Dopaminergic Therapy for Motor Symptoms in Early Parkinson Disease Practice Guideline Summary

A Report of the AAN Guideline Subcommittee

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Abstract

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

Methods
A multidisciplinary panel developed practice recommendations, integrating findings from a systematic review and following an Institute of Medicine–compliant process to ensure transparency and patient engagement. Recommendations were supported by structured rationales, integrating evidence from the systematic review, related evidence, principles of care, and inferences from evidence.

Results
Initial treatment with levodopa provides superior motor benefit compared to treatment with dopamine agonists, whereas levodopa is more likely than dopamine agonists to cause dyskinesia. The comparison of different formulations of dopamine agonists yielded little evidence that any one formulation or method of administration is superior. Long-acting forms of levodopa and levodopa with entacapone do not appear to differ in efficacy from immediate-release levodopa for motor symptoms in early disease. There is a higher risk of impulse control disorders associated with the use of dopamine agonists than levodopa. Recommendations on initial therapy for motor symptoms are provided to assist the clinician and patient in choosing between treatment options and to guide counseling, prescribing, and monitoring of efficacy and safety.

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Glossary

AAN = American Academy of Neurology; **AE** = adverse event; **CI** = confidence interval; **COI** = conflict of interest; **COMT** = catechol-O-methyltransferase; **CR** = controlled-release; **DA** = dopamine agonist; **DAWS** = dopamine agonist withdrawal syndrome; **EDS** = excessive daytime sleepiness; **ER** = extended-release; **ESS** = Epworth Sleepiness Scale; **GS** = Guideline Subcommittee; **ICD** = impulse control disorder; **IR** = immediate-release; **MAO-B** = monoamine oxidase type B; **MCID** = minimal clinically important difference; **PD** = Parkinson disease; **QUIP** = Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease; **RD** = risk difference; **RMD** = raw mean difference; **SSRI** = selective serotonin reuptake inhibitor; **UPDRS** = Unified Parkinson's Disease Rating Scale.

Parkinson disease (PD) is a neurodegenerative disorder that causes both motor and nonmotor symptoms and increases in prevalence with age. Motor symptoms in the early stages of PD include tremor, rigidity, and bradykinesia, with gait and balance impairment becoming more prominent with disease progression. The treatment options for the alleviation of motor symptoms in the early stages of PD are based on the enhancement of dopaminergic tone with levodopa, monoamine oxidase inhibitors, dopamine agonists (DAs), or a combination thereof. The choice of initial treatment is influenced by the potential for neuropsychiatric adverse effects associated with DAs and dyskinesia and motor fluctuations associated with levodopa. In 2002, the American Academy of Neurology (AAN) published the "Initiation of Treatment for Parkinson Disease" practice guideline,[1] 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. This article is a summary of the key findings of the practice guideline update. The complete practice guideline update, including the full systematic review, is available at aan.com/Guidelines/home/GetGuidelineContent/1048.

Description of the Analytic Process

In August 2017, the AAN Guideline Subcommittee (GS) recruited a multidisciplinary panel of authors to develop this guideline. The panel included content and methodology experts, patient representatives, and a staff representative from the Michael J. Fox Foundation for Parkinson's Research. As required by the AAN, a majority of the members (T.P., R.M.A.d.B., D.A.H., G.S.D., N.L., K.S., L.B., E.R., M.S.F., L.H., M.J.A., J.A.G., M.R., N.C., A.R.-G., T.H.) of the panel and the lead author (T.P.) are free of conflicts of interest (COIs) relevant to this practice guideline. Five of the guideline developers were determined to have COI, but the COI were judged to be not significant enough to preclude them from authorship (A.J.E., J.M.M., A.E.L., R.A.H., J.P.M.). Whereas the development of this guideline primarily followed the 2017 edition of the AAN's *Clinical Practice Guideline Process Manual*,[2] this edition of the manual was not published by the time of the guideline initiation. Therefore, disclosures were reviewed following the previous process found in the 2011 *Clinical Practice Guideline Process Manual*.[3] The full author panel was solely responsible for the final decisions about the design, analysis, and reporting of the systematic review and practice guideline, which was submitted for approval to the AAN GS.

Study Screening and Selection Criteria

Types of Participants
We included studies of participants with PD in the early stages (i.e., Hoehn & Yahr stages 1 or 2, or within 2 years of disease onset).

Types of Interventions
We included studies of DAs, levodopa, monoamine oxidase type B (MAO-B) inhibitors, and catechol-O-methyltransferase (COMT) inhibitors to treat motor symptoms of PD in the early stages of the disease.

Comparison Group
We included studies using active comparators only.

Types of Studies
For clinical questions 1 through 6, we included only randomized controlled trials. For clinical questions 7 and 8, we included randomized controlled trials, population-based epidemiologic studies, and prospective cohort studies.

Types of Outcome Measures
The preferred outcome measure was the Unified Parkinson's Disease Rating Scale (UPDRS) part III, which measures motor symptoms. To determine the change in motor symptoms, the authors calculated the raw mean difference (RMD) between scores on the UPDRS part III at baseline and at follow-up. To determine the change in dyskinesia, hallucinations, adverse event (AE)–related discontinuation, and impulse control disorders (ICDs), the risk differences (RDs) were calculated.

The author panel searched the Medline, Cochrane Central Register of Controlled Trials (CENTRAL), and ClinicalTrials.gov databases from database inception through June 2020 for relevant peer-reviewed articles that met the inclusion criteria. After review of abstracts, 255 articles were identified as potentially relevant and each article was reviewed by 2 independent panel members. The panelists selected 59 articles for inclusion in the analysis.

Figure 1 Levodopa vs Dopamine Agonist: Change in Unified Parkinson's Disease Rating Scale Motor Score
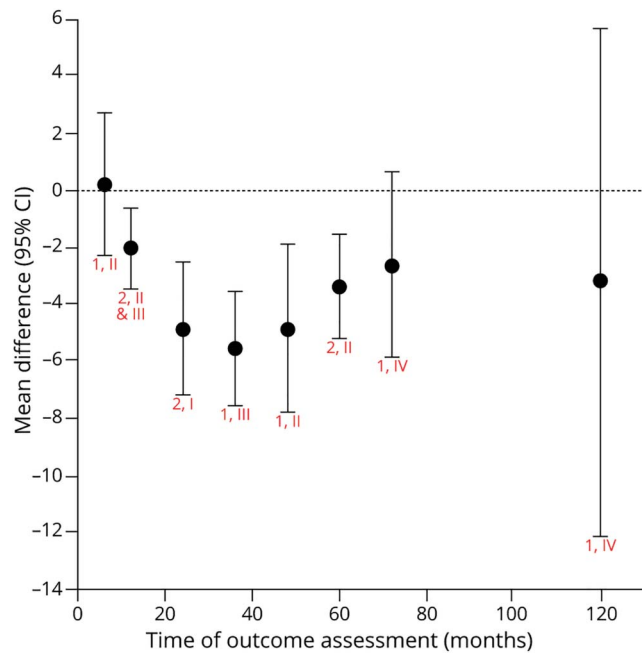

Chart shows random effects meta-analysis for each time (red text = number of articles, class). eTable 1 (links.lww.com/WNL/B569) shows raw mean difference (levodopa – dopamine agonist) for each study and time. For change in motor function, levodopa as compared to dopamine agonists is possibly no more effective at 6 months (raw mean difference 0.2 [95% confidence interval (CI) −2.3 to 2.7], low confidence); possibly more effective at 1 year (−2.1 [−3.6 to −0.7], low confidence); likely more effective at 2 years (−5.0 [−7.2 to −2.5], moderate confidence); possibly more effective at 4 years (−4.9 [−7.8 to −1.9], low confidence); and likely more effective at 5 years (−3.4 [−5.2 to −1.6], moderate confidence). There is insufficient evidence to determine whether levodopa is better or worse than dopamine agonists at 3 years (−5.6 [−7.6 to −3.6]), 6 years (−2.7 [−5.9 to 0.6]), and 10 years (−3.2 [−12.1 to 5.6]). The confidence in the evidence is algorithmically determined, as outlined in the *Clinical Practice Guideline Process Manual*.[2]

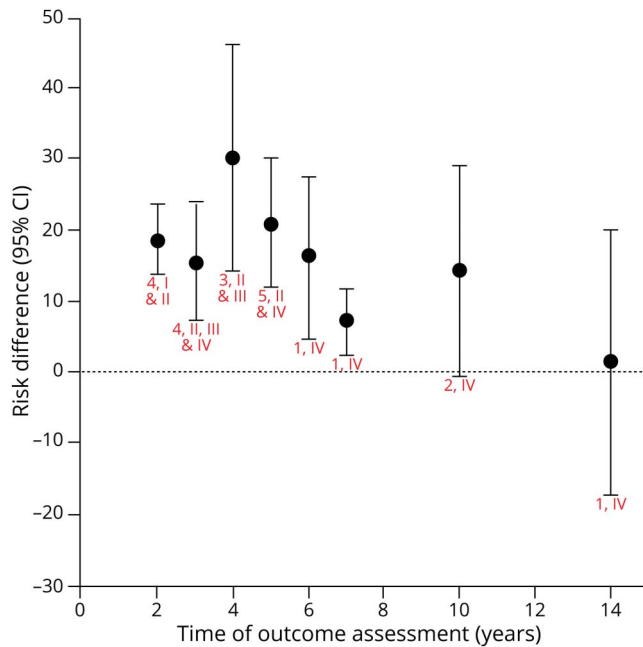**Figure 2** Levodopa vs Dopamine Agonist: Risk Difference for Dyskinesia

Chart shows random effects meta-analysis for each time (red text = number of articles, class). eTable 2 (links.lww.com/WNL/B569) shows risk difference (levodopa – dopamine agonist) for each study and time. The induction of dyskinesia, with levodopa as compared to dopamine agonists, is probably more likely at 2 years (risk difference 18.7% [95% confidence interval (CI) 13.7%–23.8%], moderate confidence); possibly more likely at 3 years (12.5% [2.8%–22.1%], low confidence); probably more likely at 4 years (29.2% [19.6%–38.8%], moderate confidence); and possibly more likely at 5 years (17.5% [4.5%–30.5%], low confidence). There is insufficient evidence to determine whether levodopa is more or less likely than dopamine agonists to induce dyskinesia at 6 years (16.5% [4.6%–27.7%]), 7 years (7.1% [2.4%–11.8%]), 10 years (14.3% [−0.4% to 29.1%]), and 14 years (1.6% [−17.3% to 20%]), all with very low confidence. The confidence in the evidence is algorithmically determined, as outlined in the *Clinical Practice Guideline Process Manual*.[2]

Each of the 59 selected articles was rated by 2 panel members using the AAN criteria for classification of therapeutic articles.[2] A modified form of the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) process was used to develop conclusions. The confidence in the evidence (high, moderate, low, or very low) was anchored to the error domain—class of evidence, indirectness of evidence, and precision of effect estimate—with the highest risk of error.[2]

Analysis of Evidence

Data Synthesis and Confidence in Evidence Statements for Levodopa vs DAs

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?

UPDRS Part III Score

The change in the UPDRS part III score from baseline to endpoint was extracted from studies comparing levodopa to DAs (with or without levodopa) and the RMD between treatments was calculated (Figure 1). Negative values favored levodopa. Where possible, estimates were combined using meta-analysis at specific time points. The minimal clinically important difference (MCID) in the UPDRS part III score was determined by consensus to be 3 points; changes of 1 point or less were considered unimportant.

The trend over time demonstrates that levodopa provides greater benefit for motor symptoms than DAs, with the majority of studies demonstrating significantly greater improvement in the participants' UPDRS part III score for up to 5 years of follow-up. Data beyond 5 years are scarce and of low quality. With longer periods of follow-up, an increasing proportion of participants (90% of patients at 6 years and 100% at 10 years) originally randomized to DAs were taking supplemental levodopa, therefore minimizing the difference between groups for this outcome.

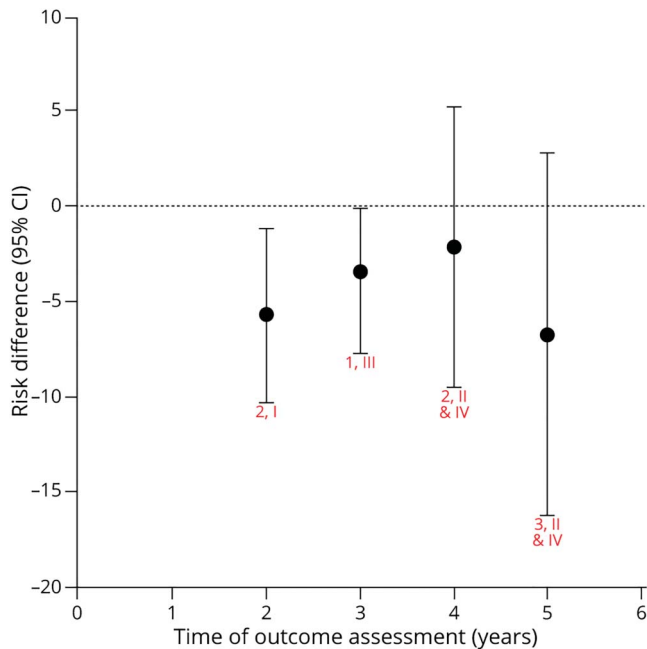**Figure 3** Levodopa vs Dopamine Agonist: Risk Differences for Development of Hallucinations

Chart shows random effects meta-analysis for each time (red text = number of articles, class). eTable 3 (links.lww.com/WNL/B569) shows risk difference (levodopa – dopamine agonist) for each study and time. Hallucinations with dopamine agonists as compared to levodopa are possibly more likely at 2 years (risk difference −5.7% [95% confidence interval (CI) −10.3% to −1.2%], low confidence); possibly no more likely at 4 years (6.6% [−13.9% to 0.7%], low confidence); and possibly no more likely at 5 years (−5.6% [−16.6% to 5.5%], low confidence). There is insufficient evidence to determine whether dopamine agonists are more or less likely than levodopa to induce hallucinations at 3 years (−3.4% [−7.7% to −0.2%], very low confidence). The confidence in the evidence is algorithmically determined, as outlined in the *Clinical Practice Guideline Process Manual*.[2]

Figure 4 Levodopa vs Dopamine Agonist: Risk Difference for Discontinuation Due to Adverse Events
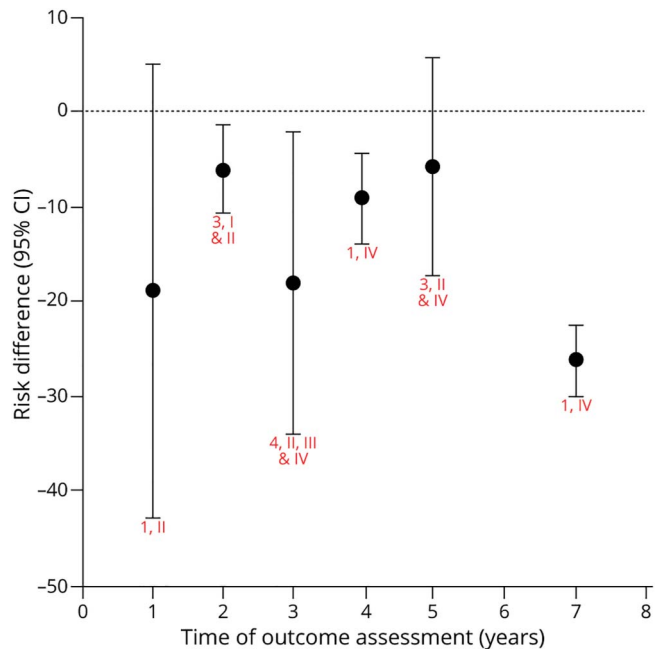

Chart shows random effects meta-analysis for each time (red text = number of articles, class). eTable 4 (links.lww.com/WNL/B569) shows risk difference (levodopa – dopamine agonist) for each study and time. The discontinuation of medication due to adverse effects, with dopamine agonists as compared to levodopa, is possibly more likely at 2 years (risk difference −6.1% [95% confidence interval (CI) −10.7% to −1.4%], low confidence); possibly no more likely at 3 years (−4.3% [−9.6% to 0.9%], low confidence); and probably no more likely at 5 years (−1% [−12.3% to 10.4%], moderate confidence). There is insufficient evidence to determine whether dopamine agonists are more or less likely than levodopa to cause medication discontinuation due to adverse effects at 1 year (−18.8% [−43% to 5%]), 4 years (−9.1% [−14% to −4.4%]), and 10 years (−26.2% [−30% to −22.5%]), all with very low confidence. The confidence in the evidence is algorithmically determined, as outlined in the *Clinical Practice Guideline Process Manual*.[2]

Dyskinesia

The proportion of participants who developed dyskinesia in each treatment group was extracted from studies comparing levodopa with DAs (with or without levodopa) and the RD was calculated (Figure 2). A positive value indicates that the risk of dyskinesia was higher with levodopa. Where possible, estimates were combined using meta-analysis at specific time points. The MCID in the risk of dyskinesia was determined by consensus to be 15%; RDs ≤5% were considered clinically unimportant.

The trend over time demonstrates that levodopa is more likely to induce dyskinesia than DAs. Data beyond 5 years of follow-up (when patients are generally taking a combination of treatments) is of low quality, leading to insufficient evidence to make a conclusion. Clinical question 8 addresses long-term disabling dyskinesia.

Hallucinations

The proportion of participants who developed hallucinations in each treatment group was extracted from studies comparing levodopa with DAs (with or without levodopa) and the RD was calculated (Figure 3). A negative value indicates that the risk of hallucinations was higher with DAs. Where possible, estimates

were combined using meta-analysis at specific time points. The MCID in the risk of hallucinations was determined by consensus to be 10%; RDs ≤3% were considered clinically unimportant.

The trend demonstrates that although DAs are more likely than levodopa to cause hallucinations at some time points, the difference between treatments for this outcome is small in early PD for the first 5 years of treatment. This may be related to the inclusion of younger patients without cognitive impairment in early PD trials.

AE-Related Discontinuation of Treatment

The proportion of participants who discontinued treatment due to adverse effects in each group was extracted from studies comparing levodopa with DAs (with or without levodopa) and the RD was calculated (Figure 4). A negative value indicates that the risk of AE-related discontinuation was higher with DAs. Where possible, estimates were combined using meta-analysis at specific time points. The MCID was determined by consensus to be 15%; RDs ≤5% were considered clinically unimportant.

Table 1 Levodopa vs Monoamine Oxidase Type B Inhibitors: Dyskinesia and Adverse Event–Related Discontinuation

Study	Class	Time point, y	RD (95% CI), %[a]
Dyskinesia			
Caraceni et al., 2001[4]	IV	3	6.3 (−3.2 to 15.6)
Conclusion (very low confidence): There is insufficient evidence to determine whether, in early PD, levodopa is more or less likely than MAO-B inhibitors (with or without levodopa) to induce dyskinesia at 3 years.			
PD MED Collaborative Group et al., 2014[5]	IV	7	7.0 (2.2–11.6)
Conclusion (very low confidence): There is insufficient evidence to determine whether, in early PD, levodopa is more or less likely than MAO-B inhibitors (with or without levodopa) to induce dyskinesia at 7 years.			
AE-related discontinuation of treatment			
Caraceni et al., 2001[4]	IV	3	−12.9 (−20.5 to −5.6)
Conclusion (very low confidence): There is insufficient evidence to determine whether, in early PD, MAO-B inhibitors are more or less likely than levodopa to cause medication discontinuation due to adverse effects at 3 years.			
PD MED Collaborative Group et al., 2014[5]	IV	7	−20.5 (−24.7 to −16.6)
Conclusion (very low confidence): There is insufficient evidence to determine whether, in early PD, MAO-B inhibitors are more or less likely than levodopa to cause medication discontinuation due to adverse effects at 7 years.			

Abbreviations: AE = adverse event; CI = confidence interval; MAO-B = monoamine oxidase type B; PD = Parkinson disease; RD = risk difference.
[a] Positive values indicate that the risk is higher with levodopa; negative values indicate that the risk is higher with MAO-B inhibitors.

Although the trend suggests that AE-related discontinuation of treatment is higher with DAs than with levodopa at all time points, confidence in the evidence is low or very low due to study quality or poor precision of estimates.

Data Synthesis and Confidence in Evidence Statements for Levodopa vs MAO-B Inhibitors

There were inadequate data on the effect of levodopa vs MAO-B inhibitors on motor symptoms, preventing effect size calculations (Table 1).

Whereas the trend over time suggests that the risk of dyskinesia is higher with levodopa than with MAO-B inhibitors, confidence in the evidence is very low due to study quality and, over time, most patients treated initially with MAO-B inhibitors were also receiving levodopa.

Over time, AE-related discontinuation of treatment is higher with MAO-B inhibitors than with levodopa, but confidence in the evidence is very low due to the quality of studies.

Data Synthesis and Confidence in Evidence Statements for DA Comparisons

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?

The confidence in evidence statements for comparisons of different formulations of DAs are summarized in Tables 2 and 3.

It is important to note that bromocriptine is not routinely used in clinical practice and piribedil is not widely used.

The available evidence suggests minimal differences in efficacy between formulations of DAs for improving motor function, with the exception of ropinirole being possibly more effective than rotigotine. The available evidence suggests that there are minimal differences between formulations of DAs in the risk of dyskinesia, hallucinations, and AE-related discontinuation.

Data Synthesis and Confidence in Evidence Statements for Long-Acting vs Immediate-Release (IR) Levodopa

5. In people with early PD, what is the comparative efficacy of long-acting formulations of levodopa (including sustained-release or controlled-release (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 AE-related discontinuation) of long-acting formulations of levodopa vs IR levodopa?

The confidence in evidence statements for comparisons of different formulations of levodopa is summarized in Table 4.

The available evidence is insufficient to make conclusions regarding the relative efficacy of long-acting vs IR levodopa for improvement in motor function or the risk of hallucinations. There do not appear to be major differences between long-acting and IR levodopa in the risk of dyskinesia or AE-related discontinuation.

Table 2 Dopamine Agonist Comparisons: Change in Unified Parkinson's Disease Rating Scale Part III Score From Baseline to Endpoint

Study	Class	Comparison	Time point	RMD (95% CI)
Thomas et al., 2006[6]	II	Ropinirole vs pramipexole	2 years	Unable to calculate
Conclusion (low confidence): In early PD, ropinirole is possibly no more effective than pramipexole in improving motor function at 2 years.				
Hauser et al., 2010[7]	I	Pramipexole ER vs pramipexole IR	18 weeks	0 (−2.4 to 2.4)
Conclusion (moderate confidence): In early PD, pramipexole ER is probably no more effective than pramipexole IR in improving motor function at 18 weeks.				
Poewe et al., 2011[8]	I	Pramipexole ER vs pramipexole IR	33 weeks	−0.5 (−2.3 to 1.3)
Conclusion (moderate confidence): In early PD, pramipexole ER is probably no more effective than pramipexole IR in improving motor function at 33 weeks.				
Kieburtz, Parkinson Study Group, 2011[9]	I	Pramipexole twice daily vs pramipexole 3 times daily	12 weeks	−0.1 (−2.46 to 2.26)
Conclusion (moderate confidence): In early PD, pramipexole taken 3 times daily is probably no more effective than pramipexole taken twice daily in improving motor function at 12 weeks.				
Stocci et al., 2008[10]	II	Ropinirole IR vs ropinirole PR	36 weeks	0.7 (−0.1 to 1.5)
Conclusion (low confidence): In early PD, ropinirole PR is possibly no more effective than ropinirole IR in improving motor function over 36 weeks.				
Korczyn et al., 1999[11]	III	Ropinirole vs bromocriptine	3 years	−1.98 (−4.74 to 0.78)
Conclusion (very low confidence): In early PD, there is insufficient evidence to support or refute the effectiveness of ropinirole compared to bromocriptine in improving motor function at 3 years.				
Giladi et al., 2007[12]	II	Rotigotine vs ropinirole	37 weeks	3.8 (1.9–5.7)
Conclusion (low confidence): In early PD, ropinirole is possibly more effective than rotigotine in improving motor function at 37 weeks.				
Castro-Caldas et al., 2006[13]	II	Piribedil vs bromocriptine	1 year	0.1 (−1.73 to 1.93)
Conclusion (low confidence): In early PD, piribedil is possibly no more effective than bromocriptine in improving motor function at 1 year.				

Abbreviations: CI = confidence interval; ER = extended-release; IR = immediate-release; PD = Parkinson disease; PR = prolonged release; RMD = raw mean difference.

Data Synthesis and Confidence in Evidence Statements for Risk of ICDs

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?

The MCID in the risk of ICDs was determined by consensus to be 2%; RDs ≤1% were considered clinically unimportant.

Confidence in Evidence Statements

Conclusion (moderate confidence): In early PD, DAs are probably more likely than levodopa to cause ICDs at 2 years (3 Class III studies, RD 23.2%, 95% confidence interval [CI] 14.3–32.1).

Conclusion (low confidence): In early PD, combination treatment with levodopa and DAs is possibly more likely than levodopa alone to cause ICDs at 2 years (1 Class III study, RD 11.2%, 95% CI 4.2–17.3).

Conclusion (low confidence): In early PD, DAs are possibly more likely than levodopa to cause ICDs at 5 years (2 Class III studies, RD 23.7%, 95% CI 1.1–46.3).

Conclusion (low confidence): In early PD, combination treatment with levodopa and DAs is possibly more likely than levodopa alone to cause ICDs at 5 years (1 Class III study, RD 24.4%, 95% CI 7.0–39.0).

Data Synthesis and Confidence in Evidence Statements for Long-term Risk of Disabling Dyskinesia

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

The MCID in the risk of disabling dyskinesias was determined by consensus to be 15%; RDs ≤5% were considered clinically unimportant.

Confidence in Evidence Statements

Conclusion (low confidence): In early PD, levodopa is possibly more likely than ropinirole to cause disabling dyskinesia at 5 years (1 Class II study, RD 14.7%, 95% CI 5.8–24.8).

Conclusion (very low confidence): In early PD, there is insufficient evidence to determine whether levodopa is more or less likely than pramipexole to cause disabling dyskinesia at 6 years (1 Class IV study, RD 0.7%, 95% CI −4.8% to 6.2%).

Conclusion (very low confidence): In early PD, there is insufficient evidence to determine whether levodopa is more or

Table 3 Dopamine Agonist Comparisons: Risk of Dyskinesia, Hallucinations, and AE-Related Discontinuation

Study	Class	Comparison	Time point	RD (95% CI)
Dyskinesia				
Korczyn et al., 1999[12]	III	Ropinirole vs bromocriptine	3 y	0.5% (−5.3% to 6.4)
Conclusion (very low confidence): **There is insufficient evidence to determine whether, in early PD, ropinirole is more or less likely than bromocriptine to induce dyskinesia at 3 y.**				
Castro-Caldas et al., 2006[2]	II	Piribedil vs bromocriptine	1 y	−1.8% (−5.8% to 2.1%)
Conclusion (low confidence): **In early PD, piribedil is possibly no more likely than bromocriptine to cause dyskinesia at 1 y.**				
Hallucinations				
Castro-Caldas et al., 2006[2]	II	Piribedil vs bromocriptine	1 y	5.3% (1.0% to 10.0%)
Conclusion (low confidence): **In early PD, piribedil is possibly more likely than bromocriptine to cause hallucinations at 1 y.**				
AE-related discontinuation				
Hauser et al., 2010[3]	I	Pramipexole ER vs pramipexole IR	18 wk	2.6% (−5.6% to 10.8%)
Conclusion (moderate confidence): **In early PD, pramipexole ER is probably no more likely than pramipexole IR to cause AE to related treatment discontinuation at 18 wk.**				
Poewe et al., 2011[4]	I	Pramipexole ER vs pramipexole IR	33 wk	1.4% (−4.4% to 7.1%)
Conclusion (moderate confidence): **In early PD, pramipexole ER is probably no more likely than pramipexole IR to cause AE–related treatment discontinuation at 33 wk.**				
Kieburtz, Parkinson Study Group 2011[5]	I	Pramipexole twice daily vs pramipexole 3 times daily	12 wk	1.1% (−8.8% to 11.1%)
Conclusion (moderate confidence): **In early PD, pramipexole taken 3 times daily is probably no more likely than pramipexole taken twice daily to cause AE–related treatment discontinuation at 12 wk.**				
Korczyn et al., 1999[1]	III	Ropinirole vs bromocriptine	3 y	0.5% (−8.1% to 9.1%)
Conclusion (very low 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 y.**				
Giladi et al., 2007[6]	II	Rotigotine vs ropinirole	37 wk	4.1% (−2.7% to 10.8%)
Conclusion (*low confidence*): **In early PD, rotigotine is possibly no more likely than ropinirole to cause AE–related discontinuation of treatment at 37 wk.**				
Castro-Caldas et al., 2006[2]	II	Piribedil vs bromocriptine	1 y	4.3% (−3.0% to 11.5%)
Conclusion (low confidence): **In early PD, piribedil is possibly no more likely than bromocriptine to cause AE–related discontinuation of treatment at 1 y.**				

less likely than ropinirole to cause disabling dyskinesia at 10 years (1 Class IV study, RD 11.6%, 95% CI −7.0 to 31.9).

Practice Recommendations

The following recommendations pertain to the initiation of pharmacologic treatment for motor symptoms in early PD, presuming that patients have received a correct diagnosis. There are no current disease-modifying pharmacologic treatments for PD[14-16]; current PD pharmacologic therapy is symptomatic only. When symptoms are not causing disability, most individuals with PD and clinicians are comfortable with a "wait and see" approach, although this requires careful monitoring and advising patients not to tolerate disability or reduction in quality of life unnecessarily. In the Parkinson's Progression Markers Initiative dataset of individuals with new PD diagnoses who were expected to be able to remain untreated for at least 6 months, 283 of 423 (67%) individuals with

PD started treatment within 2 years of study onset, an average of 0.78 (SD 0.5) years after study entry.[17] This provides an opportunity for interested individuals with de novo PD to participate in clinical trials targeting this population.

The panel developed rationale statements that precede each recommendation. Four types of premises can be used to support recommendations: (1) evidence-based conclusions from the systematic review, (2) generally accepted principles of care, (3) strong evidence from related conditions, and (4) deductive inferences from other premises. Recommendations must always be supported by at least one premise.

In addition to the evidence-based conclusions from the systematic review, the guideline developers consider the following non–evidence-based factors when formulating recommendations: (1) the relative value of the benefit compared with the risk, (2) the feasibility of complying with the intervention, (3)

Table 4 Long-Acting vs Immediate-Release Levodopa: Change in Unified Parkinson's Disease Rating Scale Part III Score From Baseline to Endpoint, Risk of Dyskinesia, Hallucinations, and Adverse Event–Related Discontinuation

Study	Class	Comparison	Time point	RMD or RD (95% CI)
Change in UPDRS part III score from baseline to endpoint				
Dupont et al., (1996)[18]	III	Madopar HBS vs Madopar	5 years	1.9 (−0.94 to 4.74)
Conclusion (very low confidence): In early PD, there is insufficient evidence to support or refute the effectiveness of Madopar HBS compared to Madopar in improving motor function at 5 years.				
Hauser et al., (2009)[19]	III	Levodopa/carbidopa vs levodopa/carbidopa/entacapone	39 weeks	0.8 (−2.2 to 0.6)
Conclusion (very low confidence): In early PD, 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.				
Dyskinesia				
Dupont et al., (1996)[18]	III	Madopar HBS vs Madopar	5 years	7.1% (−15.8% to 29.5%)
Conclusion (very low confidence): 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.				
Koller et al., (1999)[20]	IV	Levodopa IR vs levodopa CR	5 years	−1.8 (−6.4 to 2.8)
Conclusion (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.				
Fung et al., (2009)[21]	I	Levodopa/carbidopa vs levodopa/carbidopa/entacapone	12 weeks	−4.3 (−10.9 to 1.5)
Conclusion (moderate confidence): In early PD, levodopa/carbidopa is probably no more likely than levodopa/carbidopa/entacapone to cause dyskinesia at 12 weeks.				
Hauser et al., (2009)[19]	III	Levodopa/carbidopa vs levodopa/carbidopa/entacapone	39 weeks	2.2% (−2.7% to 7.0%)
Conclusion (very low 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.				
Stocchi et al., (2010)[22]	II	Levodopa/carbidopa vs levodopa/carbidopa/entacapone	2.5 years	−7.4 (−13.0 to 0)
Conclusion (low confidence): In early PD, levodopa/carbidopa/entacapone is possibly no more likely than levodopa/carbidopa to induce dyskinesia at 2.5 years.				
Hallucinations				
Koller et al., (1999)[20]	IV	Levodopa IR vs levodopa CR	5 years	1.1% (−2.3% to 4.5%)
Conclusion (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 hallucinations at 5 years.				
AE-related discontinuation				
Dupont et al., (1996)[18]	III	Madopar HBS vs Madopar	5 years	−6.9% (−17.5% to 3.6%)
Conclusion (very low confidence): There is insufficient evidence to determine whether, in early PD, Madopar HBS is more or less likely than Madopar to cause AE-related treatment discontinuation at 5 years.				
Fung et al., (2009)[21]	I	Levodopa/carbidopa vs levodopa/carbidopa/entacapone	12 weeks	−2.1% (−9.5% to 5.2%)
Conclusion (moderate confidence): In early PD, levodopa/carbidopa is probably no more likely than levodopa/carbidopa/entacapone to cause AE-related treatment discontinuation at 12 weeks.				
Hauser et al., (2009)[19]	III	Levodopa/carbidopa vs levodopa/carbidopa/entacapone	39 weeks	−3.2 (−9.1 to 2.6)
Conclusion (very low confidence): There is insufficient evidence to determine whether, in early PD, levodopa/carbidopa is more or less likely than levodopa/carbidopa/entacapone to cause AE-related treatment discontinuation at 39 weeks.				
Stocchi et al., (2010)[22]	II	Levodopa/carbidopa vs levodopa/carbidopa/entacapone	2.5 years	−3.7 (−7.8 to 0.3)
Conclusion (low confidence): In early PD, levodopa/carbidopa/entacapone is possibly no more likely than levodopa/carbidopa to cause AE-related treatment discontinuation at 2.5 years.				

Abbreviations: AE = adverse event; CI = confidence interval; CR = controlled-release; HBS = hydrodynamically balanced system; IR = immediate-release; PD = Parkinson disease; RD = risk difference; RMD = raw mean difference; UPDRS = Unified Parkinson's Disease Rating Scale.

the cost of the intervention, and (4) the expected variation in patient preferences relative to the risks, burdens, and benefits of the intervention. After drafting recommendations, the panel assigns levels of obligation (A, B, or C) to each recommendation using a modified Delphi process that synthesizes all previously listed factors. Each designation corresponds to a helping verb that denotes the recommendation's strength level. Level A is the strongest recommendation level and is denoted by the verb *must*. These recommendations are based on high confidence in the evidence and require both a high magnitude of benefit and low risk. Level B corresponds to the verb *should*. The requirements for these recommendations are less stringent but still based on the evidence and benefit–risk profile. Level C corresponds to the verb *may*. This is the lowest allowable recommendation level that the AAN considers useful within the scope of clinical practice and accommodates the highest degree of practice variation.

Levodopa vs DAs vs MAO-B Inhibitors

Recommendation 1 Rationale
Clinical trials have failed to provide evidence of disease modification when the initial therapy prescribed is levodopa,[23] a DA,[24] or an MAO-B inhibitor.[25] 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 AE-related discontinuation with MAO-B inhibitors, and that >60% of individuals randomized to MAO-B inhibitors will require additional therapy within 2 to 3 years.

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 5-year period is low. Although 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.

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 at disease onset,[26] lower body weight,[27,28] female sex,[26] and increased disease severity[29-31] 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), apathy, and a family history of ICDs and addiction.[32-35] Older patients are at greater risk for cognitive and behavioral adverse effects of DAs.[36] 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.[37]

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

Prescribing Levodopa

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 extended-release (ER) carbidopa/levodopa in early PD.

Although 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,[38,39] which may necessitate treatment discontinuation in later stages of the disease due to dose failures. Whereas levodopa/carbidopa/entacapone can be helpful for patients who experience end-of-dose wearing-off,[40] 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/day and a lower risk of dyskinesia with dosages <400 mg/day. Although the risk is higher with DAs, levodopa may cause ICDs, hallucinations, and EDS.[37] Levodopa may exacerbate postural hypotension.

Nausea is a common early and dose-dependent adverse effect of levodopa.[41] 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.[42] 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.

Recommendation 2 Statements

2a. Clinicians should initially prescribe IR levodopa rather than CR levodopa or levodopa/carbidopa/entacapone in patients with early PD (Level B).

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).

2c. Clinicians should routinely monitor patients taking levodopa for their motor response to treatment and for the presence of dyskinesia, motor fluctuations, ICDs, EDS, postural hypotension, nausea, and hallucinations, to guide dosage titration over time (Level B).

2d. Clinicians should counsel patients taking levodopa that higher dosages are more likely to cause dyskinesia (Level B).

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).

Prescribing DAs

Recommendation 3 Rationale

Before prescribing a medication, it is important to inform patients and caregivers of medication-associated adverse effects and to screen for preexisting 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, EDS, sudden-onset sleep, nausea, and hallucinations in patients with early PD.[37] DAs may exacerbate postural hypotension.

Patients may not always report certain nonmotor symptoms associated with PD or its treatment due to lack of awareness, embarrassment, or other concerns.[43] 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.

Recommendation 3 Statements

3a. Clinicians should inform the patient and caregiver (when present) of important side effects of DAs before prescribing; this discussion should specifically include ICDs, EDS, sudden-onset sleep, nausea, postural hypotension, and hallucinations (Level B).

3b. Clinicians should screen patients for cognitive impairment, EDS, sudden-onset sleep, hallucinations, orthostatic hypotension, and the presence of risk factors for ICDs before prescribing a DA (Level B).

3c. Clinicians should screen patients for the presence of adverse effects related to DAs, including ICDs, EDS, sudden-onset sleep, orthostatic hypotension, cognitive impairment, and hallucinations repeatedly in follow-up of patients prescribed DAs (Level B).

3d. Clinicians should involve caregivers in assessments for ICDs, EDS, sudden-onset sleep, orthostatic hypotension, cognitive impairment, and hallucinations in patients with PD (Level B).

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 EDS. "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.

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.[44]

The Epworth Sleepiness Scale (ESS) is a self-report questionnaire consisting of 8 questions and responses on a 4-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 8-item scores ranging from 0 to 24, where a higher score represents greater sleepiness. ESS scores above 10 are considered to represent EDS.[45]

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

Recommendation 3e Statement

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).

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. Furthermore, there was no compelling evidence that pramipexole ER vs pramipexole IR was associated with a more favorable UPDRS score or a different rate of AE-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.[46] 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, relevant patient

preferences may include the cost and the frequency (once daily, twice daily, or 3 times daily) and mode (oral vs transdermal) of administration.

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/day of ropinirole, 1.5 mg/day of pramipexole, or 4 mg/24 hours of rotigotine).[47]

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

Tapering and Discontinuing DAs

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 pharmacologic interventions, if appropriate.

Patients may experience undesirable side effects when attempting to decrease dopaminergic medications, especially DAs, including dopamine agonist withdrawal syndrome (DAWS) or low mood and apathy.[48] 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.

Recommendation 5 Statements
5a. Clinicians should recommend tapering or discontinuation of DAs if patients experience disabling medication-related adverse effects, including ICDs, EDS, sudden-onset sleep, cognitive impairment, or hallucinations (Level B).
5b. When DAs 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 (Level B).

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 DAs. Treatment of early

PD with MAO-B inhibitors is associated with a higher risk of AE-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.[49,50] 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.[51-53]

Recommendation 6 Statements
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).
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 when the diagnosis is made, and possibly in patients with probable prodromal PD before motor features are evident. The role of nonpharmacologic 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 whether quality of life is significantly improved with the earlier initiation of symptomatic treatment vs following a "wait and watch" strategy. 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, 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. 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 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 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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Conflict of Interest

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Group, Peerview Press, Pennside Partners, Perception OpCo (Cerevel Therapeutics), Pfizer, Pharma Two B, PharmaTher, Putnam Associates, Phase Five Communications, Projects in Knowledge, Prexton Therapeutics, P\S\L Group, Quintiles, Regenera Pharma, Research Catalyst, Revance Therapeutics, RMEI Medical Education, Sanofi-Aventis, Sarepta Therapeutics, Schlesinger Group, Scion NeuroStim, LLC, Seagrove Partners, Seelos Therapeutics, Sio Gene Therapies, Slingshot Insights, Sunovion Pharmaceuticals, Supernus Pharmaceuticals, Syneos Health, Takeda Pharmaceuticals, Teva Pharmaceutical Industries, Tolmar Pharmaceuticals, UCB Biosciences, US WorldMeds, Vista Research, Vivifi Biotech, and Windrose Consulting Group; serves on a speakers bureau for AbbVie, Acorda Therapeutics, Adamas Pharmaceuticals, Amneal Pharmaceuticals, Kyowa Kirin, Lundbeck, Neurocrine Biosciences, Sunovion Pharmaceuticals, Teva Pharmaceuticals, and US WorldMeds; has received research support from AbbVie, Adamas Pharmaceuticals, AstraZeneca, Atlantic Research/Chelsea Therapeutics, Axovant Sciences Ltd., Biogen, Biotie Therapies, Cavion, Centogene, Cerevance, Cerevel Therapeutics, Civitas Therapeutics, Cynapsus Therapeutics, Dart NeuroScience, Enterin, F. Hoffman-La Roche, Global Kinetics Corporation, Impax Laboratories, Intec Pharma, Integrative Research Laboratories Sweden AB, Jazz Pharmaceuticals, Kyowa Kirin, Lundbeck, Michael J. Fox Foundation for Parkinson's Research, NIH, National Institute of Neurologic Disorders and Stroke, Neuraly, NeuroDerm, Northwestern University, Parkinson Study Group, Pfizer, Pharma Two B, Prexton Therapeutics, Revance Therapeutics, Sanofi US Services, Sun Pharma Advanced Research, Sunovion Pharmaceuticals, and UCB Biopharma; holds stock in Axial Biotherapeutics and Inhibikase Therapeutics; and has received license for fee payments from USF for Parkinson's Disease Diary. A. Espay has received grant support from the NIH and the Michael J. Fox Foundation for Parkinson's Research; has received financial compensation for work as a consultant or scientific advisory board member for AbbVie, NeuroDerm, Neurocrine Biosciences, Amneal Pharmaceuticals, Adamas Pharmaceuticals, Acadia Pharmaceuticals, Acorda Therapeutics, Intrance Medical Systems, Kyowa Kirin, Sunovion Pharmaceuticals, Lundbeck, and US WorldMeds; has received publishing royalties from Lippincott Williams & Wilkins, Cambridge University Press, and Springer Publishing; and has received honoraria from US WorldMeds, Acadia Pharmaceuticals, Amneal Pharmaceuticals, and Sunovion Pharmaceuticals. J. Martello has received honoraria from AbbVie, Acorda Therapeutics, Lundbeck, Neurocrine Biosciences, and Sunovion Pharmaceuticals for being on their speakers bureau. J. Gurwell has received travel funding from Boston Scientific and the AAN; serves on the editorial advisory board for *Neurology Today*; has received honoraria from Boston Scientific; and has received research support from AbbVie, Cynapsus Therapeutics, Sunovion Pharmaceuticals, and NeuroDerm. L. Billinghurst has received travel funding from the AAN to attend Guideline Subcommittee meetings. K. Sullivan has received intellectual property interests from a discovery or technology relating to health care and has received travel funding from the

Publication History

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Name	Location	Contribution
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Gregory S. Day, MD, MSc	Department of Neurology, Mayo Clinic, Jacksonville, FL	Design or conceptualization of the study; analysis or interpretation of the data; drafting or revising the manuscript for intellectual content

Appendix *(continued)*

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Alberto J. Espay, MD	James J. and Joan A. Gardner Family Center for Parkinson's Disease and Movement Disorders, and Department of Neurology, University of Cincinnati, OH	Design or conceptualization of the study; drafting or revising the manuscript for intellectual content
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Lori Billinghurst, MD, MSc	Department of Pediatrics, McMaster University, Hamilton, Ontario, Canada	Design or conceptualization of the study; analysis or interpretation of the data

Continued

Appendix (continued)

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