS part III score from baseline to endpoint

- Ropinirole is possibly no more effective than pramipexole in improving motor function at 2 years. (Low confidence)
- Pramipexole ER is probably no more effective than pramipexole IR in improving motor function at 18 weeks. (Moderate confidence)
- Pramipexole ER is probably no more effective than pramipexole IR in improving motor function at 33 weeks. (Moderate confidence)
- Pramipexole taken 3 times daily is probably no more effective than pramipexole taken twice daily in improving motor function at 12 weeks. (Moderate confidence)
- Ropinirole prolonged release (PR) is possibly no more effective than ropinirole IR in improving motor function over 36 weeks. (Low confidence)
- There is insufficient evidence to support or refute the effectiveness of ropinirole compared to bromocriptine in improving motor function at 3 years. (Very low confidence)
- Piribedil is possibly no more effective than bromocriptine in improving motor function at 1 year. (Low confidence)

Clinical Question 3 & 4: Conclusions

Risk of adverse effects for different formulations of DAs

Risk of dyskinesia

- There is insufficient evidence to determine whether, in early PD, ropinirole is more or less likely than bromocriptine to induce dyskinesia at 3 years. (Very low confidence)
- Piribedil is possibly no more likely than bromocriptine to cause dyskinesia at 1 year. (Low confidence)

Clinical Question 3 & 4: Conclusions

Risk of adverse effects for different formulations of DAs

Risk of hallucinations

- Piribedil is possibly more likely than bromocriptine to cause hallucinations at 1 year. (Low confidence)

Clinical Question 3 & 4: Conclusions

Risk of adverse effects for different formulations of DAs

Risk of adverse event–related discontinuation

- Pramipexole ER is probably no more likely than pramipexole IR to cause adverse event-related treatment discontinuation at 18 weeks. (Moderate confidence)
- Pramipexole ER is probably no more likely than pramipexole IR to cause adverse event-related treatment discontinuation at 33 weeks. (Moderate confidence)
- Pramipexole taken 3 times daily is probably no more likely than pramipexole taken twice daily to cause adverse event-related treatment discontinuation at 12 weeks. (Moderate confidence)
- There is insufficient evidence to determine whether, in early PD, ropinirole is more or less likely than bromocriptine to induce AE-related treatment discontinuation at 3 years. (Low confidence)
- Rotigotine is possibly no more likely than ropinirole to cause AE-related discontinuation of treatment at 37 weeks. (Low confidence)
- Piribedil is possibly no more likely than bromocriptine to cause AE-related discontinuation of treatment at 1 year. (Low confidence)

Clinical Questions 5 & 6

5. In people with early PD, what is the comparative efficacy of long-acting formulations of levodopa (including SR or CR formulations of levodopa and levodopa plus entacapone) vs IR levodopa for motor symptoms?

6. In people with early PD, what is the comparative risk of adverse effects (specifically dyskinesia, wearing-off, hallucinations, and adverse event-related discontinuation) of long-acting formulations of levodopa vs IR levodopa?

Clinical Questions 5 & 6: Conclusions

Efficacy of different formulations of levodopa

Change in UPDRS part III score from baseline to endpoint

- There is insufficient evidence to support or refute the effectiveness of Madopar HBS compared to Madopar in improving motor function at 5 years. (Very low confidence)
- There is insufficient evidence to support or refute the effectiveness of levodopa/carbidopa compared to levodopa/carbidopa/entacapone in improving motor function at 39 weeks. (Very low confidence)

Clinical Questions 5 & 6: Conclusions

Risk of adverse effects for different formulations of levodopa

Risk of dyskinesia

- There is insufficient evidence to determine whether, in early PD, Madopar HBS is more or less likely than Madopar to induce dyskinesia at 5 years. (Very low confidence)
- There is insufficient evidence to determine whether, in early PD, levodopa IR is more or less likely than levodopa CR to induce dyskinesia at 5 years. (Very low confidence)
- Levodopa/carbidopa is probably no more likely than levodopa/carbidopa/entacapone to cause dyskinesia at 12 weeks. (Moderate confidence)
- There is insufficient evidence to determine whether, in early PD, levodopa/carbidopa is more or less likely than levodopa/carbidopa/entacapone to induce dyskinesia at 39 weeks. (Very low confidence)
- Levodopa/carbidopa/entacapone is possibly no more likely than levodopa/carbidopa to induce dyskinesia at 2.5 years. (Low confidence)

Clinical Questions 5 & 6: Conclusions

Risk of adverse effects for different formulations of levodopa

Risk of hallucinations

- There is insufficient evidence to determine whether, in early PD, levodopa IR is more or less likely than levodopa CR to induce hallucinations at 5 years. (Very low confidence)

Clinical Questions 5 & 6: Conclusions

Risk of adverse effects for different formulations of levodopa

Risk of adverse event-related discontinuation

- There is insufficient evidence to determine whether, in early PD, Madopar HBS is more or less likely than Madopar to cause adverse event-related treatment discontinuation at 5 years. (Very low confidence)
- Levodopa/carbidopa is probably no more likely than levodopa/carbidopa/entacapone to cause adverse event-related treatment discontinuation at 12 weeks. (Moderate confidence)
- There is insufficient evidence to determine whether, in early PD, levodopa/carbidopa is more or less likely than levodopa/carbidopa/entacapone to cause adverse event-related treatment discontinuation at 39 weeks. (Very low confidence)
- Levodopa/carbidopa/entacapone is possibly no more likely than levodopa/carbidopa to cause adverse event-related treatment discontinuation at 2.5 years. (Low confidence)

Clinical Question 7

7. In people with early PD, what is the risk of ICDs with medications used for the treatment of motor symptoms, and does the risk differ between drug formulations?

Clinical Question 7: Conclusions

Risk of ICDs with different formulations of dopaminergic medications

- DAs are probably more likely than levodopa to cause ICDs at 2 years. (Moderate confidence)
- Combination treatment with levodopa and DAs is possibly more likely than levodopa alone to cause ICDs at 2 years. (Low confidence)
- DAs are possibly more likely than levodopa to cause ICDs at 5 years. (Low confidence)
- Combination treatment with levodopa and DAs is possibly more likely than levodopa alone to cause ICDs at 5 years. (Low confidence)

Clinical Question 8

8. In people with early PD initially treated with DAs vs levodopa, what is the long-term risk of disabling dyskinesia?

Clinical Question 8: Conclusions

Long-term risk of disabling dyskinesia with DAs vs levodopa

- Levodopa is possibly more likely than ropinirole to cause disabling dyskinesia at 5 years. (Low confidence)
- There is insufficient evidence to determine whether levodopa is more or less likely than pramipexole to cause disabling dyskinesia at 6 years. (Very low confidence)
- There is insufficient evidence to determine whether levodopa is more or less likely than ropinirole to cause disabling dyskinesia at 10 years. (Very low confidence)

Practice Recommendations

Recommendation 1

Rationale

Clinical trials have failed to provide evidence of disease modification when the initial therapy prescribed is levodopa,[63] a DA,[64] or an MAO-B inhibitor.[65] Studies comparing treatment with levodopa to treatment with MAO-B inhibitors early in the disease course provide Class IV evidence. These studies demonstrate greater mobility with levodopa than with MAO-B inhibitors, a higher risk of AE-related discontinuation with MAO-B inhibitors, and that more than 60% of individuals randomized to MAO-B inhibitors will require additional therapy within 2 to 3 years.

Practice Recommendations

Recommendation 1

Rationale (continued)

Initial treatment of early PD with levodopa provides greater benefit for motor symptoms than initial treatment with DAs, as shown in the majority of studies that demonstrate greater improvement in the UPDRS part III score for the first 5 years of follow-up. Initial treatment with levodopa is more likely to induce dyskinesia than initial treatment with DAs for up to 5 years of follow-up, but the prevalence of severe or disabling dyskinesia during this five-year period is low. While initial treatment with DAs is possibly more likely to cause hallucinations than treatment with levodopa, the difference between treatments for this outcome is small for the first 5 years of treatment. Treatment with DAs in early PD is associated with a higher risk of ICDs.

Practice Recommendations

Recommendation 1

Rationale (continued)

Patient and disease characteristics influence the risk of adverse effects related to the use of levodopa and DAs and may affect initial treatment choices. Younger age of disease onset,[66] lower body weight,[25, 67] female sex,[49] and increased disease severity[68-70] are all predisposing factors for the development of levodopa-induced dyskinesia. Predisposing patient characteristics for ICDs are male sex, younger age, history of ICDs, history of mood disorders (particularly depression), the presence of apathy, and a family history of ICDs and addiction.[50, 54, 55, 71] Older patients are at greater risk for cognitive and behavioral adverse effects of DAs.[72] DAs are associated with a greater risk of excessive daytime somnolence and sleep attacks; therefore, patients whose employment requires driving or operating heavy machinery may face greater impairment from these adverse effects.[73]

Practice Recommendations

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Recommendation Statements 1a and 1b:

- **Recommendation 1a.** Clinicians should counsel patients with early PD on the benefits and risks of initial therapy with levodopa, DAs, and MAO-B inhibitors based on the individual patient's disease characteristics to inform treatment decisions (Level B).
- **Recommendation 1b.** In patients with early PD who seek treatment for motor symptoms, clinicians should recommend levodopa as the initial preferential dopaminergic therapy (Level B).

Practice Recommendations

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Recommendation Statements 1c and 1d:

- **Recommendation 1c.** Clinicians may prescribe DAs as the initial dopaminergic therapy to improve motor symptoms in select early PD in patients <60 years who are at higher risk for the development of dyskinesia (Level C).
- **Recommendation 1d.** Clinicians should not prescribe DAs to patients with early-stage PD at higher risk of medication-related adverse effects, including individuals >70 years-of-age, patients with a history of ICDs, and patients with pre-existing cognitive impairment, excessive daytime sleepiness, or hallucinations (Level B).

Practice Recommendations

Recommendation 2

Rationale

The evidence comparing IR levodopa to CR levodopa or levodopa/carbidopa/entacapone is either of very low confidence or did not detect differences between formulations for improvement in motor symptoms, dyskinesia, hallucinations, or AE-related discontinuation in early PD. There are no studies comparing IR levodopa to ER carbidopa/levodopa in early PD.

Practice Recommendations

Recommendation 2

Rationale (continued)

While there is no evidence to support superiority of one formulation of levodopa over another, there are other reasons to favor initiation of treatment with IR levodopa. CR levodopa has lower bioavailability and less predictable symptom relief compared to IR levodopa,[74, 75] which may necessitate treatment discontinuation in later stages of the disease due to dose failures. While levodopa/carbidopa/entacapone can be helpful for patients who experience end-of-dose wearing-off,[76] this is not a usual clinical feature in early PD. IR levodopa is less costly than other levodopa formulations. Clinical trials in early PD demonstrate symptomatic benefit with LC at dosages of 150-300 mg/d, and a lower risk of dyskinesia with dosages less than 400 mg/d. While the risk is higher with DAs, levodopa may cause ICDs, hallucinations, and excessive daytime sleepiness.[73] Levodopa may exacerbate postural hypotension.

Practice Recommendations

Recommendation 2

Rationale (continued)

Nausea is a common early and dose-dependent adverse effect of levodopa.[77] Taking levodopa with meals affects the absorption of levodopa in the gut by slowing gastric emptying; dietary protein intake and resulting concentrations of large neutral amino acids may decrease entry of levodopa into the brain.[78] In early PD, taking levodopa with meals may decrease nausea and improve compliance with therapy. In later disease stages, taking levodopa with meals may decrease therapeutic efficacy.

Practice Recommendations

Recommendation Statement 2:

- **Recommendation 2a.** Clinicians should initially prescribe IR levodopa rather than CR levodopa or levodopa/carbidopa/entacapone in patients with early PD (Level B).
- **Recommendation 2b.** In patients with early PD, clinicians should prescribe the lowest effective dose of levodopa (i.e., the lowest dose that provides adequate symptomatic benefit) to minimize the risk of dyskinesia and other adverse effects (Level B).
- **Recommendation 2c.** Clinicians should routinely monitor patients taking levodopa for their motor response to treatment, and for the presence of dyskinesia, motor fluctuations, ICDs, excessive daytime sleepiness, postural hypotension, nausea, and hallucinations, to guide dosage titration over time (Level B).

Practice Recommendations

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Recommendation Statement 2:

- **Recommendation 2d.** Clinicians should counsel patients taking levodopa that higher dosages are more likely to cause dyskinesia (Level B).
- **Recommendation 2e.** Clinicians should counsel patients that in later disease stages, taking levodopa with meals may affect levodopa absorption and efficacy, but this is usually not problematic at the time of levodopa initiation in early PD (Level B).

Practice Recommendations

Recommendation 3

Rationale

Before prescribing a medication, it is important to inform patients and caregivers of medication-associated adverse effects, and to screen for pre-existing conditions, personality traits, concurrent medication use, and other relevant exposures that are associated with increased risk of medication-related adverse effects. DAs (vs levodopa) are associated with an increased risk of ICDs, excessive daytime sleepiness, sudden-onset sleep, nausea, and hallucinations in patients with early PD.[73] DAs may exacerbate postural hypotension.

Practice Recommendations
Recommendation 3

Rationale (continued)

Patients may not always report certain non-motor symptoms associated with PD or its treatment due to lack of awareness, embarrassment, or other concerns.[79] Systematic and specific interrogation by practitioners concerning impulsive behaviors, sleep-related behaviors, and perceptual disturbances may set expectations and normalize reporting of embarrassing behaviors, leading to improved recognition of problematic adverse effects associated with DA use.

Practice Recommendations

Recommendation 3 Statements:

- **Recommendation 3a.** Clinicians should inform the patient and caregiver (when present) of important side effects of DAs before prescribing; this discussion should specifically include ICDs, excessive daytime sleepiness, sudden-onset sleep, nausea, postural hypotension, and hallucinations (Level B).
- **Recommendation 3b.** Clinicians should screen patients for cognitive impairment, excessive daytime sleepiness, sudden-onset sleep, hallucinations, orthostatic hypotension, and the presence of risk factors for ICDs before prescribing a DA (Level B).

Practice Recommendations

Recommendation 3 Statements:

- **Recommendation 3c.** Clinicians should screen patients for the presence of adverse effects related to DAs, including ICDs, excessive daytime sleepiness, sudden-onset sleep, orthostatic hypotension, cognitive impairment, and hallucinations repeatedly in follow-up of patients prescribed DAs (Level B).
- **Recommendation 3d.** Clinicians should involve caregivers in assessments for ICDs, excessive daytime sleepiness, sudden-onset sleep, orthostatic hypotension, cognitive impairment, and hallucinations in patients with PD (Level B).

Practice Recommendations

Recommendation 3e

Rationale

Standardized measures may be used to systematically screen patients for risk factors for adverse effects associated with medication use or disease progression; questionnaires can be especially useful when screening for or grading the severity of complex adverse effects that exist along a spectrum, such as ICDs and excessive daytime sleepiness. “Positive” scores on standard questionnaires should trigger the clinician to further explore the symptom through a focused clinical interview to determine the range and severity of symptoms, as well as need for clinical management. Effective management may necessitate tapering or discontinuation of DAs to mitigate morbidity associated with medication-related adverse effects.

Practice Recommendations

Recommendation 3e

Rationale (continued)

The Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP) is a validated self-assessment screening instrument for a range of ICDs and other compulsive behaviors that occur in patients with PD, including gambling, sexual behaviors, buying, eating behaviors, punding, hobbyism, walkabout, and compulsive medication use. Patients with higher QUIP scores are at higher risk of ICDs.[80]

Practice Recommendations

Recommendation 3e

Rationale (continued)

The Epworth Sleepiness Scale (ESS) is a self-report questionnaire consisting of eight questions and responses on a four-point Likert scale. Patients rate their usual chances of dozing off or falling asleep as they engage in different activities. The ESS score is the sum of the eight-item scores ranging from 0 to 24, where a higher score represents greater sleepiness. ESS scores above 10 are considered to represent "excessive daytime sleepiness."[81]

The QUIP and ESS are patient-completed scales with an administration time of less than 10 minutes. Both rating scales are publicly available for clinical use.

Practice Recommendations

Recommendation 3 Statements:

- **Recommendation 3e.** Clinicians may screen patients for the presence of adverse effects associated with DAs using questionnaires validated for this purpose, including the QUIP for ICDs, and the ESS for the assessment of impaired wakefulness (Level C).

Practice Recommendations
Recommendation 4

Rationale

Multiple DA medications and formulations (e.g., short-acting, long-acting, oral, and transdermal) are approved for the treatment of patients with early PD. This systematic review did not uncover strong evidence supporting the use of ropinirole vs pramipexole for the treatment of early PD. Further, there was no compelling evidence that pramipexole ER vs pramipexole IR was associated with a more favorable UPDRS score or a different rate of adverse event-related treatment discontinuation at 18 weeks. There are preliminary observational data that long-acting and transdermal formulations of DAs have lower rates of ICDs than short-acting formulations.[82] In the absence of compelling evidence concerning safety or efficacy, the selection of a medication and formulation should take into account patient preferences with the goal of optimizing compliance with treatment recommendations. Specific to DAs, relative patient preferences may include the frequency (once daily, twice daily, or three times daily) and mode (oral vs transdermal) of administration as well as the cost.

Practice Recommendations

Recommendation 4

Rationale (continued)

Regardless of the formulation, the practice of prescribing a DA has been to start at the lowest possible dosage and increase slowly until the desired effect or adverse effect occurs. Clinicians may opt to increase dosages gradually, stopping at the lowest dosage that is recognized to have clinical efficacy (6–9 mg/d of ropinirole, 1.5 mg/d of pramipexole, or 4 mg/24hrs of rotigotine).[83]

Practice Recommendations

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Recommendation 4 Statements:

- **Recommendation 4a.** Clinicians should integrate patient preferences concerning formulation, mode of administration, and cost when prescribing a DA (Level B).
- **Recommendation 4b.** Clinicians should prescribe the lowest dose of DA required to provide therapeutic benefit (Level B).

Practice Recommendations

Recommendation 5

Rationale

Adverse effects associated with DAs can lead to substantial impairments in psychosocial functioning, interpersonal relationships, and quality of life for the patient and caregivers. The consequences of medication-related adverse effects may be mitigated through adjustments to prescribed medications, including DAs, or through additional behavioral or pharmacological interventions, if appropriate.

Practice Recommendations
Recommendation 5

Rationale (continued)

Patients may experience undesirable side effects when attempting to decrease dopaminergic medications, especially DAs, including dopamine withdrawal syndrome (DAWS) or low mood and apathy.[84] One Class IV study incorporated in this systematic review suggested that treatment withdrawal may be more common in patients taking DAs than in those taking levodopa.[20] These side effects can make it difficult to taper or discontinue DAs. Staged reduction in dosing may reduce the severity of withdrawal symptoms and improve compliance with medication recommendations.

Practice Recommendations

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Recommendation 5 Statements:

- **Recommendation 5a.** Clinicians should recommend tapering or discontinuation of DAs if patients experience disabling medication-related adverse effects, including ICDs, excessive day-time sleepiness, sudden-onset sleep, cognitive impairment, or hallucinations (Level B).
- **Recommendation 5b.** When DAs must be discontinued due to adverse effects, clinicians should monitor patients for symptoms of dopamine withdrawal syndrome and when possible, gradually decrease the dosage to minimize symptoms (Level B).

Practice Recommendations

Recommendation 6

Rationale

Initial treatment of early PD with levodopa provides greater benefit for mobility than initial treatment with MAO-B inhibitors. Initial treatment with levodopa is more likely to induce dyskinesia than initial treatment with MAO-B inhibitors for up to the first 5 years of follow-up. Most patients on monotherapy with a MAO-B inhibitor will require additional therapy within 2 to 3 years compared to those being treated with levodopa or DAs. Treatment of early PD with MAO-B inhibitors is associated with a higher risk of AE-related discontinuation compared with treatment with levodopa.

Practice Recommendations
Recommendation 6

Rationale (continued)

There are no studies comparing the efficacy of the 2 MAO-B inhibitors, selegiline and rasagiline, in the treatment of early PD. Studies of monotherapy with selegiline and rasagiline have demonstrated superiority to placebo for treatment of motor symptoms in people with early PD.[85, 86] Prescribing information for selegiline and rasagiline caution against their use with selective serotonin reuptake inhibitors (SSRIs); however, serotonin syndrome is rarely reported in patients with PD on concomitant therapy with an MAO-B inhibitor and an SSRI.[87-89]

Practice Recommendations

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Recommendation 6 Statements:

- **Recommendation 6a.** Clinicians should counsel patients with early PD on the greater motor benefits of initial therapy with levodopa compared with MAO-B inhibitors to inform treatment decisions (Level B).
- **Recommendation 6b.** Clinicians may prescribe MAO-B inhibitors as the initial dopaminergic therapy for mild motor symptoms in patients with early PD (Level C).

Suggestions for Future Research

Future research will hopefully establish effective disease-modifying therapy that would be initiated as soon as the diagnosis is made and possibly initiated in patients with probable prodromal PD before motor features are evident. The role of nonpharmacological therapy, such as exercise and physiotherapy, in patients not receiving pharmacotherapy needs to be established using carefully controlled research designs. Further studies are required to address the question of whether patient quality of life is significantly improved with the earlier initiation of symptomatic treatment rather than following a "wait and watch" strategy. Future research is needed to determine whether genetic status should influence decisions on how to initiate therapy. Personalized medicine approaches must be considered in future research studies, with the goal of moving away from a "one-size-fits-all" therapeutic approach to initiating treatment for motor symptoms in early PD. For example, further work is required to advance initial pharmacogenomic studies that have suggested patient-specific differences in response to some anti-Parkinson drugs, such as rasagiline and entacapone.

Suggestions for Future Research (cont.)

Similarly, further research is required to establish definitive genetic predispositions to important treatment complications such as the risk of developing ICDs with DAs or a greater risk of earlier severe dyskinesia with levodopa. This would then guide the use of these agents in early treatment. This might also permit further, more definitive research studies on the relative risk of levodopa vs DAs in inducing the pathogenetic mechanisms that underlie dyskinesia. Finally, a high priority of future research efforts should be to determine whether newer, more effective methods of providing stable levodopa plasma levels initiated soon after diagnosis will delay the onset of dyskinesia. These could include the use of newer ER levodopa formulations, alternative modes of levodopa administration (e.g., transdermal) or longer-acting COMT inhibitors.

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Questions?