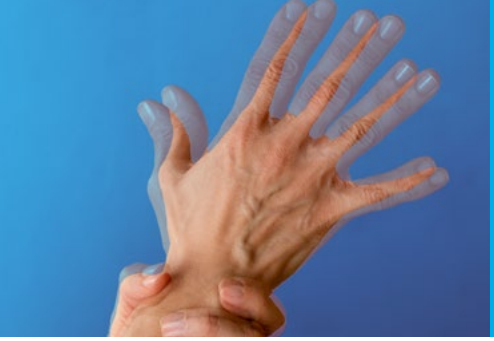

AAN Summary of Practice Guideline for **Clinicians**

Dopaminergic Therapy for Motor Symptoms in Early Parkinson Disease Practice Guideline

This is a summary of the American Academy of Neurology (AAN) guideline, "Dopaminergic Therapy for Motor Symptoms in Early Parkinson Disease Practice Guideline," which was published in *Neurology*® online on November 15, 2021, and appears in the November 16, 2021, print issue.

Please refer to the full guideline at AAN.com/guidelines for the full systematic review of the evidence as well as descriptions of the processes for classifying evidence, deriving conclusions, and making recommendations.

Levodopa vs Dopamine Agonists vs Monoamine Oxidase Type B (MAO-B) Inhibitors

Recommendation 1

Level	Recommendation
Level B	Clinicians should counsel patients with early PD on the benefits and risks of initial therapy with levodopa, dopamine agonists, and MAO-B inhibitors based on the individual patient's disease characteristics to inform treatment decisions.
Level C	Clinicians may prescribe dopamine agonists 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 B	Clinicians should not prescribe dopamine agonists 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.

Rationale

Clinical trials have failed to provide evidence of disease modification when the initial therapy prescribed is levodopa,[1] a dopamine agonist,[2] or an MAO-B inhibitor.[3] Studies comparing treatment with levodopa to treatment with MAO-B inhibitors early in the disease course provide Class IV evidence. These studies demonstrate greater improvement in mobility with levodopa than with MAO-B inhibitors, a higher risk of adverse event-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.

Initial treatment of early Parkinson disease (PD) with levodopa provides greater benefit for motor symptoms than initial treatment with dopamine agonists, as shown in the majority of studies that demonstrate greater improvement in the Unified Parkinson's Disease Rating Scale (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 dopamine agonists for up to 5 years of follow-up, but the prevalence of severe or disabling dyskinesia during this 5-year period is low. While initial treatment with dopamine agonists 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 dopamine agonists in early PD is associated with a higher risk of impulse control disorders (ICDs).

Patient and disease characteristics influence the risk of adverse effects related to the use of levodopa and dopamine agonists and may affect initial treatment choices. Younger age of disease onset,[4] lower body weight,[5, 6] female sex,[7] and increased disease severity[8-10] 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.[11-14] Older patients are at greater risk for cognitive and behavioral adverse effects of dopamine agonists.[15] Dopamine agonists 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.[16]

Prescribing Levodopa

Recommendation 2

Rationale

The evidence comparing immediate-release (IR) levodopa to controlled-release (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 adverse event-related discontinuation in early PD. There are no studies comparing IR levodopa to extended-release (ER) carbidopa/levodopa in early PD.

While there is no evidence to support superiority of one formulation of levodopa over another, there are other reasons to favor initiating treatment with IR levodopa. CR levodopa has lower bioavailability and less predictable symptom relief compared to IR levodopa,[17, 18] 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,[19] 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 levodopa/carbidopa 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.[16] Levodopa may exacerbate postural hypotension.

Nausea is a common early and dose-dependent adverse effect of levodopa.[20] 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.[21] 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.

Level	Recommendation
Level B	Clinicians should initially prescribe IR levodopa rather than CR levodopa or levodopa/carbidopa/entacapone in patients with early PD.
Level B	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	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	Clinicians should counsel patients taking levodopa that higher dosages are more likely to cause dyskinesia.
Level B	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.

Prescribing Dopamine Agonists

Recommendation 3a–d

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. Dopamine agonists (vs levodopa) are associated with an increased risk of ICDs, excessive daytime sleepiness, sudden-onset sleep, nausea, and hallucinations in patients with early PD.[16] Dopamine agonists may exacerbate postural hypotension.

Patients may not always report certain non-motor symptoms associated with PD or its treatment due to lack of awareness, embarrassment, or other concerns.[22] 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 dopamine agonist use.

Level	Recommendation
Level B	Clinicians should inform the patient and caregiver (when present) of important side effects of dopamine agonists before prescribing; this discussion should specifically include ICDs, excessive daytime sleepiness, sudden-onset sleep, nausea, postural hypotension, and hallucinations.
Level B	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 dopamine agonist.
Level B	Clinicians should screen patients for the presence of adverse effects related to dopamine agonists, including ICDs, excessive daytime sleepiness, sudden-onset sleep, orthostatic hypotension, cognitive impairment, and hallucinations repeatedly in follow-up of patients prescribed dopamine agonists.
Level B	Clinicians should involve caregivers in assessments for ICDs, excessive daytime sleepiness, sudden-onset sleep, orthostatic hypotension, cognitive impairment, and hallucinations in patients with PD.

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 dopamine agonists to mitigate morbidity associated with medication-related adverse effects.

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 impulsive-compulsive behaviors.[23]

The Epworth Sleepiness Scale (ESS) is a self-report questionnaire consisting of 8 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."[24]

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

Level	Recommendation
Level C	Clinicians may screen patients for the presence of adverse effects associated with dopamine agonists using questionnaires validated for this purpose, including the QUIP for ICDs, and the ESS for the assessment of impaired wakefulness.

Recommendation 4

Rationale

Multiple dopamine agonist 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 dopamine agonists have lower rates of ICDs than short-acting formulations.[25] 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 dopamine agonists, relevant patient preferences may include the cost and the frequency (once daily, twice daily, or three times daily) and mode (oral vs transdermal) of administration.

Regardless of the formulation, the practice of prescribing a dopamine agonist 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).[26]

Level	Recommendation
Level B	Clinicians should integrate patient preferences concerning formulation, mode of administration, and cost when prescribing a dopamine agonist.
Level B	Clinicians should prescribe the lowest dose of dopamine agonist required to provide therapeutic benefit.

Tapering and Discontinuing Dopamine Agonists

Recommendation 5

Rationale

Adverse effects associated with dopamine agonists 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 dopamine agonists, or through additional behavioral or pharmacological interventions, if appropriate.

Patients may experience undesirable side effects when attempting to decrease dopaminergic medications, especially dopamine agonists, including dopamine agonist withdrawal syndrome (DAWS) or low mood and apathy.[27] These side effects can make it difficult to taper or discontinue dopamine agonists. Staged reduction in dosing may reduce the severity of withdrawal symptoms and improve compliance with medication recommendations.

Level	Recommendation
Level B	Clinicians should recommend tapering or discontinuation of dopamine agonists if patients experience disabling medication-related adverse effects, including ICDs, excessive daytime sleepiness, sudden-onset sleep, cognitive impairment, or hallucinations.
Level B	When dopamine agonists must be discontinued due to adverse effects, clinicians should monitor patients for symptoms of DAWS and, when possible, gradually decrease the dosage to minimize symptoms.

Prescribing MAO-B Inhibitors

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 may be more likely to induce dyskinesia than initial treatment with MAO-B inhibitors. 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 dopamine agonists. Treatment of early PD with MAO-B inhibitors is associated with a higher risk of adverse event-related discontinuation compared with treatment with levodopa.

There are no studies comparing the efficacy of 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.[28, 29] 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.[30-32]

Level	Recommendation
Level B	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).
Level C	Clinicians may prescribe MAO-B inhibitors as the initial dopaminergic therapy for mild motor symptoms in patients with early PD (Level C).

This practice guideline was endorsed by the Parkinson's Foundation on July 30, 2021.

References

1. Verschuur CVM, Suwijn SR, Boel JA, et al. Randomized Delayed-Start Trial of Levodopa in Parkinson's Disease. *N Engl J Med* 2019;380:315-324.
2. Schapira AH, McDermott MP, Barone P, et al. Pramipexole in patients with early Parkinson's disease (PROUD): a randomised delayed-start trial. *Lancet neurol* 2013;12:747-755.
3. Olanow CW, Rascol O, Hauser R, et al. A double-blind, delayed-start trial of rasagiline in Parkinson's disease. [Erratum appears in *N Engl J Med*. 2011 May 12;364(19):1882]. *New England Journal of Medicine* 2009;361:1268-1278.
4. Warren Olanow C, Kieburtz K, Rascol O, et al. Factors predictive of the development of Levodopa-induced dyskinesia and wearing-off in Parkinson's disease. Mov Disord 2013;28:1064-1071.
5. Sharma JC, Ross IN, Rascol O, Brooks D. Relationship between weight, levodopa and dyskinesia: the significance of levodopa dose per kilogram body weight. *Eur J Neurol* 2008;15:493-496.
6. Rascol O, Brooks DJ, Korczyn AD, De Deyn PP, Clarke CE, Lang AE. A five-year study of the incidence of dyskinesia in patients with early Parkinson's disease who were treated with ropinirole or levodopa. *New England Journal of Medicine* 2000;342:1484-1491.
7. Olanow WC, Kieburtz K, Rascol O, et al. Factors predictive of the development of Levodopa-induced dyskinesia and wearing-off in Parkinson's disease. *Movement Disorders* 2013;28:1064-1071.
8. Cilia R, Akpalu A, Sarfo FS, et al. The modern pre-levodopa era of Parkinson's disease: insights into motor complications from sub-Saharan Africa. *Brain* 2014;137:2731-2742.
9. Nadjar A, Gerfen CR, Bezard E. Priming for l-dopa-induced dyskinesia in Parkinson's disease: a feature inherent to the treatment or the disease? *Prog Neurobiol* 2009;87:1-9.
10. Hauser RA, McDermott MP, Messing S. Factors associated with the development of motor fluctuations and dyskinesias in Parkinson disease. *Arch Neurol* 2006;63:1756-1760.
11. Marin-Lahoz J, Sampedro F, Martinez-Horta S, Pagonabarraga J, Kulisevsky J. Depression as a Risk Factor for Impulse Control Disorders in Parkinson Disease. *Ann Neurol* 2019;86:762-769.
12. Smith KM, Xie SX, Weintraub D. Incident impulse control disorder symptoms and dopamine transporter imaging in Parkinson disease. *J Neurol Neurosurg Psychiatry* 2016;87:864-870.
13. Gatto EM, Aldinio V. Impulse Control Disorders in Parkinson's Disease. A Brief and Comprehensive Review. *Front Neurol* 2019;10:351.
14. Antonini A, Barone P, Bonuccelli U, Annoni K, Asgharnejad M, Stanzione P. ICARUS study: Prevalence and clinical features of impulse control disorders in Parkinson's disease. *Journal of Neurology, Neurosurgery and Psychiatry* 2017;88:317-324.
15. Latt MD, Lewis S, Zekry O, Fung VSC. Factors to Consider in the Selection of Dopamine Agonists for Older Persons with Parkinson's Disease. *Drugs Aging* 2019;36:189-202.
16. Yeung EYH, Cavanna AE. Sleep Attacks in Patients With Parkinson's Disease on Dopaminergic Medications: A Systematic Review. *Mov Disord Clin Pract* 2014;1:307-316.
17. Hsu A, Yao HM, Gupta S, Modi NB. Comparison of the pharmacokinetics of an oral extended-release capsule formulation of carbidopa-levodopa (IPX066) with immediate-release carbidopa-levodopa (Sinemet®), sustained-release carbidopa-levodopa (Sinemet® CR), and carbidopa-levodopa-entacapone (Stalevo®). *J Clin Pharmacol* 2015;55:995-1003.
18. Dhall R, Kreitzman DL. Advances in levodopa therapy for Parkinson disease: Review of RYTARY (carbidopa and levodopa) clinical efficacy and safety. *Neurology* 2016;86:S13-24.
19. Ruottinen HM, Rinne UK. Entacapone prolongs levodopa response in a one month double blind study in parkinsonian patients with levodopa related fluctuations. *J Neurol Neurosurg Psychiatry* 1996;60:36-40.

20. Fahn S, Oakes D, Shoulson I, et al. Levodopa and the progression of Parkinson's disease. *N Engl J Med* 2004;351:2498-2508.

21. Wang L, Xiong N, Huang J, et al. Protein-Restricted Diets for Ameliorating Motor Fluctuations in Parkinson's Disease. *Front Aging Neurosci* 2017;9:206.

22. Hurt CS, Rixon L, Chaudhuri KR, Moss-Morris R, Samuel M, Brown RG. Barriers to reporting non-motor symptoms to health-care providers in people with Parkinson's. *Parkinsonism Relat Disord* 2019;64:220-225.

23. Weintraub D, Mamikonyan E, Papay K, Shea JA, Xie SX, Siderowf A. Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale. *Mov Disord* 2012;27:242-247.

24. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 1991;14:540-545.

25. Rizos A, Sauerbier A, Antonini A, et al. A European multicentre survey of impulse control behaviours in Parkinson's disease patients treated with short- and long-acting dopamine agonists. *Eur J Neurol* 2016;23:1255-1261.

26. Choi J, Horner KA. Dopamine Agonists. Treasure Island Florida: *StatPearls Publishing*, 2020.

27. Okai D, Samuel M, Askey-Jones S, David AS, Brown RG. Impulse control disorders and dopamine dysregulation in Parkinson's disease: a broader conceptual framework. *Eur J Neurol* 2011;18:1379-1383.

28. Parkinson Study G. A controlled trial of rasagiline in early Parkinson disease: the TEMPO Study. *Arch Neurol* 2002;59:1937-1943.

29. Parkinson Study Group. Effects of tocopherol and deprenyl on the progression of disability in early Parkinson's disease. *N Engl J Med* 1993;328:176-183.

30. Hilli J, Korhonen T, Laine K. Lack of clinically significant interactions between concomitantly administered rasagiline and escitalopram. *Prog Neuropsychopharmacol Biol Psychiatry* 2009;33:1526-1532.

31. Panisset M, Chen JJ, Rhyee SH, Conner J, Mathena J, investigators Ss. Serotonin toxicity association with concomitant antidepressants and rasagiline treatment: retrospective study (STACCATO). *Pharmacotherapy* 2014;34:1250-1258.

32. Richard IH, Kurlan R, Tanner C, et al. Serotonin syndrome and the combined use of deprenyl and an antidepressant in Parkinson's disease. Parkinson Study Group. *Neurology* 1997;48:1070-1077.

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