Dopaminergic Therapy for Motor Symptoms in Early Parkinson Disease Practice Guideline

A Report of the AAN Guideline Subcommittee

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GLOSSARY

AAN: American Academy of Neurology

ADL: activities of daily living

AE: adverse event

CI: confidence interval

COI: conflict of interest

COMT: catechol-o-methyl transferase

CR: controlled-release

CV: curriculum vitae

DA: dopamine agonist

ER: extended-release

GRADE: Grading of Recommendations Assessment, Development, and Evaluation

GS: Guideline Subcommittee

HR: hazard ratio

ICB: impulsive and compulsive behavior

ICD: impulse control disorder

IR: immediate-release

LC: levodopa/carbidopa

LCE: levodopa/carbidopa/entacapone

LEDD: levodopa equivalent daily dose

MAO-B: monoamine oxidase type B

OR: odds ratio

PD: Parkinson disease

PDQ-39: 39-item Parkinson's Disease Questionnaire

PR: prolonged-release

RMD: raw mean difference

SE: standard error

SMD: standardized mean difference

SR: slow-release

UPDRS: Unified Parkinson's Disease Rating Scale

ABSTRACT

Objective: 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, while 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.

INTRODUCTION

Parkinson disease (PD) is a neurodegenerative disorder that causes both motor and non-motor symptoms and increases in prevalence with age. PD currently affects approximately 1% of individuals aged 70 to 79 and 2% of individuals over the age of 80 years.[1] Symptoms of PD progress gradually over time and affected individuals require ongoing medical care and consultation with neurologists from disease onset until the end of life.

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 concerns regarding the potential for neuropsychiatric adverse effects associated with DAs and dyskinesia associated with levodopa.

Rationale for this practice guideline

In 2002, the American Academy of Neurology (AAN) published the "Initiation of Treatment for Parkinson Disease" practice guideline, which contains recommendations regarding the use of selegiline and other dopaminergic medications for patients with PD.[2] The authors concluded that selegiline has a very mild symptomatic benefit but offers no neuroprotective benefit and that either levodopa or a DA can be used for PD patients requiring initiation of symptomatic therapy. The authors determined that levodopa provides superior motor benefit but is associated with a higher risk of dyskinesia than the other considered medications. The authors found no evidence

to suggest that initiating treatment with sustained-release levodopa provided an advantage over IR levodopa. In the nearly two decades that have passed since the publication of the 2002 guideline, many new medications and new formulations of older medications have become available for the treatment of PD. The goal of this guideline is to review the current evidence on the options available for initiating dopaminergic treatment of motor symptoms in early-stage PD and provide guidance to clinicians on the following clinical questions.

Clinical questions

1. In people with early PD, what is the comparative efficacy of levodopa vs 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 [AE]-related discontinuation) with 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 AE-related discontinuation) of different formulations of DAs?
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 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 AE-related discontinuation) of long-acting formulations of levodopa vs IR levodopa?

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

For adverse effects, the guideline focused specifically on dyskinesia, hallucinations, and AE-related discontinuation. While ICDs are an important AE of treatment, ICDs are infrequently included as an outcome in randomized controlled trials. Data on the risk of ICDs was included whenever reported by trials, population-based epidemiologic studies, and prospective cohort studies.

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 experts (T.P., R.M.A.d.B., A.E.L., A.J.E., M.J.A., D.B.S., D.H., J.M.M., A.E.L., R.A.H., E.R., J.P.M., N.C., J.G.), methodology experts (T.P., D.S.), an AAN Quality Measures Subcommittee member (J.P.M.), AAN GS members (G.S.D., N.L., K.S., L.B., M.J.A., A.R.G., G.G.), patient representatives (M.F., L.H.), and a staff representative from the Michael J. Fox Foundation for Parkinson's Research (T.H). The panel members were required to submit AAN's relationship disclosure forms and copies of their curriculum vitae (CV). The panel leadership, consisting of the lead developer and AAN methodologist (T.P.), the AAN staff person (M.D.O.B.), and Guideline Subcommittee leadership reviewed the relationship disclosure forms and CV for financial and intellectual conflicts of interest (COI). These documents were screened specifically to exclude both those individuals

with a clear financial conflict and those whose profession and intellectual bias would diminish the credibility of the review in the eyes of the intended users. 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 development panel and the lead author (T.P.) are free of COI relevant to the subject matter of 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 these developers from authorship (A.J.E., J.M.M., A.E.L., R.A.H., J.P.M.). While the development of this guideline primarily followed the 2017 edition of the AAN's *Clinical Practice Guideline Process Manual,* this edition of the manual was not fully published by the time of the guideline initiation. Therefore, disclosures were reviewed following the previous edition of the process found in the 2011 *Clinical Practice Guideline Process Manual*.[3] The developers determined to have COI (A.J.E., J.M.M., A.E.L., R.A.H., J.P.M.) were not permitted to review or rate the evidence. These individuals were consulted in an advisory capacity to help with the validation of the key questions, the scope of the literature search, and the identification of seminal articles to validate the literature search. The panel members with COI were allowed to participate in the recommendation development process. 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.

This evidence-based practice guideline follows the 2017 edition of the AAN's guideline development process manual.[4] We summarize the process here and provide a detailed description in the appendices at the end of this guideline. The public and experts had an opportunity to review the draft of this guideline during a 30-day public comment period when the document

was posted on the AAN website. During this period, AAN staff sent invitations to review and comment on the guideline to key stakeholders. The guideline was reviewed by the GS before the public comment period and was re-reviewed and edited after public comment.

Study screening and selection criteria

Types of participants

We included studies of participants with PD in the early stages (i.e., Hoehn and Yahr stages 1 or 2, or within 2 years of disease onset). We excluded studies with participants at Hoehn and Yahr stages above 2, or with disease onset more than 2 years prior to study onset.

Types of interventions

We included studies of DAs, levodopa, MAO-B inhibitors, and catechol-o-methyl transferase (COMT) inhibitors to treat motor symptoms of PD in the early stages of the disease.

Comparison group

We included studies using active comparators only, such as levodopa vs a DA or IR levodopa vs sustained-release levodopa.

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

While the authors report data from any validated scale for the measurement of motor symptoms in PD, 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, AE-related discontinuation, and 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 March 2018 for relevant peer-reviewed articles that met the inclusion criteria (see appendix 3 for search strategies). The initial search yielded 7,269 articles. After these results were de-duplicated and animal studies were removed, 3,842 abstracts were passed on for review. Two panelists reviewed each article title and abstract and selected articles for inclusion based on the inclusion criteria and the potential relevance to the clinical questions. Reviews, meta-analyses, retrospective cohort studies, case control studies, and case series were excluded, as were studies with 20 or fewer participants, studies including participants who had diseases other than PD, and articles that were not peer reviewed. Of the reviewed abstracts, 221 were identified as potentially relevant and their corresponding articles were obtained for full-text review. Each of the 221 articles was reviewed by 2 panel members working independently of each other. The panelists selected 53 articles for inclusion in the analysis. An updated literature search completed in June 2020 identified an additional 34 potentially relevant articles, 6 of which were selected for inclusion in the analysis using the same screening process.

Each of the 59 selected articles was rated by 2 panel members using the AAN criteria for classification of therapeutic articles.[4] 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.[4]

Relative to the class of evidence (a measure of internal validity), the risk of error was determined by the number and class of studies included in the synthesis. Evidence syntheses based solely on multiple Class I studies were anchored to high confidence, those based solely on 1 Class I study or multiple Class II studies were anchored to moderate confidence, those based solely on 1 Class II study or multiple Class III studies were anchored to low confidence, and those based solely on 1 Class III study or multiple Class IV studies were anchored to very low confidence. Confidence in the evidence synthesis including multiple studies of different risk-of-bias classes was anchored to the study with the highest risk of bias. If the synthesis included any Class IV study, confidence was anchored to very low; any Class III study, low; or any Class II study, moderate.

Relative to the indirectness domain (a measure of external validity), confidence in the evidence is anchored to the study included in the synthesis that had the most severe indirectness rating. Only syntheses where all studies were judged to have minor degrees of indirectness were anchored to high confidence. Syntheses containing any study judged to have extreme indirectness were anchored to very low confidence, those with any study judged to have severe

indirectness were anchored to low confidence, and those with any study judged to have moderate indirectness were anchored to moderate confidence.

An effect size was calculated for each study intervention/outcome pair. For the change in the UPDRS part III score from baseline to follow-up, the RMD between the intervention and comparator was calculated. For dyskinesia, hallucinations, AE-related discontinuation, and ICDs, the RD between intervention and comparator was calculated. For our analysis, an RMD of 3 points in the change of the UPDRS part III score was considered the minimal clinically meaningful difference; an RMD equal to or smaller than 1 point was considered clinically unimportant. For dyskinesia, an RD of 15% was considered the minimal clinically meaningful difference; an RD less than or equal to 5% was considered clinically unimportant. For hallucinations, an RD of 10% was considered the minimal clinically meaningful difference; an RD less than or equal to 3% was considered clinically unimportant. For AE-related discontinuation, an RD of 15% was considered the minimal clinically meaningful difference; an RD less than or equal to 5% was considered clinically unimportant. For ICDs, an RD of 2% was considered the minimal clinically meaningful difference; an RD less than or equal to 1% was considered clinically unimportant. If multiple studies were available that evaluated the same intervention/outcome pair, only those studies with the lowest risk of bias were used in formulating the confidence in evidence statements. Analyses were performed based on the length of the follow-up period, with only studies of similar duration grouped together. All minimal clinically meaningful differences and clinically unimportant differences were determined by the author panel by consensus before analyses were performed.

Relative to precision (a measure of random error), the confidence in the evidence anchor depends upon whether the pooled effect size of the studies included no effect (i.e., the effect is not significant) and whether the summary confidence interval (CI) included effect sizes judged to be clinically important, marginal (between important and unimportant thresholds), or unimportant.

If the pooled effect size was not significant and the 95% CI included only unimportant effect sizes, the confidence of no effect was anchored to high; if the 95% CI included marginal effect sizes, confidence of no effect was anchored to moderate; if the 95% CI included important and marginal effect sizes, confidence of no effect was anchored to low; if the 95% CI included important effect sizes, confidence of no effect was anchored to very low. If the pooled effect was significant and the pooled 95% CI included only important effect sizes, confidence was anchored to high; if significant and the CI included potentially marginal effects, confidence was anchored to moderate; if significant and the CI included potentially unimportant effects, confidence was anchored to low.

The confidence in the evidence determined by the lowest confidence from the major error domains (class of evidence, indirectness, and precision) served as the anchor. The confidence in the evidence could be upgraded or downgraded by a maximum of one level based upon several other domains: the magnitude of effect, direction of bias, and the presence of a dose response. Confidence in the evidence was upgraded by one level if the lower limit of the 95% CI for the magnitude of a significant effect point estimate was more than twice as large as that judged to be important. Conversely, confidence was downgraded by one level if the magnitude of a significant effect-size point estimate was less than the important threshold. Confidence was

upgraded if the direction of bias in studies included in the synthesis were known (an unusual situation) and a significant effect was present in the opposite direction of the bias. Confidence was also upgraded if an expected dose response relationship was detected in the majority of the studies that tested for a dose response relationship and was downgraded if an expected dose response relationship was not observed.

The phrasing of all conclusion statements is highly structured and based on the confidence in the evidence. When confidence in the evidence is high that treatment x is superior to treatment y, the phrases “is highly likely more effective than” or “is more likely than” are used. When confidence in the evidence is moderate that treatment x is superior to treatment y, the phrases “is likely more effective than” or “is probably more likely than” are used. When confidence in the evidence is low that treatment x is superior to treatment y, the phrases “is possibly more effective than” or “is possibly more likely than” are used. When confidence in the evidence is high that there is no difference between treatments x and y, the phrases “is highly likely no more effective than” or “is no more likely than” are used. When confidence in the evidence is moderate that there is no difference between treatments x and y, the phrases “is likely no more effective than” or “is probably no more likely than” are used. When confidence in the evidence is low that there is no difference between treatments x and y, the phrases “is possibly no more effective than” or “is possibly no more likely than” are used. When confidence in the evidence is very low, the phrases “there is insufficient evidence to support or refute the effectiveness of” or “there is insufficient evidence to determine if x is more or less likely than y” are used.

ANALYSIS OF EVIDENCE

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?

It should be noted that several of the DAs used in the studies described below are not routinely used in practice, including bromocriptine, pergolide, cabergoline, and lisuride.

Levodopa vs levodopa plus selegiline vs bromocriptine

One Class IV study randomized 782 patients with early PD to flexible-dose levodopa, flexible-dose levodopa plus 10 mg/d of selegiline, or 120 mg or less per day of bromocriptine. Participants had not previously received dopaminergic treatment. Participants and evaluators were not blinded to treatment. The principal outcomes assessed were motor disability and mortality. Reports were published after three,[4] ten,[5] and fourteen years[6] of follow-up.

In the three-year interim report,[5] improvement in disability was measured in all three groups using the modified Webster score during the first year. Participants who received levodopa (adjusted difference 0.93, 95% CI 0.27–1.50; p=0.0058) or levodopa plus selegiline (adjusted difference 1.25, 95% CI 0.61–1.89; p=0.0002) had significantly greater improvement in disability compared to participants who received bromocriptine. After an average follow-up of three years, dyskinesia occurred in 27% of participants receiving levodopa, 34% of participants receiving levodopa plus selegiline, and 2% of participants receiving bromocriptine. The RD

relative for dyskinesia was 25% (95% CI 19.3%–30.9%) in participants receiving levodopa vs bromocriptine, and 32.1% (95% CI 26.1%–38.0%) in participants receiving levodopa plus selegiline vs bromocriptine. A significantly higher proportion of participants receiving bromocriptine were withdrawn from treatment compared to those receiving levodopa, RD 36.7% (95% CI 28.3%–44.3%) or levodopa plus selegiline, RD 40.8% (95% CI 32.7%–48.1%).

In the ten-year follow-up report,[6] the levodopa plus selegiline treatment arm was terminated after 6 years due to increased mortality in participants in this treatment arm. Results were presented on mortality, motor disability, and long-term motor complications according to the treatment arm to which all participants were originally randomized. The median duration before introduction of levodopa to participants in the bromocriptine group was 2.1 years. Five years after initial randomization, the mean daily dose of levodopa in the bromocriptine group was 328 mg, compared to 609 mg in the levodopa group. Over the first 5 years, the difference between the levodopa and bromocriptine groups remained fairly constant at approximately 1 point on the Webster scale. After 5 years of follow-up, the difference in Webster score between the levodopa and bromocriptine groups was 1.0 (95% CI 0.2–2.1), with the bromocriptine group yielding worse disability scores. The difference in disability diminished between the 2 groups with further follow-up. By the ninth year of follow-up, the difference was 0.2 (95% CI -1.5 to 1.5). After a minimum of 10 years of follow-up, there was a significantly lower risk of dyskinesia in participants initially randomized to bromocriptine compared to those randomized to levodopa. The RD for dyskinesia with levodopa compared to bromocriptine was 9.2% (95% CI 0.5%–17.6%), and the RD for levodopa plus selegiline compared to bromocriptine was 10.7% (95% CI

2.2%–19.0%). There was no significant difference in the risk of moderate to severe dyskinesia between groups.

The final, fourteen-year report[7] included 166 participants (21% of the original cohort). After a median follow-up period of 14 years, 11 of the 67 participants originally randomized to bromocriptine remained on the drug (mean dose of 49 mg/d). None of these participants were on monotherapy. The mean daily dose of levodopa was 696 mg in participants originally randomized to levodopa and 618 mg in participants originally randomized to bromocriptine. With respect to motor disability, Webster scores showed a small but significant advantage in the levodopa arm compared to the bromocriptine arm, which remained significant after correction of baseline differences (data presented graphically only). The prevalence of dyskinesia, including moderate or severe dyskinesia, was not significantly different between the levodopa and bromocriptine arms.

Levodopa vs levodopa plus selegiline vs bromocriptine vs bromocriptine plus selegiline

One Class II study compared the effect of levodopa, levodopa plus selegiline, bromocriptine, and bromocriptine plus selegiline in 101 PD patients in Hoehn and Yahr stages 1 through 3.[8] In patients randomized to the bromocriptine groups, levodopa could be added to treatment if needed after a minimum daily dose of 20 mg of bromocriptine was reached. The mean daily dose of levodopa was 426 mg in the levodopa group, 382 mg in the levodopa plus selegiline group, 117 mg in the bromocriptine group, and 85 mg in the bromocriptine plus selegiline group. Although the primary outcome of this study was related to disease progression, the effect of each treatment on motor symptoms was assessed after 12 months. The change between groups on the UPDRS

part III score, while greater in those receiving levodopa, was not statistically significant, with an RMD of -3.2 (95% CI -7.5 to 1.1). Adverse effects of treatment are not described in the manuscript, which states that no clinically significant adverse effects were encountered. There was no difference between groups in the incidence of side effects.

Levodopa vs bromocriptine

The Sydney Multicentre Study of Parkinson's Disease was a randomized controlled trial of 129 individuals with de novo PD comparing bromocriptine (less than 30 mg/d) to levodopa/carbidopa (LC) (less than 600 mg/d). The primary outcomes studied were dyskinesia and on-off phenomena. Outcomes were reported at 3 years in a Class II study[9] and 5 years in a Class IV study.[10] At 3 years,[9] only 1 participant originally randomized to bromocriptine remained on bromocriptine alone; all other participants were either switched to levodopa, or levodopa was added to bromocriptine due to insufficient treatment response. Involuntary movements were the main reason for breaking the treatment code in patients receiving levodopa. Dyskinesia began at a mean of 16 months (with a range of 7–24 months) after commencing LC. Six of the 32 participants remaining on levodopa at 2 years developed dyskinesia. The RD for dyskinesia with levodopa compared to bromocriptine was 18.8% (95% CI 2.9%–35.3%). With respect to the severity of parkinsonism, more patients improved to a greater extent on levodopa compared to bromocriptine. After 2 years, the modified Columbia score for patients still on their initial randomized therapy improved in 18 of 26 patients randomized to levodopa by a mean of 42% (with a range of 6%–60%). The modified Columbia score improved in 5 of the 14 patients randomized to bromocriptine by a mean of 16% (with a range of 9%–33%).

At 5 years of follow-up,[10] no patients were on bromocriptine alone. The mean daily dose of levodopa was 471 mg in those randomized to and remaining on levodopa alone, 559 mg in those randomized to levodopa who had bromocriptine added on over the course of treatment, 615 mg in those randomized to bromocriptine who had levodopa added on over the course of treatment, and 554 mg in those randomized to bromocriptine who switched to levodopa over the course of treatment. These dose differences were not statistically significant. With respect to the severity of parkinsonism at 5 years, 11 of the 30 patients initially randomized to bromocriptine deteriorated compared to baseline on the modified Columbia score, while 11 of the 31 patients initially randomized to levodopa deteriorated compared to baseline. At 5 years, dyskinesia was significantly more frequent in patients originally randomized to levodopa compared to bromocriptine, with a RD of 27.3% (95% CI 10.1%–42.3%). The severity of dyskinesia was rated as mild in 71% of the levodopa group and 76% of the bromocriptine group.

A Class IV study compared bromocriptine with levodopa over 3 years of follow-up in 28 individuals with PD who had previously been untreated with dopaminergic medications.[11] Fifteen patients received bromocriptine at a mean daily dose of 50 mg, and 13 received levodopa at a mean daily dose of 444 mg. The primary outcome of the study was not specified. There was no statistical difference in scores on the Columbia University Rating Scale between the bromocriptine and levodopa groups at any point in the study. Both groups of patients improved compared to pre-treatment values over the three-year period. Over the three-year follow-up period, abnormal movements occurred in 4 of the 13 patients randomized to levodopa; 3 of these patients developed peak dose dyskinesia and 1 had foot dystonia. In those treated with bromocriptine, acute psychosis developed in 1 of the 15 patients, there was a primary lack of

efficacy in 3 patients, and a secondary decrease in efficacy in 2 patients, requiring levodopa to be added.

A Class IV study of 60 previously untreated patients with PD compared initial treatment with levodopa to initial treatment with bromocriptine. Levodopa was later added to the bromocriptine group when a decline in efficacy of the maximum tolerated dose of bromocriptine occurred or when bromocriptine-induced side effects necessitated lowering the dose.[12] All but 4 patients initially randomized to bromocriptine had levodopa added to their treatment by the end of the five-year follow-up period. The primary endpoint was defined as the moment when the first motor complication occurred: peak dose or biphasic dyskinesia/dystonia, or wearing-off or on-off phenomena. A significantly greater proportion of patients randomized to levodopa had motor complications at 5 years compared to those randomized to bromocriptine, with an RD of 33.7% (95% CI, 10%–53.8%). A significantly greater proportion of those randomized to levodopa had peak dose dyskinesia at 5 years compared to bromocriptine, with an RD of 36.3% (95% CI 11.6%–55.3%). There was a significant difference in the mean time to reach the endpoint of first motor complication, with the levodopa group reaching this at 2.7 years from first treatment, compared to 4.9 years in the bromocriptine group ($p<0.01$). When counting from the start of levodopa therapy, there was no difference between groups in the mean time to reach the first motor complication, with the members of the bromocriptine group who also started levodopa developing motor complications at 2.2 years vs 2.7 years in the levodopa group. The most common motor complication was wearing-off in those randomized to bromocriptine and dyskinesia in those randomized to levodopa. There was no difference between groups in the

UPDRS part III score at 5 years. There was no difference between groups in the occurrence of hallucinations or confusion.

Levodopa vs bromocriptine vs levodopa plus bromocriptine

A Class III study compared early combination therapy with levodopa plus bromocriptine to levodopa and bromocriptine monotherapy over 4 years in 22 patients with PD not previously treated with levodopa or bromocriptine.[13] The primary outcome of the study was not specified. Participants were randomized to bromocriptine monotherapy (mean dose of 18 mg/d, n=6), levodopa monotherapy (mean dose of 417 mg/d, n=9), or levodopa plus bromocriptine combination therapy (mean dose of bromocriptine 14 mg/d, mean dose of levodopa 386 mg/d, n=7). The effect of the therapies on the patients' motor symptoms was evaluated using a modified version of the Columbia University Rating Scale. Participants randomized to bromocriptine monotherapy experienced a maximal decrease in score by 1 month, but the degree of improvement was not significant when compared with baseline scores. After 1 month, the mean motor score became progressively worse despite increasing bromocriptine doses and exceeded baseline scores after 15 months. At no time did bromocriptine monotherapy result in significant improvement of motor examination scores. With levodopa monotherapy, a statistically significant improvement in motor examination scores was present at 3 months ($p<0.03$) and peak improvement occurred at 6 months ($p<0.0001$). The motor examination score remained consistently below baseline throughout the study. With combination levodopa and bromocriptine therapy, peak improvement in motor examination score occurred at 3 months, but the degree of improvement never reached significance compared with baseline. A one-way ANOVA revealed no significant difference between the 3 groups at any time. For late

complications of therapy, significantly more participants treated with levodopa experienced dystonia compared to those treated with bromocriptine monotherapy, with an RD of 66.7% (95% CI 19.3%–90.3%). There was no difference in motor fluctuations, chorea, or freezing between treatment groups.

Levodopa vs levodopa plus bromocriptine

Three studies compared treatment with levodopa to treatment with levodopa plus bromocriptine in early PD. One Class II study compared levodopa (maximum dose of 750 mg/d) plus bromocriptine (10 mg three times per day) with levodopa (maximum dose of 750 mg/d) plus placebo in 31 participants with early PD who had been taking up to 750 mg of levodopa per day for less than two years.[14] In participants randomized to levodopa plus bromocriptine, a non-masked investigator substituted bromocriptine for levodopa according to a substitution schedule, with the goal of reducing the pre-study levodopa dosage by 60%. Participants were followed for one year. The mean dose of levodopa at one year was 136 mg/d in the levodopa plus bromocriptine group, and 361 mg/d in the levodopa plus placebo group ($p<0.01$). The mean scores on the Northwestern University Disability Scale for the combination treatment group at three, six, and 12 months were 46.2, 46.4, and 46.0 respectively, while the levodopa monotherapy group had mean scores of 45.7, 45.6, and 45.5. The difference between the two groups using an analysis of covariance for repeated measure design was statistically significant ($p=0.04$), favoring combination therapy. Withdrawal due to side effects occurred in three of the 16 participants in the combination therapy group, and none of the participants in the levodopa monotherapy group.

One Class IV study of patients with early PD evaluated whether the addition of bromocriptine in patients already on levodopa allowed levodopa dose reduction and reduced the frequency of motor complications compared to levodopa monotherapy.[15] Participants demonstrating a response to levodopa introduced two to six months prior to entering the study were randomized to receive bromocriptine (maximum of 30 mg/d) or placebo and followed for a period of 44 months. Once the target bromocriptine dosage was reached, attempts were made to lower the levodopa dosage. The mean daily levodopa dosage at 44 months was significantly lower in participants randomized to levodopa plus bromocriptine (515.4 mg), compared to levodopa plus placebo (725.6 mg) (p<0.01). The mean daily bromocriptine dose was 24.2 mg. The number of patients reporting choreic dyskinesia at 44 months was significantly higher in the levodopa group compared to the levodopa plus bromocriptine group, with an RD of 27.3% (95% CI 1.1%–50.5%). The change in the UPDRS part III scores from baseline to 44 months was not significantly different between groups, with an RMD of 9.9 (95% CI -1.9 to 21.7) favoring levodopa plus bromocriptine.

One Class IV study[16,17] compared levodopa to levodopa plus bromocriptine in 587 drug naïve de novo patients with PD. The study began with three months of levodopa monotherapy for both groups, followed by gradual substitution of up to 30–50% of the levodopa dosage with bromocriptine in the levodopa plus bromocriptine group between the third and sixth months of the study. Patients were followed for four years assessing the primary endpoints of time of onset of the first manifestation of any side effect, and the cumulative sum score covering all assessments during the study. At four years, the mean daily dose of levodopa was 439 mg in the monotherapy group, and was 308 mg, with 13.8 mg of bromocriptine, in the levodopa plus

bromocriptine group. Motor side effects were more common in the levodopa monotherapy group, with a RD of 8.8% (95% CI 1.8%–15.6%). The mean time until first occurrence of some motor side effect was 3.18 years in the levodopa monotherapy group and 3.43 years in the levodopa plus bromocriptine group; the standard error (SE) was 0.08 years for both groups. The cumulative probability of experiencing the first motor complication within four years decreased with the amount of levodopa that was substituted with bromocriptine. There was no difference between groups in the risk of hallucinations. AE-related discontinuation was significantly higher in the levodopa plus bromocriptine group, with a RD of 9.1% (95% CI 4.4%–14.0%).

Levodopa vs MAO-B inhibitors vs DAs

There is one large Class IV study comparing the long-term effectiveness of DAs and MAO-B inhibitors with levodopa as the initial treatment for PD.[18] In this trial, individuals with early PD that was untreated or had been treated for less than six months could be randomized to levodopa, DAs, or MAO-B inhibitors. Either MAO-B inhibitors or levodopa could be omitted from the randomization if considered inappropriate for a particular patient. A total of 1620 participants were randomized, with 632 receiving a DA, 460 receiving a MAO-B inhibitor, and 528 receiving levodopa. The primary outcomes of the study were the mobility dimension on the 39-item patient-rated Parkinson's Disease Questionnaire (PDQ-39), and cost effectiveness.

The mean daily levodopa dosage at one year was 131 mg (SD 172) in participants randomized to MAO-B inhibitors, 96 mg (SD 157) in those allocated to DAs, and 347 mg (SD 139) in those allocated to levodopa. At 7 years, the mean daily levodopa dosage was 489 mg (SD 246) in the MAO-B inhibitor group, 526 mg (SD 266) in the DA group, and 531 mg (SD 229) in the

levodopa group. The two-year probability of requiring a drug from another class added to their treatment was significantly lower (p<0.0001) in those allocated to levodopa (20%) compared to those allocated to MAO-B inhibitors (64%), and those allocated to DAs (40%). PDQ-39 mobility scores did not differ significantly between the levodopa group and levodopa-sparing group at any follow-up assessment. However, the average score during the first seven years of follow up was 1.8 points (95% CI 0.5–3.0; p=0.005) better with levodopa than with levodopa-sparing therapy, and averaged 1.4 points (95% CI 0.0–2.9; p=0.05) better in patients initiating therapy with MAO-B inhibitors than DAs.

Patients in the levodopa group were more likely to develop dyskinesia than those in the levodopa-sparing group, with a hazard ratio (HR) of 1.52 (95% CI 1.16–2.00; p=0.003). Rates of dyskinesia were similar (HR 0.85, 95% CI 0.6–1.22; p=0.4) in the DA and MAO-B inhibitor groups. The rate of discontinuation of allocated drug over seven years was significantly lower in participants allocated to levodopa (7%), compared to MAO-B inhibitors (72%) and DAs (50%) (p<0.0001). Similarly, AE-related discontinuation was significantly lower in participants allocated to levodopa (2%) compared to MAO-B inhibitors (23%) and DAs (28%) (p<0.0001).

One Class IV study compared levodopa with the DAs lisuride or bromocriptine, or the MAO-B inhibitor selegiline in the treatment of early PD in 475 participants over three years.[19,20] Participants were randomized to levodopa (maximum dose of 750 mg/d), lisuride (maximum dose of 3 mg/d), bromocriptine (maximum dose of 60 mg/d), or selegiline (maximum dose of 10 mg/d). Those initially randomized to the DAs or to selegiline could add levodopa whenever required. The primary outcome was the occurrence of motor fluctuations and dyskinesia.

Participants randomized to levodopa were significantly more likely to have dyskinesia at three years compared to those given DAs, with an RD of 12.1% (95% CI 3.2%–20.9%). There was no difference in the occurrence of dyskinesia between the groups assigned to levodopa and selegiline, or between the groups assigned to DAs and selegiline. Treatment withdrawal was significantly higher in participants randomized to DAs compared to those in the levodopa group (RD 26.3%, 95% CI 17.9%–34.4%). Participants randomized to selegiline were more likely to withdraw from treatment than those in the levodopa group (RD 12.9%, 95% CI 5.6%–20.5%).

Levodopa vs pramipexole

One study compared pramipexole with levodopa as an initial treatment for PD. Individuals with PD requiring dopaminergic therapy at the time of enrollment were randomized to pramipexole (n=151, mean dose of 2.78 mg/d, maximum dose of 4.5 mg/d) or levodopa (n=150, mean dose of 406 mg/d, maximum dose of 600 mg/d), with open label levodopa prescribed to both groups as needed. Reports were published after two years,[21] four years,[22] and six years[23] of follow-up. The primary outcome of the study was the amount of time until the first occurrence of any of three specified dopaminergic complications: wearing-off, dyskinesia, or on-off fluctuations.

In the two-year follow-up report,[21] which was rated Class I, the proportion of participants requiring supplemental levodopa was significantly greater in the pramipexole group (53%) than in the levodopa group (39%), with an HR of 1.54 (95% CI 1.09–2.17; p=0.02). The proportion of participants who reached the primary endpoint (first dopaminergic complications) by two years was significantly higher in the levodopa group compared to the pramipexole group, with an RD of 22.9% (95% CI 11.9%–33.1%). Dyskinesia (RD 20.7%, 95% CI 11.8%–29.4%) was

significantly more common in participants randomized to levodopa than pramipexole. The mean improvement from baseline to two years in the UPDRS part III score was significantly greater in participants randomized to levodopa than pramipexole, with a mean difference between treatments of -3.9 (95% CI -5.7 to -2.1; $p<0.001$). Significantly fewer patients receiving levodopa experienced hallucinations (RD -5.9%, 95% CI -11.9 to -0.3%), while AE-related discontinuation was similar between groups.

The four-year follow-up report[22] was rated Class II as fewer than 80% of participants completed the study. The percentage of participants requiring open-label levodopa was higher in the pramipexole group (72%) than in the levodopa group (59%), with an HR of 1.64 (95% CI 1.22–2.21; $p=0.001$). The mean total daily levodopa dosage was 434 (SD 498 mg) in the pramipexole group and 702 (SD 442 mg) in the levodopa group. The percentage of participants reaching the primary end point of dyskinesia, wearing-off, or on-off fluctuations, was significantly higher in participants allocated to levodopa than those allocated to pramipexole, with an RD of 22.3% (95% CI 11.5%–32.5%). Dyskinesia (RD 29.5%, 95% CI 18.6%–39.4%) was more common in participants in the levodopa group than those in the pramipexole group. The mean improvement in the UPDRS part III score from baseline to month 48 was significantly greater in participants randomized to levodopa, with a mean treatment effect of -4.9 (95% CI -7.8 to -1.9; $p=0.001$). There was no difference between groups in the rate of hallucinations.

The six-year follow-up report[23] was rated Class IV as this was an open label, two-year extension of the previous study. Of the original trial participants, 108 patients randomized to pramipexole and 114 patients randomized to levodopa entered the open label extension study. At the final

visit, 69% continued to take pramipexole and 91% were taking levodopa. Dyskinesia was significantly higher in the levodopa group, with an RD of 16.5% (95% CI 4.6%–27.7%). Only 7 participants (3 in the initial pramipexole group and 4 in the initial levodopa group) reported dyskinesia that was at least moderately disabling, and only 10 participants (6 in the initial pramipexole group and 4 in the initial levodopa group) reported having painful dyskinesia at the final visit. The change in the UPDRS part III score from baseline favored the levodopa group but was not statistically significant (treatment effect -2.7, 95% CI -5.9 to 0.6; p=0.1).

Levodopa vs ropinirole

There is one Class I study comparing ropinirole with levodopa in individuals with early PD.[24] Included participants were not previously treated with levodopa or DAs. Eighty-seven participants were randomized to ropinirole, with a mean dose at two years of 12.2 mg/d, and 75 participants were randomized to levodopa, with a mean dose at two years of 558.7 mg/d. Motor function at two years was superior in participants randomized to levodopa, with the adjusted mean change in UPDRS part III scores from baseline to endpoint increasing by 0.70 points with ropinirole and decreasing by 5.64 points with levodopa.

The incidence of dyskinesia was significantly higher in participants randomized to levodopa, with an RD of 23.2% (95% CI 12.5%–34.4%). Participants on ropinirole also took longer to develop dyskinesia than those on levodopa with an HR of 8.28 (95% CI 2.46–27.93; p<0.001). The RD for the occurrence of hallucinations and AE-related discontinuation was not significantly different between groups.

One Class II study compared ropinirole with levodopa in individuals with early PD who required dopaminergic therapy.[25] Participants were randomized to treatment with ropinirole up to 24 mg/d, or levodopa up to 1200 mg/d for five years. Of the 268 individuals randomized, 179 received ropinirole and 89 received levodopa. The primary outcome of the study was the incidence of dyskinesia. At study completion, the mean daily dose of ropinirole was 16.5 mg (SD 6.6) plus 427 mg (SD 221) of open label levodopa supplementation in individuals randomized to ropinirole, and 753 mg (SD 398) of levodopa in individuals randomized to levodopa. Dyskinesia developed in a significantly higher proportion of participants randomized to levodopa, with an RD of 25.1% (95% CI 13.2%–36.8%). The proportion of participants with disabling dyskinesia was significantly higher in the levodopa group compared to the ropinirole group, with an RD of 14.7% (95% CI 5.8%–24.8%). The mean decrease from baseline in UPDRS part III score was significantly greater with levodopa than ropinirole, with a mean difference of 4.48 (95% CI 1.25–7.72; p=0.008).

There were no significant differences between groups in study withdrawal due to lack of efficacy, or AE-related study withdrawal. Hallucinations were significantly more frequent in the ropinirole group, with an RD of 11.7% (95% CI 3.3%–18.7%).

Patients in the previous study were invited to participate in an open label extension study[26] (Class IV) which followed participants for a total of ten years post randomization to initial therapy with ropinirole or levodopa. Of the original 268 participants randomized, only 69 entered the extension study, with 28 from the original ropinirole group and 20 from the original levodopa group completing the extension study. At the final visit at 10 years, 76% of those originally

randomized to ropinirole continued to take it, at a mean dose of 14.5 mg/d, and 93% were taking levodopa, at a mean dose of 631.7 mg/d. In participants originally randomized to levodopa, 33% were taking ropinirole at the ten-year visit, at a mean dose of 11.3 mg/d, and 93% were taking levodopa, at a mean dose of 800.2 mg/d. No significant differences between groups were identified in the change in UPDRS part III scores from the original double-blind study baseline to the extension endpoint. The risk of having dyskinesia was significantly higher in patients originally randomized to levodopa compared to ropinirole, with an RD of 25.4% (95% CI 2.0%–44.1%). Median time to the development of dyskinesia was significantly longer in patients originally randomized to ropinirole, 3156 days (8.6 years), compared to levodopa, 2563 days (seven years), with an adjusted HR of 0.4 (95% CI 0.2–0.8; p=0.007). There was no significant difference between groups in the odds of exhibiting at least mildly disabling dyskinesia.

Levodopa plus ropinirole vs levodopa

One Class II study compared add-on prolonged-release (PR) ropinirole with additional levodopa in PD patients suboptimally controlled on levodopa.[27] Participants were randomized to ropinirole PR, with a maximum daily dose of 24 mg (mean dose 10 mg, n=105), or additional levodopa, with a maximum daily dose of 1000 mg added to the patient's baseline levodopa dosage (mean dose added 284 mg/day, n=104) and followed for two years. The primary endpoint was the time to onset of dyskinesia confirmed at two subsequent study visits. The number of patients developing dyskinesia was significantly higher in the levodopa monotherapy group, with an RD of 14.4% (95% CI 6.5%–23.1%). There was a significant delay in the time to onset of dyskinesia for participants treated with ropinirole PR compared with those treated with levodopa alone, with

an HR of 6.46, $p<0.001$. There was no significant difference in the mean change in UPDRS part III score from baseline to week 28, or in the number of AE-related withdrawals between groups.

Levodopa vs cabergoline

The long-acting DA cabergoline was compared to levodopa in 419 newly diagnosed PD patients in a Class II study.[28] Participants were followed until confirmed development of motor complications, or up to a minimum of three years and maximum of five years. Participants randomized to cabergoline received a flexible dose up to 4 mg/d (mean dose 2.8 mg/d). Levodopa could be added if necessary. Participants randomized to levodopa received up to 600 mg/d. The primary efficacy endpoint was the development of motor complications confirmed at two consecutive three-monthly visits.

The mean daily levodopa dosage at five years was 431 mg in participants randomized to cabergoline and 784 mg in participants randomized to levodopa. The presence of dyskinesia was significantly higher in participants randomized to levodopa with an RD of 11.7% (95% CI 4.8%–18.5%). Mean UPDRS part III scores over time were significantly lower ($p<0.01$) in the levodopa group than in the cabergoline group, with mean values of 13.8 in the cabergoline group vs 12.9 in the levodopa group at one year, 18.6 vs 17.2 at three years, and 19.2 vs 16.3 at five years. The RMD between groups at five years was 2.9 (95% CI 0.7–5.1). There was no significant difference between groups in AE-related premature study discontinuation or hallucinations.

One Class II study[29] compared cabergoline to levodopa for three years in 412 previously untreated PD patients. Participants were randomized to cabergoline, with a maximum daily dose of 4 mg (median dose of 3 mg), or levodopa, with a maximum daily dose of 600 mg (median dose of 500 mg). Open label levodopa could be added in both treatment arms. The primary endpoint of the study was the onset of motor complications confirmed at two subsequent visits. Participants randomized to levodopa were significantly more likely to reach the primary endpoint than those treated with cabergoline, with an RD of 11.7% (95% CI 3.0%–20.2%). Participants randomized to levodopa were also significantly more likely to develop peak dose dyskinesia, with an RD of 8.0% (95% CI 2.2–13.9). Compared to baseline, after four years, levodopa recipients showed an average 30% improvement in motor disability on the UPDRS part III, while cabergoline recipients showed a 22% improvement. There was no difference between groups in treatment withdrawal.

One Class IV study[30] compared cabergoline to levodopa for five years in 98 previously untreated PD patients. If it was necessary to start additional therapy for PD symptoms, levodopa or cabergoline could be added to the randomized treatment. Participants were randomized to cabergoline, with a maximum dose of 6 mg/d (mean dose of 2.9 mg), or levodopa, with a maximum dose of 600 mg/d (mean dose 336 mg). Participants in the cabergoline group added a mean dose of 325 mg/d of levodopa, while participants in the levodopa group added a mean dose of 1.6 mg/d of cabergoline. The primary endpoint was the development of motor complications, defined as dyskinesia, wearing-off, or on-off motor fluctuations. Motor complications and changes from baseline to five years in the UPDRS part III score were not significantly different between the initial cabergoline and levodopa groups. AE-related discontinuation was

significantly more frequent in the cabergoline treated group, with an RD of 18.4% (95% CI 4.9%–32.1%).

Levodopa vs pergolide

One Class III study compared pergolide to levodopa monotherapy in patients with early PD.[31] The three-year study randomized 294 patients to pergolide monotherapy, up to a maximum dose of 5mg/d (mean dose at 3 years of 3.23 mg/d) or levodopa monotherapy, up to a maximum dose of 1200 mg/d (mean dose at 3 years of 504 mg/d). The main outcome measures of the study included clinical efficacy, severity, time to onset of motor complications, and disease progression. There was significantly greater clinical improvement compared to baseline with levodopa than with pergolide as measured on part III of the UPDRS at both one and three years. At one year, the RMD was -1.92 (95% CI -3.4 to -0.43). At three years, the RMD was -5.6 (95% CI -7.6 to -3.6). The incidence of dyskinesia was significantly lower with pergolide compared to levodopa, with an RD of -17.9% (95% CI -26.3% to -9.4%). Time to onset of dyskinesia, defined by the first positive UPDRS part IVa score, was longer in the pergolide group than in the levodopa group. The HR for developing dyskinesia in the pergolide group vs the levodopa group was 0.48 (95% CI 0.29–0.80). AE-related discontinuation was not significantly different between groups. Hallucinations were more common in the pergolide group, with an RD of 3.4% (95% CI 0.2%–7.7%).

One Class IV study compared pergolide to levodopa over a period of ten months as an initial treatment for individuals with PD.[32] Thirty-six participants were randomized to a daily dose of 0.2 mg of trihexyphenidyl, 500 mg of levodopa, or 0.2 mg of pergolide. At ten months, there was

no significant difference in total UPDRS scores between participants in the levodopa group and the pergolide group (RMD -3.96, 95% CI -10.91 to 2.99).

Levodopa vs levodopa plus lisuride

One Class IV study[33] compared levodopa monotherapy with levodopa plus lisuride in individuals with early PD. Eighty-two participants were randomized to five years of treatment with levodopa monotherapy or combination therapy with levodopa and lisuride, with10 mg/d of selegiline added to both groups after one year. The primary outcome of the study was the progression of levodopa dosage and total scores on the UPDRS. At five years, the dose of levodopa in the monotherapy group was 446.7 mg/d vs 387.5 mg/d in the combination therapy group, but the difference was not statistically significant. No significant difference between groups was observed in the incidence of dyskinesia.

Synthesis of data and confidence in evidence statements for levodopa vs DAs

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. Negative values favored levodopa. Where possible, estimates were combined using meta-analysis at specific time points. The minimal clinically important difference in the UPDRS part III score was determined by consensus to be three points; changes of one point or less were considered unimportant.

Table 1. Change in UPDRS part III score from baseline to endpoint

Study	Class	Time point	RMD (95% CI)
Watts 2010	II	6 months	0.2 (-2.32 to 2.72)
Conclusion (low confidence): In early PD, levodopa is possibly no more effective than DAs (with or without levodopa) in improving motor function at six months.			
Oertel 2006	III	1 year	-1.92 (-3.4 to -0.43)
Olanow 1995	II	1 year	-3.2 (-7.5 to 1.1)
Summary effect estimate (random effects meta-analysis)			-2.06 (-3.46 to -0.65)
Conclusion (low confidence): In early PD, levodopa is possibly more effective than DAs (with or without levodopa) in improving motor function at one year.			
Parkinson Study Group 2000	I	2 years	-3.9 (-5.7 to -2.1)
Whone 2003	I	2 years	-6.34 (-9.14 to -3.54)
Summary effect estimate (random effects meta-analysis)			-4.88 (-7.22 to -2.53)
Conclusion (moderate confidence): In early PD, levodopa is likely more effective than DAs (with or without levodopa) in improving motor function at two years.			
Oertel 2006	III	3 years	-5.6 (-7.6 to -3.6)
Conclusion (very low confidence): In early PD, 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.			
Parkinson Study Group 2004	II	4 years	-4.9 (-7.8 to -1.9)
Conclusion (low confidence): In early PD, levodopa is possibly more effective than DAs (with or without levodopa) in improving motor function at 4 years.			
Bracco 2004	II	5 years	-2.9 (-5.1 to -0.7)
Rascol 2000	II	5 years	-4.48 (-7.72 to -1.25)
Summary effect estimate (random effects meta-analysis)			-3.4 (-5.22 to -1.58)
Conclusion (moderate confidence): In early PD, levodopa is likely more effective than DAs (with or without levodopa) in improving motor function at 5 years.			
Parkinson Study Group 2009	IV	6 years	-2.7 (-5.9 to 0.6)
Conclusion (very low confidence): In early PD, 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.			
Hauser 2007	IV	10 years	-3.2 (-12.1 to 5.6)
Conclusion (very low confidence): In early PD, 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.			

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 five years of follow-up. Data beyond five years are scarce and of low quality. With longer periods of follow-up, an increasing proportion of

participants originally randomized to DAs were taking supplemental levodopa, therefore minimizing the difference between groups for this outcome.

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. 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 minimal clinically important difference in the risk of dyskinesia was determined by consensus to be 15%; RDs equal to or less than 5% were considered clinically unimportant.

Table 2. Risk of dyskinesia

Study	**Class**	**Time point**	**RD (95% CI)**
Hely 1989	II	2 years	18.8% (2.9%–35.3%)
Parkinson Study Group 2000	I	2 years	20.7% (11.8%–29.4%)
Watts 2010	II	2 years	14.4% (6.5%–23.1%)
Whone 2003	I	2 years	23.2% (12.5%–34.4%)
Summary effect estimate (random effects meta-analysis)			18.7% (13.7%–23.8%)
Conclusion (moderate confidence): In early PD, levodopa is probably more likely than DAs (with or without levodopa) to induce dyskinesia at two years.			
Caraceni 2001	IV	3 years	12.1% (3.2%–20.9%)
Oertel 2006	III	3 years	17.9% (9.4%–26.3%)
PD Research Group UK 1993	IV	3 years	25% (19.3%–30.9%)
Rinne 1998	II	3 years	8% (2.2%–13.9%)
Summary effect estimate (random effects meta-analysis) (excludes Caraceni 2001 and PD Research Group UK 1993)			12.5% (2.8%–22.1%)
Conclusion (low confidence): In early PD, levodopa is possibly more likely than DAs (with or without levodopa) to induce dyskinesia at three years.			
Gimenez-Roldan 1997	II	4 years	27.3% (1.1%–50.5%)
Parkinson Study Group 2004	II	4 years	29.5% (18.6%–67.9%)

Weiner 1993	III	4 years	38.9% (-10.2% to 67.9%)
Summary effect estimate (random effects meta-analysis) (excludes Weiner 1993)			29.2% (19.6%–38.8%)
Conclusion (moderate confidence): In early PD, levodopa is probably more likely than DAs (with or without levodopa) to induce dyskinesia at four years.			
Allain 2000	IV	5 years	14.6% (-4.6% to 32.5%)
Bracco 2004	II	5 years	11.7% (4.8%–18.5%)
Hely 1994	IV	5 years	27.3% (10.1%–42.3%)
Montastruc 1994	IV	5 years	36.3% (11.6%–55.3%)
Rascol 2000	II	5 years	25.1% (13.2%–36.8%)
Summary effect estimate (random effects meta-analysis) (excludes Allain 2000, Hely 1994, and Montastruc 1994)			17.5% (4.5%–30.5%)
Conclusion (low confidence): In early PD, levodopa is possibly more likely than DAs (with or without levodopa) to induce dyskinesia at five years.			
Parkinson Study Group 2009	IV	6 years	16.5% (4.6%–27.7%)
Conclusion (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 six years.			
PD Med Collaborative Group 2014	IV	7 years	7.1% (2.4%–11.8%)
Conclusion (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 seven years.			
Hauser 2007	IV	10 years	25.4% (2%–44.1%)
Lees 2001	IV	10 years	9.2% (0.5%–17.6%)
Summary effect estimate (random effects meta-analysis)			14.3% (-0.4% to 29.1%)
Conclusion (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 ten years.			
Katzenschlager 2008	IV	14 years	1.6% (-17.3% to 20%)
Conclusion (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 fourteen years.			

The trend over time demonstrates that levodopa is more likely to induce dyskinesia than DAs. Data beyond five years of follow-up is of low quality, leading to insufficient evidence to make a conclusion.

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. 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 minimal clinically important difference in the risk of hallucinations was determined by consensus to be 10%; RDs equal to or less than 3% were considered clinically unimportant.

Table 3. Risk of hallucinations

Study	**Class**	**Time point**	**RD (95% CI)**
Parkinson Study Group 2000	I	2 years	-5.9% (-11.9% to 0.3%)
Whone 2003	I	2 years	-5.5% (-13% to 1.4%)
Summary effect estimate (random effects meta-analysis)			-5.7% (-10.3% to -1.2%)
Conclusion (low confidence): In early PD, DAs (with or without levodopa) are possibly more likely than levodopa to induce hallucinations at two years.			
Oertel 2006	III	3 years	-3.4% (-7.7% to -0.2%)
Conclusion (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 hallucinations at three years.			
Parkinson Study Group 2004	II	4 years	-6.6% (-13.9% to 0.7%)
Przuntek 1996	IV	4 years	1% (-2.9% to 4.9%)
Summary effect estimate (random effects meta-analysis) (excludes Przuntek 1996)			-6.6% (-13.9% to 0.7%)

Conclusion (low confidence): In early PD, DAs (with or without levodopa) are possibly no more likely than levodopa to induce hallucinations at four years.			
Bracco 2004	II	5 years	-0.4% (-4.7% to 3.8%)
Montastruc 1994	IV	5 years	-13.1% (-32.9% to 5.6%)
Rascol 2000	II	5 years	-11.7% (-18.7% to -3.3)
Summary effect estimate (random effects meta-analysis) (excludes Montastruc 1994)			-5.6% (-16.6% to 5.5%)
Conclusion (low confidence): In early PD, DAs (with or without levodopa) are possibly no more likely than levodopa to induce hallucinations at five years.			

The trend demonstrates that while 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. 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 minimal clinically important difference was determined by consensus to be 15%; RDs equal to or less than 5% were considered clinically unimportant.

Table 4. Risk of AE-related discontinuation of treatment

Study	**Class**	**Time point**	**RD (95% CI)**
Bakheit 1990	II	1 year	-18.8% (-43% to 5%)
Conclusion (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 cause medication discontinuation due to adverse effects at one year.			

Parkinson Study Group 2000	I	2 years	-4.6% (-11.3% to 2%)
Watts 2010	II	2 years	-5.6% (-14.6% to 3.2%)
Whone 2003	I	2 years	-9.6% (-19% to 0%)
Summary effect estimate (random effects meta-analysis)			-6.1% (-10.7% to -1.4%)
Conclusion (low confidence): In early PD, DAs (with or without levodopa) are possibly more likely than levodopa to cause medication discontinuation due to adverse effects at two years.			
Caraceni 2001	IV	3 years	-26.3% (-33.3% to -17.9%)
Oertel 2006	III	3 years	-6.7% (-14.8% to 1.4%)
PD Research Group UK 1993	IV	3 years	-36.7% (-44.3% to -28.3%)
Rinne 1998	II	3 years	-2.6% (-9.5% to 4.3%)
Summary effect estimate (random effects meta-analysis) (excludes Caraceni 2001 and PD Research Group UK 1993)			-4.3% (-9.6% to 0.9%)
Conclusion (low confidence): In early PD, DAs (with or without levodopa) are possibly no more likely than levodopa to cause medication discontinuation due to adverse effects at three years.			
Przuntek 1996	IV	4 years	-9.1% (-14% to -4.4%)
Conclusion (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 cause medication discontinuation due to adverse effects at four years.			
Bracco 2004	II	5 years	-5.9% (-13.1% to 1.3%)
Rascol 2000	II	5 years	5.8% (-5.5% to 17.7%)
Utsumi 2012	IV	5 years	-18.4% (-32.1% to -4.9%)
Summary effect estimate (random effects meta-analysis) (excludes Utsumi 2012)			-1% (-12.3% to 10.4%)
Conclusion (moderate confidence): In early PD, DAs (with or without levodopa) are probably no more likely than levodopa to cause medication discontinuation due to adverse effects at five years.			
PD Med Collaborative Group 2014	IV	7 years	-26.2% (-30% to -22.5%)
Conclusion (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 cause medication discontinuation due to adverse effects at ten years.			

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

Synthesis of data and confidence in evidence statements for levodopa vs MAO-B inhibitors

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

Dyskinesia

Table 5. Risk of dyskinesia

Study	**Class**	**Time point**	**RD (95% CI)***
Caraceni 2001	IV	3 years	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 to induce dyskinesia at three years.			
PD Med Collaborative Group 2014	IV	7 years	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 to induce dyskinesia at seven years.			

*Positive values indicate that the risk is higher with levodopa.

While 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.

AE-related discontinuation of treatment

Table 6. Risk of AE-related discontinuation of treatment

Study	**Class**	**Time point**	**RD (95% CI)***

Caraceni 2001	IV	3 years	-12.9% (-20.5% to -5.6%)
Conclusion (very low confidence): There is insufficient evidence to determine whether, in early PD, levodopa is more or less likely than MAO-B inhibitors to cause medication discontinuation due to adverse effects at three years.			
PD Med Collaborative Group 2014	IV	7 years	-20.5% (-24.7% to -16.6%)
Conclusion (very low confidence): There is insufficient evidence to determine whether, in early PD, levodopa is more or less likely than MAO-B inhibitors to cause medication discontinuation due to adverse effects at seven years.			

*Negative values indicate that the risk is higher with MAO-B inhibitors.

While the trend over time shows that AE-related discontinuation of treatment is higher with MAO-B inhibitors than with levodopa, confidence in the evidence is very low due to the quality of studies.

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?

Ropinirole vs pramipexole

One Class II study[34] compared ropinirole with pramipexole in 52 previously untreated individuals with PD. Participants were randomized to a daily dose of up to 24 mg of ropinirole or 4.2 mg of pramipexole and followed for two years. The primary outcome of the study was self-reported wearing-off periods confirmed by a 30% worsening in the UPDRS part III score within five hours after a DA dose. There was no significant difference between groups in the proportion

of participants who experienced wearing-off periods over the course of the study, or in the UPDRS part III scores. Inadequate data were presented in the article to calculate the RMD between ropinirole and pramipexole for the UPDRS part III score.

Conclusion (low confidence): In early PD, ropinirole is possibly no more effective than pramipexole in improving motor function at 2 years.

Pramipexole IR vs pramipexole ER

One Class I study[35] compared extended-release (ER) pramipexole to IR pramipexole and placebo in 259 individuals with early PD who had not been previously treated with levodopa. Participants were randomized to placebo, pramipexole ER (mean dose of 3.05 mg/d) or pramipexole IR (mean dose of 3.03 mg/d) and followed for 18 weeks. Open label levodopa rescue was allowed during the maintenance phase. The primary efficacy endpoint was the change from baseline to week 18 in the sum score of parts II and III of the UPDRS. There was no difference between pramipexole ER and IR in the combined part II and III UPDRS score, or in the part III score alone (RMD 0, 95% CI -2.4 to 2.4). Both pramipexole ER and IR were superior to placebo. There was no significant difference between pramipexole ER and IR in AE-related discontinuation (RD 2.6%, 95% CI -5.6% to 10.8%) or the development of ICDs (RD -0.05%, 95% CI -5.1% to 4.9%).

Conclusion (moderate confidence): In early PD, pramipexole ER is probably no more effective than pramipexole IR in improving motor function at 18 weeks.

Conclusion (moderate confidence): In early PD, pramipexole ER is probably no more likely than pramipexole IR to cause AE-related treatment discontinuation at 18 weeks.

One Class I study[36] compared pramipexole ER to pramipexole IR and placebo in 539 individuals with early PD. Participants were randomized to placebo, pramipexole ER (up to 4.5 mg/d, with a mean dose of 2.9 mg/d) or pramipexole IR (up to 4.5 mg/d, with a mean dose of 2.9 mg/d) and followed for 33 weeks. The primary outcome was the change from baseline to week 33 in the participants' combined score on parts II and III of the UPDRS. The adjusted mean decrease in the combined UPDRS part II and III score at 33 weeks was -8.2 for pramipexole ER and -8.7 for pramipexole IR, with a difference of 0.5 (95% CI -2.3 to 1.3). In the per protocol set, the adjusted mean decreases were -8.5 for ER and -9.4 for IR, a difference of -0.9 (95% CI -2.7 to 0.9). In neither of these analyses did the lower bound of the 95% CI exceed the predefined margin of -3 to establish noninferiority; therefore, no significant difference was found between pramipexole ER and IR. There was also no significant difference between the pramipexole ER and IR groups in AE-related discontinuation (RD 1.4%, 95% CI -4.4% to 7.1%) or the development of ICDs (RD 0.4%, 95% CI -2.5% to 3.3%) during the study.

Conclusion (moderate confidence): In early PD, pramipexole ER is probably no more effective than pramipexole IR in improving motor function at 33 weeks.

Conclusion (moderate confidence): In early PD, pramipexole ER is probably no more likely than pramipexole IR to cause AE-related treatment discontinuation at 33 weeks.

Pramipexole twice daily vs pramipexole three times daily

One Class I study compared twice daily pramipexole to three times daily pramipexole in 311 participants with early PD.[37] Participants were randomized to 0.5 mg of pramipexole three times daily, 0.75 mg of pramipexole twice daily, 0.5 mg of pramipexole twice daily, or placebo and followed for 12 weeks. The primary outcome was the change in the total score on the UPDRS from baseline to week 12. There was no difference between the three pramipexole groups in the treatment effect relative to placebo as measured with the total score on the UPDRS or with scores on part III of the UDPRS, with all three groups showing similar benefit. There was no difference between the treatment groups in AE-related discontinuation.

Conclusion (moderate confidence): In early PD, pramipexole taken three times daily is probably no more effective than pramipexole taken twice daily in improving motor function at 12 weeks.

Conclusion (moderate confidence): In early PD, pramipexole taken three times daily is probably no more likely than pramipexole taken twice daily to cause AE-related treatment discontinuation at 12 weeks.

Ropinirole IR vs ropinirole PR

One Class II non-inferiority crossover study compared 24 hour prolonged-release (PR) ropinirole and ropinirole IR in early PD.[38] Participants with early PD (n=161) requiring dopaminergic therapy received ropinirole IR (0.75–24 mg/d) or ropinirole PR (2–24 mg/d), and were randomized to one of four formulation sequences: IR-IR-PR; IR-PR-PR; PR-PR-IR; or PR-IR-IR. The primary outcome studied was the mean change between period baseline and endpoint in

the UPDRS part III score, as assessed at the end of each maintenance period. The mean change in the UPDRS part III score from period baseline (adjusted for period carryover effect and period baseline score) was -0.1 (SE 0.28) for ropinirole PR, and 0.6 (SE 0.30) for ropinirole IR. As the upper limit of the 95% CI for the adjusted mean treatment difference was less than the predefined threshold of three points, ropinirole PR was demonstrated to be non-inferior to ropinirole IR. When patients switched formulation of ropinirole, their mean UPDRS part III score was maintained, indicating similar doses of each formulation had similar efficacy.

Conclusion (low confidence): In early PD, ropinirole PR is possibly no more effective than ropinirole IR in improving motor function over 36 weeks.

Ropinirole vs bromocriptine

One study compared ropinirole to bromocriptine in 335 patients with early PD who had limited or no previous dopaminergic therapy.[39,40] This study was rated Class II for its interim data published at six months, and Class III for its three-year data. Selegiline use was permitted during the study, with randomization stratified for use. The mean daily dose of ropinirole was 8.3 mg at six months and 12.0 mg at three years. In the bromocriptine group, the mean daily dose of bromocriptine was 16.8 mg at six months and 24.1 mg at three years. Score on part III of the UPDRS at six months were significantly lower in participants randomized to ropinirole compared to those randomized to bromocriptine (RMD -2.7, 95% CI -5.2 to -0.2), but only in those not taking selegiline. There was no difference between groups at six months in the proportion of patients with psychiatric AEs, or with AE-related discontinuation. At three years, there was no difference between the ropinirole and bromocriptine groups in UPDRS part III

scores (RMD -1.98, 95% CI -4.74 to 0.78), AE-related discontinuation (RD 0.5%, 95% CI -8.1% to 9.1%), use of supplementary levodopa, dyskinesia (RD 0.5%, 95% CI -5.3% to 6.4%), or psychiatric AEs (RD 2.3%, 95% CI -5.4% to 10.0%).

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 three years.

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 three years.

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 three years.

Rotigotine vs ropinirole

One Class II non-inferiority study compared the rotigotine transdermal patch to ropinirole for 37 weeks in 561 patients with early PD who were not taking levodopa.[41] Participants were randomized to rotigotine (maximum dose of 8 mg/d, 92% reached maximum dose), ropinirole (maximum dose of 24 mg/d, 26% reached maximum dose, median dose 14.1 mg/d), or placebo. Treatments were titrated to the optimal effective dose or the maximum permitted dose. The primary endpoint was the proportion of patients with a minimum of 20% decrease in their combined UPDRS part II and part III scores. A significantly greater proportion of individuals

treated with ropinirole (68%) reached the primary endpoint compared to those treated with rotigotine (52%). Participants treated with ropinirole also had a significantly greater decrease in their combined UPDRS part II and part III scores from baseline to the end of treatment, with an RMD of 3.8 (95% CI 1.9–5.7). The difference between ropinirole and the rotigotine transdermal patch for the primary efficacy parameters did not show non-inferiority. There was no difference between the rotigotine and ropinirole groups in AE-related discontinuation (RD 4.1%, 95% CI -2.7% to 10.8%).

Conclusion (low confidence): In early PD, ropinirole is possibly more effective than rotigotine in improving motor function at 37 weeks.

Conclusion (low confidence): In early PD, rotigotine is possibly no more likely than ropinirole to cause AE-related discontinuation of treatment at 37 weeks.

Bromocriptine SR vs bromocriptine IR

One Class II study compared slow-release (SR) bromocriptine with bromocriptine IR in patients with PD for 8 weeks.[42] This study included a sub-analysis of 60 participants with de novo PD. Participants randomized to bromocriptine SR took medication twice daily (mean total dose of 14.2 mg/d), while those randomized to bromocriptine IR took medication three times daily (mean total dose of 13.5 mg/d). There were no significant differences noted between the SR and IR formulations in the global improvement rating or the safety rating.

Piribedil vs bromocriptine

One Class II study compared piribedil plus levodopa to bromocriptine plus levodopa in 425 patients with PD who had been receiving levodopa for more than 3 months but less than 5 years.[43] Motor symptoms had to be insufficiently controlled. Participants were randomized to piribedil up to 150 mg/d or bromocriptine up to 25 mg/d for one year. The primary outcome was the improvement in UPDRS part III score from baseline to 12 months. There was no difference between the piribedil and bromocriptine groups in the change in UPDRS part III score at one year (RMD 0.1, 95% CI -1.73 to 1.93), AE-related discontinuation (RD 4.3%, 95% CI -3.0% to 11.5%), or dyskinesia (RD -1.8%, 95% CI -5.8% to 2.1%). There was a higher risk of hallucinations with piribedil than with bromocriptine, with an RD of 5.3% (95% CI 1.0%–10.0%).

Conclusion (low confidence): In early PD, piribedil is possibly no more effective than bromocriptine in improving motor function at one year.

Conclusion (low confidence): In early PD, piribedil is possibly no more likely than bromocriptine to cause dyskinesia at one year.

Conclusion (low confidence): In early PD, piribedil is possibly no more likely than bromocriptine to cause AE-related discontinuation of treatment at one year.

Conclusion (low confidence): In early PD, piribedil is possibly more likely than bromocriptine to cause hallucinations at one year.

Summary of confidence in evidence statements for DA comparisons

The confidence in evidence statements for comparisons of different formulations of DAs are summarized in the tables below. It is important to note that piribedil and bromocriptine are not routinely used in clinical practice.

Table 5. Change in UPDRS part III score from baseline to endpoint

Study	Class	Comparison	Time point	RMD (95% CI)
Thomas 2006	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 2010	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 2011	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 2011	I	Pramipexole twice daily vs pramipexole three times daily	12 weeks	-0.1 (-2.46 to 2.26)
Conclusion (moderate confidence): In early PD, pramipexole taken three times daily is probably no more effective than pramipexole taken twice daily in improving motor function at 12 weeks.				
Stocchi 2008	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 1999	III	Ropinirole vs bromocriptine	3 years	-1.98 (-4.74–0.78)
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 three years.				
Giladi 2007	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 2006	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 one year.				

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.

Table 6. Risk of dyskinesia

Study	Class	Comparison	Time point	RD (95% CI)
Korczyn 1999	III	Ropinirole vs bromocriptine	3 years	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 three years.				
Castro-Caldas 2006	II	Piribedil vs bromocriptine	1 year	-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 one year.				

Table 7. Risk of hallucinations

Study	Class	Comparison	Time point	RD (95% CI)
Castro-Caldas 2006	II	Piribedil vs bromocriptine	1 year	5.3% (1.0%–10.0%)
Conclusion (low confidence): In early PD, piribedil is possibly more likely than bromocriptine to cause hallucinations at one year.				

Table 8. Risk of AE-related discontinuation

Study	Class	Comparison	Time point	RD (95% CI)
Hauser 2010	I	Pramipexole ER vs pramipexole IR	18 weeks	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-related treatment discontinuation at 18 weeks.				
Poewe 2011	I	Pramipexole ER vs pramipexole IR	33 weeks	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 weeks.				
Kieburtz 2011	I	Pramipexole twice daily vs pramipexole three times daily	12 weeks	1.1% (-8.8% to 11.1%)
Conclusion (moderate confidence): In early PD, pramipexole taken three times daily is probably no more likely than pramipexole taken twice daily to cause AE-related treatment discontinuation at 12 weeks.				
Korczyn 1999	III	Ropinirole vs bromocriptine	3 years	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 three years.				
Giladi 2007	II	Rotigotine vs ropinirole	37 weeks	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 weeks.				
Castro-Caldas 2006	II	Piribedil vs bromocriptine	1 year	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 one year.				

The available evidence suggests that there are minimal differences between formulations of DAs in the risk of AE-related discontinuation.

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

Levodopa IR vs long-acting levodopa

One Class IV study compared levodopa IR to controlled-release levodopa in 618 levodopa naïve patients for five years.[44] Patients were randomized to treatment with levodopa IR or CR at a flexible dose based on optimal clinical response. The primary endpoint of the study was disease progression, defined as the onset of motor fluctuations. The mean bioequivalent dose of levodopa CR was significantly higher at 5 years compared to levodopa IR, with a mean difference of 84 mg/d (95% CI 50.2–117.8). There was no difference between groups in the proportion of participants who developed motor fluctuations at 5 years. There was no difference between groups in the frequency of hallucinations (RD 1.1%, 95% CI -2.3% to 4.5%) or dyskinesia (RD -1.8, 95% CI -6.4 to 2.8).

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

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

One Class III study compared an SR form of levodopa, Madopar HBS (hydrodynamically balanced system), with standard Madopar for five years in 134 patients with de novo PD.[45] Participants were randomized to Madopar HBS (mean daily dose at 5 years of 638 mg, 4.3 doses/d) or Madopar (mean daily dose at 5 years of 719 mg, 4.6 doses/d). There was no significant difference between groups at 5 years in total scores on the UPDRS (RMD 1.9, 95% CI -0.94 to 4.74). There was no difference between groups in AE-related discontinuation (RD -6.9%, 95% CI -17.5% to 3.6%) or dyskinesia (RD: 7.1%, 95% CI -15.8% to 29.5%).

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.

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.

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 discontinuation at 5 years.

Levodopa vs levodopa plus entacapone

One Class I study[46] compared levodopa/carbidopa/entacapone (LCE) with LC in 184 patients with early PD over a 12-week period. The primary outcome studied was the change from baseline to week 12 in total scores on the Parkinson's Disease Questionnaire-8, a short-form version of the PDQ-39. UPDRS part III scores improved from baseline to week 4 and to week 12 in both treatment groups with no significant difference between groups (data was presented graphically only, so we were unable to calculate the RMD). Mean UPDRS part IV scores were very low at baseline and did not change significantly over the 12-week treatment period. The percentage of patients who reported at least one wearing-off symptom in the LCE group was 78.5% at baseline, 69.8% at 4 weeks, and 61.8% at 12 weeks. The percentage of patients who reported a least one wearing-off symptom in the LC group was 84.6% at baseline, 61.5% at four weeks, and 61.5% at 12 weeks, with no significant difference between groups. There was no

difference between groups in AE-related discontinuation (RD LC vs LCE -2.1%, 95% CI -9.5% to 5.2%) or dyskinesia (RD LC vs LCE -4.3%, 95% CI -10.9% to 1.5%).

Conclusion (moderate confidence): In early PD, LC is probably no more likely than LCE to cause AE-related treatment discontinuation at 12 weeks.

Conclusion (moderate confidence): In early PD, LC is probably no more likely than LCE to cause dyskinesia at 12 weeks.

One Class III study[47] compared LCE with LC in 423 patients with early PD, not previously treated with levodopa. Participants were randomized to LCE 100/25/200 mg three times per day or LC 100/25 mg three times per day. Additional levodopa could be added if required, up to a total dose of 750 mg/d. If this occurred, the last-observed measures before the introduction of additional levodopa were carried forward. The primary outcome was the change from baseline to week 39 in the sum of UPDRS parts II and III scores. There was a significant difference between groups in the primary outcome, with the LCE group having a greater decrease from baseline compared to the LC group on the combined UPDRS parts II and III score, with an adjusted mean difference of 1.7 (95% CI 0.34–3.32). The mean difference between groups on the UPDRS part III score was not significant (RMD LC vs LCE -0.8, 95% CI -2.2 to 0.6). There was no difference between groups in the incidence of dyskinesia (RD LC vs LCE 2.2%, 95% CI -2.7% to 7.0%), wearing-off (RD LC vs LCE 6.1%, -1.1% to 13.2%), or AE-related discontinuation (RD -3.2%, 95% CI -9.1% to 2.6%).

Conclusion (very low confidence): In early PD, there is insufficient evidence to support or refute the effectiveness of LC compared to LCE in improving motor function at 39 weeks.

Conclusion (very low confidence): There is insufficient evidence to determine whether, in early PD, LC is more or less likely than LCE to induce dyskinesia at 39 weeks.

Conclusion (very low confidence): There is insufficient evidence to determine whether, in early PD, LC is more or less likely than LCE to cause AE-related discontinuation at 39 weeks.

One Class II study[48] compared LC with LCE in 747 patients with early PD requiring initiation of levodopa. Participants were allowed to be on stable doses of DAs throughout the study period. Participants were randomized to LC (mean dose of 306.8 mg/d) or LCE (mean dose of 305.2 mg/d), both given four times daily at 3.5 hours intervals for 2.5 years. The primary endpoint was time to onset of dyskinesia. Patients treated with LCE had an increased risk of developing dyskinesia compared to those receiving LC, with a Cox proportional HR of 1.29 (95% CI 1.0–1.65; p=0.038). The survival time estimate for the first quartile of patients was 90.7 weeks (95% CI 65.3–104.0) for the LCE group and 117.1 weeks (95% CI 92.1–132.6) for the LC group. The RD in dyskinesia was -7.4% (95% CI -13.0% to 0%). There was no difference between groups in AE-related discontinuation (RD -3.7%, 95% CI -7.8% to 0.3%), the change from baseline to week 130 in the combined UPDRS part II and III score (inadequate data provided to calculate RMD), or the frequency of wearing-off (RD -6.0%, 95% CI -13.0% to 1.0%).

Further analysis of the study data published in a separate publication[49] showed that the risk of dyskinesia increased in a dose-dependent manner (p<0.001). The frequency of dyskinesia at study termination by nominal levodopa dosage was 12.1% for those taking less than 400 mg/d, 36.8% for those taking 400 mg/d, 45.3% for those taking 401–600 mg/d, and 55.8% for those taking more than 600mg/d. Predictive factors for the emergence of dyskinesia in the stepwise Cox proportional hazards model were (in order of importance): young age at PD onset, nominal levodopa dose, lower weight, region (North America), treatment allocation to LCE, female gender, and baseline UPDRS motor activities of daily living (ADL) score. The risk of developing wearing-off effects increased in a dose-dependent manner (p<0.001). The frequency of wearing-off effects was: 27.2% for those taking less than 400 mg/d, 48% for those taking 400 mg/d, 59.3% for those taking 401–600 mg/d, and 72.6% for those taking more than 600 mg/d. Predictive factors for wearing-off in the stepwise Cox proportional hazards model were (in order of importance): young age at PD onset, baseline UPDRS motor ADL score, region (North America), nominal levodopa dose, female gender, and baseline UPDRS part III score.

Conclusion (low confidence): In early PD, LCE is possibly no more likely than LC to induce dyskinesia at 2.5 years.

Conclusion (low confidence): In early PD, LCE is possibly no more likely than LC to cause AE-related discontinuation of treatment at 2.5 years.

Summary of confidence in evidence statements for long-acting vs IR levodopa

Table 9. Change in UPDRS part III score from baseline to endpoint

Study	Class	Comparison	Time point	RMD (95% CI)
Dupont 1996	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 2009	III	LC vs LCE	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 LC compared to LCE in improving motor function at 39 weeks.				

Table 10. Risk of dyskinesia

Study	Class	Comparison	Time point	RD (95% CI)
Dupont 1996	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 1999	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 2009	I	LC vs LCE	12 weeks	-4.3 (-10.9 to 1.5)
Conclusion (moderate confidence): In early PD, LC is probably no more likely than LCE to cause dyskinesia at 12 weeks.				
Hauser 2009	III	LC vs LCE	39 weeks	2.2% (-2.7% to 7.0%)
Conclusion (very low confidence): There is insufficient evidence to determine whether, in early PD, LC is more or less likely than LCE to induce dyskinesia at 39 weeks.				
Stocchi 2010	II	LC vs LCE	2.5 years	-7.4 (-13.0 to 0)
Conclusion (low confidence): In early PD, LCE is possibly no more likely than LC to induce dyskinesia at 2.5 years.				

Table 11. Risk of hallucinations

Study	Class	Comparison	Time point	RD (95%CI)
Koller 1999	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.				

Table 12. Risk of AE-related discontinuation

Study	Class	Comparison	Time point	RD (95%CI)
Dupont 1996	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 2009	I	LC vs LCE	12 weeks	-2.1% (-9.5% to 5.2%)
Conclusion (moderate confidence): In early PD, LC is probably no more likely than LCE to cause AE-related treatment discontinuation at 12 weeks.				
Hauser 2009	III	LC vs LCE	39 weeks	-3.2 (-9.1 to 2.6)
Conclusion (very low confidence): There is insufficient evidence to determine whether, in early PD, LC is more or less likely than LCE to cause AE-related treatment discontinuation at 39 weeks.				
Stocchi 2010	II	LC vs LCE	2.5 years	-3.7 (-7.8 to 0.3)
Conclusion (low confidence): In early PD, LCE is possibly no more likely than LC to cause AE-related treatment discontinuation at 2.5 years.				

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 ICARUS study[50] was a cohort study with prospective data collection (Class III) of adults with idiopathic PD who had been treated for at least six months with any approved pharmacological PD treatment with clinical benefit. Patients (N=1069) were followed for two years while taking levodopa, DAs, or a combination thereof for PD therapy and were screened at multiple points for the presence of ICDs. At baseline, 306 of the 1069 participants (28.6%) screened positive ICDs, at one year, 292 of the remaining 995 participants in the study (29.3%) screened positive, and, at two years, 245 of the remaining 925 participants in the study (26.5%)

screened positive. A higher proportion of men (32.5%) screened positive for ICDs at baseline than women (21.7%). ICD-positive patients were younger, younger at PD onset, and had longer disease duration. At two years, the RD for ICDs in patients treated with levodopa compared to DAs was -0.68% (95% CI -9.9% to 7.8%), while the RD in patients treated with levodopa compared to levodopa plus DAs was -11.2% (95% CI -17.3% to -4.23%).

The prevalence of ICDs and impulsive and compulsive behaviors (ICBs) by PD therapy was assessed as part of the Norwegian ParkWest study.[51] The Norwegian ParkWest study (Class III) was a population-based longitudinal study of PD. Patients with newly diagnosed PD (N=314) and control participants were recruited from four counties in Norway and followed prospectively for five years. Prevalence of ICDs was significantly higher in patients with PD (20.8%, 26/125) compared to controls (5.7%, 9/159), with an odds ratio (OR) of 4.4 (95% CI 2.0–9.7). The highest frequency of ICBs was observed among patients using DAs only (9 of 18 participants, 50%), followed by those on both DAs and levodopa (23 of 60 participants, 38.3%), and patients taking levodopa (6 of 43 participants, 13.9%). The RD for ICBs in patients treated with levodopa compared to DAs was -36.1% (95% CI -58.3% to -11.2%), while the RD in patients treated with levodopa compared to levodopa plus DAs was -24.4% (95% CI -39% to -7%). Compared to controls, the corresponding ORs of having an ICB were 7.4 (95% CI 2.6–20.9) for those on DAs only and 4.6 (95% CI 2.3–9.3) for combination users. Patients using levodopa only had no increased odds of ICBs compared to controls (OR 1.2, 95% CI 0.5–3.2). In multivariable models, DA treatment and depressive symptoms were significant predictors of ICB status.

In a prospective cohort study of non-demented outpatients with PD (Class IV), patients were followed until they reached the first of the following predetermined endpoints: new onset ICDs; discontinuation of DA therapy, death or loss to follow-up, or June 30, 2011.[52] Data on ICDs were reported for the 46 of 164 participants in the cohort who were taking DAs. Eighteen of those 46 participants developed new onset ICDs, a cumulative frequency of 39.1% after a median DA treatment duration of 21 months. Compared to patients on DAs without ICDs, those with ICDs had a significantly higher lifetime prevalence of cigarette smoking and caffeine use, a greater prevalence of motor complications, and higher peak DA dosages.

ICDs were studied in a prospective cohort study of 290 individuals with PD (Class III), who participated in two surveys fifteen months apart.[53] ICDs and related behaviors were present at baseline in 42.5% of participants, and in 38.7% participants at follow-up. Male sex (OR 6.10, 95% CI 2.16–17.18) and higher DA dose (for 100 mg levodopa equivalent daily dose [LEDD] increase, OR 2.25, 95% CI 1.29–3.91) at baseline were the only factors significantly associated with ICD outcome at follow-up among patients with ICDs at baseline. The optimal LEDD cut off for predicting poor ICD outcome was less than a 161 mg LEDD, corresponding to 1.6 mg/d of pramipexole or 8 mg/d of ropinirole. In patients with no ICDs at baseline, an increase in depressive symptoms as measured with the Beck Depression Inventory between baseline and follow-up (for 1-point score increase, OR 1.095, 95% CI 1.004–1.195) was the only factor significantly associated with ICDs at follow-up.

The cumulative rate of incident ICD behaviors was studied in the Parkinson Progression Markers Initiative (PPMI).[54] This was a cohort study of newly diagnosed, untreated (at enrollment)

patients with PD (N=320) and healthy controls followed for up to three years (Class III). The cumulative rate of incident ICD behaviors at one year was 7.8%, was 18.1% at two years, and was 25.1% at three years. The observed cumulative rate of incident ICD symptoms was higher in participants on dopamine replacement therapy at each time point, but the difference compared to participants not taking dopamine replacement therapy was not significant at any time point. Younger age at baseline was significantly associated with a higher risk of incident ICD symptoms (OR 0.97, p=0.02).

A second publication using the same dataset (PPMI)[55] studied ICDs in PD patients who did not have ICDs at baseline and followed 354 patients for a mean of four years (Class III). The investigators evaluated the effect of depression on the development of ICDs and calculated the HR for the development of ICDs with DA use. Presence of ICD was evaluated at baseline and follow-up visits using the QUIP. At 2 years, the RD for the development of ICDs with no DA use compared to DA use was -0.20 (95% CI -0.33 to -0.09).

The incidence rate of ICDs was 19.38 cases per 100 patient years for depressed patients and 10.3 cases for nondepressed patients. Proportional hazards analysis for depression showed an increased risk of ICDs in patients depressed at baseline (HR 1.96, 95% CI 1.32–2.9, p<0.001).

The use of DAs also carried an increased risk of ICD development (HR 1.74, 95% CI 1.22–2.5; p=0.002). The model including the two predictors showed they both maintained similar effects on ICD risk, and depressed patients had a higher risk of ICDs when on DAs.

The relationship between depression and ICD development was significant for both symptomatic depression and treated depression. The association between baseline depression and longitudinal ICD development remained significant after adjusting for age, sex, time since PD diagnosis, motor score, genetic status, anxiety, apathy, and RBD. Both depression and DA use remained significant in a model including all the above-mentioned potential confounders.

The factors associated with ICBs in PD were studied in a 2-year longitudinal retrospective cohort study[56] (Class III). Patients with PD (N=148) followed for at least two years at the Aomori Hospital Movement Disorder Clinic periodically completed the QUIP, and characteristics of patients with and without ICBs were compared. Thirty of 141 (21%) had at least one ICB at baseline, with 12 of 30 having persistence of their ICB at two-year follow-up. DA use was higher at baseline in patients with ICBs (20/30; 67%), compared to those without ICBs (46/111; 41%) p=0.01. Pergolide use was higher in patients with ICBs at baseline than those without ICBs (23% vs 5.4%, p=0.0003). ICB persisters had more pergolide use (p=0.0005) than ICB remitters. In patients without ICBs at baseline who developed ICBs over the two-year study (14/111), 57% (8/14) had DA treatment initiated, compared to 29% (28/97) of those without ICBs (p=0.04). The RD for ICBs at two years in those using levodopa monotherapy vs DAs was -0.23 (95% CI -0.36 to -0.04).

ICBs were studied in prospective study of 106 patients with PD and 125 healthy controls[57] for 5 years of follow-up (Class III). The investigators compared the rate of ICBs at baseline and at follow up in patients with PD and healthy controls and evaluated risk factors including the use of DAs. At baseline, ICBs were present in 21 of 106 PD patients and 13 of 125 controls. PD

patients with ICBs were more frequently males and were more often treated with DAs than PD patients without ICBs. The frequency of ICBs at follow up in PD patients was 19/92 (21%) at 1 year, 19/86 (22%) at 2 years; 22/85 (26%) at 3 years, and 21/73 (29%) at 5 years. Over the follow-up period, PD patients with ICBs had higher DA doses than PD patients without ICBs. Logistic regression models for the presence and occurrence of any ICB showed that the use of DAs at baseline was a predictor for the presence or occurrence of any ICB (OR 4.92, 95% CI 2.01–12.02).

A multicenter longitudinal study of ICDs was performed in 411 individuals with early PD, who were followed annually for 5 years[58] (Class IV). The investigators calculated the incidence of ICDs according to DA use. At baseline, 81/411 (19.7%) had ICDs. Compared to patients without ICDs at baseline, those with ICDs were younger and had longer disease duration. After adjustment for age and disease duration, those with ICDs were more likely to be obese, regular coffee drinkers and to have higher scores on the UPDRS parts I and IV. They used DAs more frequently (93% vs 69%) and at higher doses (mean levodopa equivalent dose 211 mg vs 145 mg). Frequency of use and dose of levodopa were similar in the two groups.

Forty-three percent of patients had an ICD at one or more visits. ICD prevalence increased from 19.7% at baseline to 32.8% at 5 years. Of 306 (46 never DA users, 260 ever DA users) patients without ICDs at baseline with at least one additional visit, 94 (4 never DA users, 90 ever DA users) developed ICDs, corresponding to a 5-year cumulative incidence of 46.1% (95% CI 37.4–55.7). In never users, this was 12.4% (95% CI 4.8–30). In ever DA users, this was 51.5%, (95% CI 41.8–62.1).

Men developed ICDs more frequently than women over time; younger patients had a higher prevalence of ICDs at all visits. DA use in the past 12 months was associated with a 2.23-fold higher ICD prevalence. Analysis of ever users shower a 39% higher prevalence of ICDs per 1-SD increase in cumulative duration of use, and a 32% higher prevalence of ICDs per 1-SD increase in dose. After discontinuation of DAs, ICDs progressively resolved.

Conclusion (moderate confidence): In early PD, DAs are probably more likely than levodopa to cause ICDs at two years.

Conclusion (low confidence): In early PD, combination treatment with levodopa and DAs is possibly more likely than levodopa alone to cause ICDs at two years.

Conclusion (low confidence): In early PD, DAs are possibly more likely than levodopa to cause ICDs at five years.

Conclusion (low confidence): In early PD, combination treatment with levodopa and DAs is possibly more likely than levodopa alone to cause ICDs at five years.

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

Disabling response fluctuations and dyskinesia were studied in a cohort study[59] of consecutive de novo PD patients starting on levodopa or DAs (Class IV). Of the 127 participants, 77 started on levodopa and 50 started on DAs; all were followed for a median of 8.1 years. The primary endpoints were the onset of response fluctuations, dyskinesia, and the amount of time before these complications became disabling. Participants in the levodopa group were older and had more severe PD than those in the DA group. The median duration of monotherapy for participants who started on DAs was 2.5 years (95% CI 1.9–3.1). Dyskinesia occurred in 74% of participants who started on levodopa after a median of 3.9 years (95% CI 3.3–4.4), and in 50% of those who started on DAs after a median of 6.4 years (95% CI 4.0–8.8), with an HR of 2.04 (95% CI 1.26–3.30). Disabling response fluctuations and dyskinesia occurred in 59.7% of those who started on levodopa after a median of 7.3 years (95% CI 6.1–8.4), and in 52% of those who started on DAs after a median of 6.1 years (95% CI 4.4–7.9), with an HR of 0.88 (95% CI 0.54–1.44). Adjusting for age and severity of PD at the start of dopaminergic therapy did not change the statistical conclusions.

The risk and course of motor complications in a population-based incident PD cohort was studied as part of the Norwegian ParkWest project, a prospective, population-based, multicenter, longitudinal cohort study (Class IV).[60] Newly diagnosed and untreated PD patients (n=189) from the general population were recruited and followed for a median of five years. Age, sex, time since motor onset, and motor severity at baseline were the primary risk factors of interest. Initial treatment (with levodopa or a DA) and actual levodopa equivalent dose at onset of motor complications were also evaluated. The point prevalence of dyskinesia in all participants were

3.8% at one year, 4.5% at two years, 5.2% at three years, 9.8% at four years, and 12.7% at five years.

The cumulative incidence of dyskinesia was 6.3% at one year, 9.5% at two years, 12.7% at three years, 18.0% at four years, and 24.3% at five years. Independent risk factors for dyskinesia were female sex (HR 2.73, 95% CI 1.49–4.98) and a higher baseline UPDRS part III score (HR per unit 1.05, 95% CI 1.02–1.08). Thirty-six of the 189 patients (19%) had never used levodopa. Among these, 4 out of 36 (11%) had dyskinesia. In comparison, 27.5% of levodopa-treated patients had dyskinesia. In a multivariate Cox regression analysis (with adjustment for baseline age, sex, time since motor onset, and motor severity), initial treatment with levodopa was associated with an increased risk of developing motor fluctuations (HR 1.84, 95% CI 1.09–3.10), but not dyskinesia (HR 0.88, 95% CI 0.42–1.85). Actual levodopa dose was independently associated with both motor fluctuations (HR per 100 mg/d 1.13, 95% CI 1.01–1.26) and dyskinesia (HR per 100 mg/d 1.28, 95% CI 1.16–1.42). Few patients rated their dyskinesia as severe (0.6%) or painful (1.8%) within the first 5 years of diagnosis.

One randomized controlled study[23] compared the risk of at least moderately disabling dyskinesia with levodopa to pramipexole at six years after initial randomization. The RD of 0.7% (95% CI -4.8% to 6.2%) was not significant.

One randomized controlled study compared the risk of disabling dyskinesia with levodopa to ropinirole at five years (Class II)[25] and ten years (Class IV)[26] after initial randomization. The RD

between levodopa and ropinirole was significant at five years (RD 14.7%, 95% CI 5.8%–24.8%), but not at ten years (RD 11.6%, 95% CI -7.0% to 31.9%).

A prospective cohort study of predictors of motor complications in early PD was performed in the Oxford PD Centre Discovery Cohort.[61] PD patients within 3.5 years of diagnosis (mean 1.35 years; 92% H&Y stage 1 or 2) underwent clinical examination every 18 months (N=740) for up to 10 years. The study evaluated the incidence of dyskinesias and motor fluctuations over time and clinical characteristics associated with increased risk. The presence and intensity of motor complications was determined using the MDS-UPDRS part IV questions 1 (dyskinesia) and 3 (motor fluctuations).

186/734 participants (25%) developed dyskinesias and 254/733 (35%) developed motor fluctuations over time. Higher levodopa dose, favorable medication response, younger age at symptom onset, and greater nonmotor symptom burden (anxiety and low mood) were significantly associated with dyskinesia and motor fluctuations. Lower BMI was associated with dyskinesia; higher education level was associated with motor fluctuations.

Motor complications were studied in a 13 year follow-up of people with PD in the CamPaiGN cohort[62] (Class IV). This is an incident population-based PD cohort of newly diagnosed cases in the county of Cambridgeshire, UK (N=141). All cases were followed up at 2-year intervals, with a mean follow-up of 7.8 years, and maximum follow-up of 13 years. The incidence of motor fluctuations and levodopa-induced dyskinesias was calculated using the UPDRS section 4. Cox regression analysis was used to investigate covariates that might

influence development of motor fluctuations and dyskinesias, including LEDD at baseline, and levodopa use at baseline.

Levodopa-induced dyskinesia developed in 39 patients, with a cumulative incidence of 14.5% at 5 years and 55.7% at 10 years. Median time to dyskinesia was 8.7 years. No association was found between LEDD at baseline, levodopa use at baseline, and levodopa-induced dyskinesia.

Conclusion (low confidence): In early PD, levodopa is possibly more likely than ropinirole to cause disabling dyskinesia at five years.

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 six years.

Conclusion (very low confidence): In early PD, there is insufficient evidence to determine whether levodopa is more or less likely than ropinirole to cause disabling dyskinesia at ten years.

Discussion

Despite nearly 20 years of research, the conclusions from this systematic review of the literature are unchanged from the original guideline on initiation of treatment of motor symptoms in PD. While there are more data available than at the time of the initial guideline, the many recent studies did not use blinded evaluators to assess outcomes. Consequently, the overall risk of bias was high for most studies, leading to low or very low confidence in the evidence based on our

classification system. Only Class IV data were available for studies beyond five years in duration, greatly limiting any evidence-based conclusions for this time frame.

The overall trend with time shows that initial treatment of motor symptoms with levodopa provides superior motor benefit compared to treatment with DAs, while levodopa is more likely to cause dyskinesia. Although the risk of hallucinations was higher with DAs than with levodopa, the difference between treatments for this outcome was small for the first five years of treatment of early PD. Similarly, AE-related discontinuation of treatment was more common with DAs than with levodopa, but the confidence in the evidence was low or very low at most time points.

The comparison of different formulations of DAs yielded little evidence that any one formulation or method of administration is superior, with the exception of ropinirole possibly being superior to rotigotine when measured by the change in the UPDRS part III score. Long-acting forms of levodopa and levodopa with entacapone do not appear to differ from levodopa with respect to UPDRS part III score, dyskinesia, or AE-related discontinuation of treatment, at least in early disease.

There is a paucity of high-quality research evaluating the risk of ICDs with DAs compared to levodopa. However, the available evidence supports a higher risk of ICDs associated with the use of DAs, especially when used concomitantly with levodopa. Finally, there are very few data on the long-term risks of disabling dyskinesia with levodopa compared to DAs.

CLINICAL CONTEXT

The following recommendations pertain to the initiation of pharmacologic treatment for motor symptoms in early PD, with the presumption that patients have been evaluated and received a correct diagnosis. Alternate options, including exercise and clinical trial participation, are not part of these formal guideline recommendations. Exercise is now widely considered to be an essential part of PD care starting in the earliest stages, but this evidence was not systematically evaluated as part of the current guideline and the guideline makes no practice recommendations on this topic. If individuals with early PD are judged not to need pharmacologic treatment at the time of evaluation, options include referring them to disease-modifying clinical trials (e.g., trials studying the effects of exercise, new pharmacologic agents) which typically require "*de novo*" individuals with PD (i.e., individuals with PD not requiring pharmacologic symptomatic therapy). Though less common, there may also be clinical trials for initial PD therapy that may be combined with the pharmacotherapies below.

There are no current disease-modifying pharmacologic treatments for PD,[56-58] 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 PPMI 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%) of individuals with PD started treatment within 2 years of study onset, an average of 0.78 (SD 0.5) years after study entry.[59] This provides an opportunity for interested individuals with *de novo* PD to participate in clinical trials targeting this population.

PRACTICE RECOMMENDATIONS

Much more than evidence must be considered when crafting practice recommendations. The evidence-based conclusions from our systematic review form the foundation of the AAN guideline development process, but other factors influence the structure of recommendations. The panel developed rationale statements that document, in a transparent manner, the deductive logic justifying each recommendation. These rationale statements 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.

When there is sufficient evidence to support an inference for the use of an intervention (i.e., the balance of benefits and harms favors the intervention), the development panel assigns one of three recommendation designations: A, B, or C. Each designation corresponds to a helping verb that denotes the level of strength of the recommendation. Level A is the strongest recommendation level and is denoted by the use of the verb *must*. These recommendations are rare because they 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*. Such recommendations tend to be more common because the requirements are less stringent but still based on the evidence and benefit-risk profile. Level C corresponds to the verb *may*. These recommendations represent the lowest allowable recommendation level that the AAN considers useful within the scope of clinical practice and accommodates the highest degree of practice variation.

Non–evidence-based factors that need to be transparently and systematically considered when formulating recommendations include (1) the relative value of the benefit compared with the risk, (2) the feasibility of complying with the intervention (e.g., the intervention's availability), (3) the cost of the intervention, and (4) the expected variation in patient preferences relative to the risks, burdens, and benefits of the intervention. The panel assigned levels of obligation (A, B, C, U, or R) to each recommendation by using a modified Delphi process that synthesizes all previously listed factors. The opinions of the guideline panel, with regard to the importance of each factor, were elicited through an online questionnaire, with statistical analysis of responses. The panel voted anonymously and independently on each recommendation in three rounds of online voting. Using precisely defined rules for consensus for each recommendation, the panel either achieved consensus, revised the recommendation, or did not carry the recommendation forward. In some cases, the panel reviewed, revised, and revoted on recommendations on the basis of public commentary and other input during the guideline development process, reflecting the dynamic nature of this process. Suggestions for future research were created during guideline development.

Levodopa vs DA vs MAO-B inhibitors

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.

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.

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]

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 in 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 pre-existing cognitive impairment, excessive daytime sleepiness, or hallucinations (Level B).

Prescribing levodopa

Recommendation 2 rationale

The evidence comparing IR levodopa to CR levodopa or LCE 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.

Although 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. Whereas LCE 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.

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.

Recommendation 2 statements

2a. Clinicians should initially prescribe IR levodopa rather than CR levodopa or LCE 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, excessive daytime sleepiness, 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 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.

Patients may not always report certain nonmotor 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.

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, excessive daytime sleepiness, sudden-onset sleep, nausea, postural hypotension, and hallucinations (Level B).

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).

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).

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).

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.

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 ICBs.[80]

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.

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. 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 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.[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.

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]

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 pharmacological interventions, if appropriate.

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.

Recommendation 5 statements

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).

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).

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 is more likely to induce dyskinesia than initial treatment with MAO-B inhibitors for up to the first five years of follow-up. Most patients on monotherapy with a MAO-B inhibitor will require additional therapy within two to three 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 the two 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 MAOB-inhibitor and an SSRI.[87-89]

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 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. 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 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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Lori Billinghurst, MD, MSc	Department of Pediatrics, McMaster University, Hamilton, Ontario, Canada	Design or conceptualization of the study; analysis or interpretation of the data
Kelly Sullivan, PhD	Department of Biostatistics, Epidemiology, and Environmental Health Sciences, Jiann-Ping Hsu College of Public Health, Georgia Southern University, Statesboro	Design or conceptualization of the study; analysis or interpretation of the data
Michael S. Fitts	University of Alabama at Birmingham	Design or conceptualization of the study; analysis or interpretation of the data; drafting or revising the manuscript for intellectual content

Nicholas Cothros, MD, PhD	University of Calgary, Alberta	Analysis or interpretation of the data; drafting or revising the manuscript for intellectual content
Deborah A. Hall, MD, PhD	Department of Neurological Sciences, Rush University Medical Center, Chicago, IL	Design or conceptualization of the study; analysis or interpretation of the data; drafting or revising the manuscript for intellectual content
Miriam Rafferty, DPT, PhD	Shirley Ryan AbilityLab and Department of Physical Medicine and Rehabilitation, Feinberg School of Medicine, Northwestern University, Chicago, IL	Design or conceptualization of the study; analysis or interpretation of the data; drafting or revising the manuscript for intellectual content
Lynn Hagerbrant	Michael J. Fox Foundation for Parkinson's Research, New York, NY	Design or conceptualization of the study; analysis or interpretation of the data; drafting or revising the manuscript for intellectual content
Tara Hastings, MA	Michael J. Fox Foundation, New York, NY	Design or conceptualization of the study; analysis or interpretation of the data; drafting or revising the manuscript for intellectual content
Mary Dolan O'Brien, MLIS	American Academy of Neurology, Minneapolis, MN	Design or conceptualization of the study; analysis or interpretation of the data; drafting or revising the manuscript for intellectual content
Heather Silsbee	American Academy of Neurology, Minneapolis, MN	Design or conceptualization of the study; drafting or revising the manuscript for intellectual content
Gary Gronseth, MD	Department of Neurology, University of Kansas, Kansas City	Design or conceptualization of the study; analysis or interpretation of the data; drafting or revising the manuscript for intellectual content
Anthony E. Lang, MD	The Edmond J. Safra Program in Parkinson's Disease and the	Design or conceptualization of the study; drafting or revising

	Morton and Gloria Shulman Movement Disorders Clinic, Toronto Western Hospital and the University of Toronto, Ontario	the manuscript for intellectual content

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APPENDICES

Appendix 1. AAN Guideline Subcommittee mission

The mission of the Guideline Subcommittee is to develop, disseminate, and implement evidence-based systematic reviews and clinical practice guidelines related to the causation, diagnosis, treatment, and prognosis of neurologic disorders.

The Guideline Subcommittee is committed to using the most rigorous methods available within its budget, in collaboration with other available AAN resources, to most efficiently accomplish this mission.

Appendix 2. AAN Guideline Subcommittee members 2019–2021

Alexander Rae-Grant, MD (Chair), John J. Halperin, MD (Vice-Chair), Lori L. Billinghurst, MD, Brian Callaghan, MD, Anne Constantino, MD, Jeremy K. Cutsforth-Gregory, MD, Wendy S. Edlund, MD, Scott A. Heller, MD, Koto Ishida, MD, Mark Douglas Johnson, MD, Mark Robert Keezer, MD, Benzi Kluger, MD, Nicole J. Licking, DO, Mia T. Minen, MD, Pushpa Narayanaswami, MBBS, MD, Alison M. Pack, MD, Sonja Potrebic, MD, PhD, Vishwanath Sagi, MD, Navdeep Sangha, MD, Nicolaos Scarmeas, MD, Kelly Sullivan, PhD, Sarah Tanveer, Benjamin D. Tolchin, MD, Shawniqua T. Williams, MD

Appendix 3. Complete search strategy

Literature Search Strategy: Initiation of treatment for Parkinson's disease
Clinical Trials.gov
drug therapy OR pharmacological OR physical therapy OR exercise | Parkinson Disease
1065 hits

Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>

Search history sorted by search number ascending

#	Searches	Results	Type
1	*parkinsonian disorders/ or *parkinson disease/ or *lewy body disease/	54293	Advanced
2	(parkinson* or "lewy body").ti,kw.	62951	Advanced
3	1 or 2	71462	Advanced

4	Levodopa/	15289	Advanced
5	(levodopa or l dopa).mp.	24625	Advanced
6	Catechol O-Methyltransferase Inhibitors/	944	Advanced
7	(("catechol o methyltransferase" or comt) adj3 (inhibit* or antagonist* or block*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	1518	Advanced
8	Antiparkinson Agents/	10078	Advanced
9	(anti parkinson* or antiparkinson*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	12496	Advanced
10	exp monoamine oxidase inhibitors/ or mao.mp. or ("monoamine oxidase" adj3 (anti or block* or inhibit*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	27902	Advanced
11	exp dopamine agonists/ or exp cholinergic antagonists/	108339	Advanced
12	(anticholinergic* or anti cholinergic*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	11684	Advanced
13	exp Physical Therapy Modalities/ or physical therapy.mp. or exp Exercise Therapy/	143799	Advanced
14	((physical or exercise or gait or balance or muscle) adj2 (train* or therap*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	105497	Advanced
15	(kinesiotherap* or physiotherap*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word,	21995	Advanced

	protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]		
16	exp Exercise/	161704	Advanced
17	exp Physical Exertion/ or physical training.mp. or exp "Physical Education and Training"/	69997	Advanced
18	or/4-17	532072	Advanced
19	1 and 18	17353	Advanced
20	19 and randomized controlled trial.pt.	1205	Advanced
21	19 and randomi*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	1703	Advanced
22	19 and (prospective study/ or cohort*.mp. or cross-section*.mp. or "population based".mp.) [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	1220	Advanced
23	19 and prospective*.ti,ab,kw.	549	Advanced
24	20 or 21 or 22 or 23	2886	

CENTRAL – 120

Embase <1988 to 2018 Week 10>

Search history sorted by search number ascending			
#	**Searches**	**Results**	**Type**
1	*parkinsonism/ or *parkinson disease/ or *diffuse lewy body disease/	89138	Advanced
2	*parkinsonism/dt, dm, rh, th or *parkinson disease/dt, dm, rh, th or *diffuse lewy body disease/dt, dm, rh, th	25410	Advanced
3	exp antiparkinson agent/	89886	Advanced
4	exp dopamine receptor stimulating agent/	151627	Advanced
5	exp cholinergic receptor blocking agent/	133025	Advanced
6	exp levodopa/	34191	Advanced

7	exp catechol methyltransferase inhibitor/	4958	Advanced
8	exp exercise/	255952	Advanced
9	exp physiotherapy/	67172	Advanced
10	exp kinesiotherapy/	59144	Advanced
11	exp "physical activity capacity and performance"/	701444	Advanced
12	or/3-11	1065416	Advanced
13	2 and 12	20759	Advanced
14	1 and 12	39474	Advanced
15	14 and conference abstract.pt.	9363	Advanced
16	13 or 15	30122	Advanced
17	16 and randomized controlled trial/	1432	Advanced
18	16 and (cohort* or prospective* or population*).mp.	4076	Advanced
19	17 or 18	5252	Advanced
20	19 not case report/	5159	Advanced
21	20 not (letter* or note* or comment* or news*).pt.	5084	Advanced
22	limit 21 to human	4751	

Appendix 4. Evidence profile tables

1. In people with early PD, what is the comparative efficacy of **levodopa vs DAs vs MAO-B inhibitors** for motor symptoms? (**Treatment)**

2. In people with early PD, what is the comparative risk of adverse effects (including motor complications) of **levodopa vs DAs vs MAO-B inhibitors**? (**Treatment)**

Levodopa vs DA vs MAO-B

Parkinson's disease research group in the UK 1993	Triple-masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than 2 primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class rating

Comparisons of therapeutic effects of levodopa, levodopa and selegiline, and bromocriptine in patients with early, mild PD: three-year interim report	No, randomized open trial	Yes	Yes	No	Yes	Unclear	IV
	Population N Trial length	Intervention and comparator	Outcomes				
	Early PD, not receiving dopaminergic treatment (mean disease duration 14 months) N=782 3 years	Levodopa (flexible dose) mean dose at 1 year 420 mg/d Levodopa (flexible dose) plus selegiline 10 mg mean dose at 1 year 352 mg/d Bromocriptine (max dose 120 mg) mean dose at one year 36 mg	Main outcomes: disability assessment on H&Y, modified Webster and North Western University disability scales, mortality **Improvement in Webster rating during first year** Levodopa (n=213): 3.1 Levodopa plus selegiline (n=233): 3.4 Bromocriptine (n=224): 2.1 Adjusted difference 0.93 (95% CI 0.27–1.50; *p*=0.0058) levodopa vs bromocriptine Adjusted difference 1.25 (95% CI 0.61–1.89; *p*=0.0002) levodopa plus selegiline vs bromocriptine Mean length of time to develop dyskinesia and motor oscillations did not differ significantly between the levodopa and levodopa plus selegiline groups, 24.5 vs 29.0 months **Number of patients with dyskinesia after mean follow-up of 3 years** Levodopa: 67/249 (27%) RR vs bromocriptine: 14.15 (95% CI 5.96–33.6) RD: 25% (95% CI 19.3%–30.9%) Levodopa plus selegiline: 92/271 (34%) RR vs bromocriptine: 17.86 (95% CI 7.59–42.12) RD: 32.1% (95% CI 26.1%–38.0%) Bromocriptine: 5/263 (2%) **Number of patients with oscillations after mean follow-up of 3 years** Levodopa: 82/249 (33%) RR vs bromocriptine: 6.66 (95% CI 3.84–11.58) RD: 28% (95% CI 21.5–34.4) Levodopa plus selegiline: 95/271 (35%) RR vs bromocriptine: 7.09 (95% CI 4.11–12.27) RD: 30.1% (95% CI 23.7%–36.3%)				

			Bromocriptine: 13/263 (5%) **Number of patients withdrawn from treatment group** Levodopa: 80/249 Levodopa plus selegiline: 76/271 Bromocriptine: 181/263 RD levodopa vs bromocriptine: -36.7% (95% CI -44.3 to -28.3) RD levodopa plus selegiline vs bromocriptine: -40.8% (95% CI -48.1% to -32.7%)

Lees 2001 Ten-year follow-up of three different initial treatments in de-novo PD (extension of above trial)	Triple-masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than 2 primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class rating
	No, open randomized study	Yes	Yes	Yes	Yes	No	IV
	Population N Trial length	Intervention and comparator	Outcomes				
	PD patients of any age requiring dopaminergic treatment N=782 10 years	Arm 1: Levodopa n=249 Arm 2: Levodopa and selegiline n=271 This treatment arm was terminated after 6 years due to increased mortality. Arm 3: Bromocriptine n=262	Principal outcome measures: mortality and disability Average improvement in disability scores during the first year after randomization was significantly less for those patients initially randomized to bromocriptine compared to those randomized to levodopa or levodopa and selegiline. Over the first 5 years, the difference between arm 1 and arm 3 remained fairly constant at around 1 point on the Webster scale. After 5 years of follow-up, the difference in Webster score between arm 1 and arm 3 was 1.0 (95% CI 0.2–2.1), with arm 3 having worse disability scores. By the ninth year of follow-up, the difference was 0.2 (95% CI -1.5 to 1.5). **Motor complications** Dyskinesia rate per 1000 person-years and n Levodopa: 145.3 (134/249) Levodopa and selegiline: 143.4 (150/271) Bromocriptine: 105.9 (117/262) Rate ratio bromocriptine vs levodopa: 0.73 (95% CI 0.57–0.93) RD levodopa vs bromocriptine: 9.2% (95% CI 0.5%–17.6%)				

			RD levodopa plus selegiline vs bromocriptine: 10.7% (95% CI 2.2%–19.0%) **Moderate/severe dyskinesia** Levodopa: 34.6 (44/249) Levodopa plus selegiline: 44.2 (62/271) Bromocriptine: 30.6 (44/262) Rate ratio bromocriptine vs levodopa: 0.89 (95% CI 0.58–1.35) RD levodopa vs bromocriptine: 0.9% (95% CI -5.7% to 7.5%) RD levodopa plus selegiline vs bromocriptine: 6.1% (95% CI -0.7% to 12.8%) Dystonia rate per 1000 person-years and n Levodopa: 116.2 (115/249) Levodopa and selegiline: 108.9 (122/271) Bromocriptine: 97.8 (108/262) Rate ratio bromocriptine vs levodopa: 0.84 (95% CI 0.65–1.09) RD levodopa vs bromocriptine: 5% (95% CI -3.6% to 13.5%) RD levodopa plus selegiline vs bromocriptine: 3.8% (95% CI -4.6%–12.1%) **Moderate/severe dystonia** Levodopa: 24.3 (32/249) Levodopa plus selegiline: 26.9 (40/271) Bromocriptine: 23.1 (34/262) Rate ratio bromocriptine vs levodopa: 0.95 (95% CI 0.59–1.54) RD levodopa vs bromocriptine: -0.1% (95% CI -6.0% to 5.8%) RD levodopa plus selegiline vs bromocriptine: 1.8% (95% CI -4.2% to 7.7%) **On/off fluctuations** Levodopa: 179.7 (146/249) Levodopa plus selegiline: 157.5 (161/271) Bromocriptine: 162.1 (154/262) Rate ratio bromocriptine vs levodopa: 0.9 (95% CI 0.72–1.13) RD levodopa vs bromocriptine: -0.1% (95% CI -8.6%–8.3%) RD levodopa plus selegiline vs bromocriptine: 0.6% (95% CI -7.7% to 8.9%)

			Moderate to severe on/off fluctuations Levodopa: 45.3 (56/249) Levodopa plus selegiline: 49.2 (69/271) Bromocriptine: 47.4 (65/262) Rate ratio bromocriptine vs levodopa: 1.05 (95% CI 0.73–1.5) RD levodopa vs bromocriptine: -2.3% (95% CI -9.6% to 5.1%) RD levodopa plus selegiline vs bromocriptine: 0.7% (95% CI -6.7% to 8.0%)

Katzenschlager 2008 (same study as Lees 2001) Fourteen-year final report of the randomized PDRG-UK trial comparing three initial treatments in PD	Triple-masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than 2 primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class rating
	No, open randomized study	Yes	Yes	Yes	Yes	No	IV
	Population N Trial length	Intervention and comparator	Outcomes				
	PD patients of any age requiring dopaminergic treatment N=782 Median follow-up 14 years	Levodopa n=249; 42 participated in follow-up Levodopa and selegiline n=271; 57 participated in follow-up. This treatment arm was terminated after 6 years due to increased mortality. Bromocriptine n=262; 67 participated in follow-up	Principal outcome measures were mortality and motor disability. Dyskinesias and motor fluctuations were secondary outcome measures. Motor disability Webster scores showed a small but significant advantage in the levodopa arm which remained significant after correction of baseline differences. **Motor complications at final follow-up** Any dyskinesia Levodopa: 24/42 (58%) Bromocriptine: 35/63 (56%) RD: 1.6% (95% CI -17.3% to 20.0%) Moderate/severe dyskinesia Levodopa: 16/42 (39%) Bromocriptine: 22/63 (35%) RD: 3.2% (95% CI -14.8% to 21.6%) Any fluctuations				

			Levodopa: 21/42 (50%) Bromocriptine: 35/63 (56%) RD: -5.6% (95% CI -24.1% to 13.4%) Moderate/severe fluctuations Levodopa: 14/42 (33%) Bromocriptine: 22/63 (35%) RD: -1.6% (95% CI -19.0 to 16.9)

Olanow 1995 The effect of deprenyl and levodopa on the progression of PD Data extracted at 12 months to assess effect on motor symptoms, not at washout (which assessed effect on disease progression)	Triple-masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than 2 primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class rating
	Yes	Yes	Unclear	Yes	Yes	Yes	II
	Population N Trial length	Intervention and comparator	Outcomes				
	Patients with PD, H&Y stage I to III N=101 12 months (for effect on motor symptoms data)	**Deprenyl + Sinemet** n=20 Sinemet mean dose 382 mg Deprenyl 10 mg **Sinemet** n=21 Mean dose 426 mg **Deprenyl + Bromocriptine** n=22 (Sinemet could be added if required after 20 mg of bromocriptine received) Bromocriptine mean dose 28.5 mg Sinement mean dose 85 mg	Primary endpoint: change in total UPDRS score between baseline and final visit (14 months, washout) **UPDRS motor scores at 12 months (prior to washout)** Deprenyl + Sinemet (n=20) Baseline: 14.6 (SE 1.5) 12 months: 7.6 (SE 1.3) Sinemet (n=21) Baseline: 12.8 (SE 1.0; SD 4.6) 12 months: 10.6 (SE 1.1; SD 5.0) Change: -2.2 (SD 6.8, 95% CI -5.1 to 0.7) Deprenyl + bromocriptine (n=22) Baseline: 14.2 (SE 1.0) 12 months: 11.2 (SE 1.0) Bromocriptine (n=19) Baseline: 11.4 (SE 1.3; SD 5.7) 12 months: 12.4 (SE 1.0; SD 4.4) Change: 1.0 (SD 7.1, 95% CI -2.2 to 4.2) No statistically significant difference between groups. RMD UPDRS motor score Sinemet vs bromocriptine at 12 months: -1.8 (95% CI -4.7 to 1.1)				

		Deprenyl 10 mg **Bromocriptine** n=19 (Sinemet could be added if required after 20 mg of bromocriptine received) Bromocriptine mean dose 27.6 mg Sinemet mean dose 117 mg	RMD change in UPDRS motor score at 12 months: -3.2 (95% CI -7.5 to 1.1)

Hely 1989 The Sydney Multicentre Study of PD: A report on the first 3 years	Triple-masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than 2 primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class rating
	Yes	Yes	Yes	Yes	Yes	Unclear	II
	Population N Trial length	Intervention and comparator	Outcomes				
	De novo PD patients N=129 3 years	Bromocriptine (<30 mg/d) (n=66) Mean dose at 3 years 35 mg/d LC (<600/150 mg/d) (n=63) Mean dose at 3 years 380 mg	Primary outcomes: Dyskinesia and on-off phenomena Involuntary movements were the main reason for breaking the treatment code in patients receiving levodopa. Dyskinesia began at a mean of 16 months (range 7–24 months) after commencing LC. 6 of 32 patients developed dyskinesia after 2 years on levodopa. Foot dystonia appeared at a mean of 21 months (range 12–30 months) after starting levodopa. 5 of 32 developed dystonia after 2 years on levodopa. No involuntary movements have occurred in the bromocriptine group (n=27 at two years). RD of dyskinesia at 2 years, levodopa vs bromocriptine: 18.8% (95% CI 2.9%–35.3%) RD of dystonia at 2 years, levodopa vs bromocriptine: 15.6% (95% CI 0.4%–31.8%)				

			Mild end of dose deterioration, denominator not given Levodopa: 6 Bromocriptine: 3 **Modified Columbia score for patients still on initial randomized therapy after 1 year** Number of patients who improved Levodopa: 30/46 Bromocriptine: 15/29 Percentage improvement Levodopa: 35% (range 7%–79%) Bromocriptine: 25% (range 5%–46%) **Modified Columbia score for patients still on initial randomized therapy after 2 years** Number of patients who improved Levodopa: 18/26 Bromocriptine: 5/14 Percentage improvement Levodopa: 42% (range 6%–60%) Bromocriptine: 16% (range 9%–33%)

Hely 1994 The Sydney Multicentre Study of PD: a randomized, prospective five-year study comparing low dose bromocriptine with low dose levodopa-carbidopa	Triple-masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than 2 primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class rating
	No	Yes	Yes	Yes	Yes	Yes	IV
	Population N Trial length	Intervention and comparator	Outcomes				
	De novo PD patients N=126 5 years	Bromocriptine (n=62) LC (n=64) After titration period, levodopa could be added to bromocriptine group and vice versa.	Primary outcomes: Dyskinesia and on-off phenomena **Dyskinesia at 5 years** Patients originally randomized to bromocriptine: 17/62 Patients originally randomized to levodopa: 35/64 RD: 27.3% (95% CI 10.1%–42.3%) **End of dose failure at 5 years** Patients originally randomized to bromocriptine: 23/62 Patients originally randomized to levodopa: 26/64 RD: 3.5% (95% CI -13.2% to 19.9%) **Dystonia at 5 years**					

			Patients originally randomized to bromocriptine: 10/62 Patients originally randomized to levodopa: 21/64 RD: 16.7% (95% CI 1.6%–30.8%)

Montastruc 1989 A randomized controlled study of bromocriptine versus levodopa in previously untreated Parkinsonian patients: A 3-year follow-up	Triple-masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than 2 primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class rating
	No	Yes	Unclear	No	No	Unclear	IV
	Population N Trial length	Intervention and comparator	Outcomes				
	Previously untreated patients with PD N=28 3 years	Bromocriptine n=15 Mean dose 50 mg Levodopa n=13 Mean dose 444 mg	Columbia Rating Scale Parkinsonian Disability: No statistical difference between bromocriptine and levodopa groups at any time of the study. **Abnormal movements** Levodopa: 4/13, 3 with peak dose dyskinesia, 1 with foot dystonia **Acute psychosis** Bromocriptine: 1/15 **Primary lack of efficacy** Bromocriptine: 3/15 **Secondary decrease in efficacy** Bromocriptine: 2/15				

Montastruc 1994 A randomized controlled study comparing bromocriptine to which levodopa was later added, with levodopa alone in previously	Triple-masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than 2 primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class rating
	No	Yes	Unclear	Yes	Yes	Yes	IV
	Population N Trial length	Intervention and comparator	Outcomes				

untreated patients with PD: A five-year follow-up	Patients 30–75 years of age with untreated PD, most H&Y stage I or II N=60 5 years	Initial treatment with bromocriptine alone to which levodopa was later added. Levodopa added to bromocriptine when a decline in efficacy of the maximum tolerated dose of bromocriptine occurred or when bromocriptine induced side effects necessitated lowering the dose. n=31 Levodopa alone from the start. n=29 Dose based on response. Maximum bromocriptine dose 90 mg/d.	Endpoint defined as the moment when the first motor complication occurred; peak dose or biphasic dyskinesia/dystonia or wearing-off or on-off phenomena. **Proportion of patients with motor complications at 5 years** Bromocriptine + levodopa: 14/25 Levodopa: 26/29 RD levodopa vs bromocriptine: + levodopa 33.7% (95% CI 10%–53.8%) **Proportion of patients with peak dose dyskinesia at 5 years** Bromocriptine + levodopa: 3/25 Levodopa: 14/29 RD: 36.3% (95% CI 11.6%–55.3%) **Proportion of patients with peak dose dystonia at 5 years** Bromocriptine + levodopa: 1/25 Levodopa: 2/29 RD: 2.9% (95% CI -13.4% to 18.3%) **Proportion of patients with wearing-off at 5 years** Bromocriptine + levodopa: 10/25 Levodopa: 10/29 RD: -5.5% (95% CI -29.7% to 19.1%) **Delay to reaching first motor complication from diagnosis** Bromocriptine + levodopa: 8.1 (SE 0.7) Levodopa: 5.4 (SE 0.7) $p<0.01$ **Delay to reaching first motor complication from first treatment** Bromocriptine + levodopa: 4.9 (SE 0.5) Levodopa: 2.7 (SE 0.5) $p<0.01$ **Delay to reaching first motor complication from levodopa** Bromocriptine+ levodopa: 2.2 (SE 0.4) Levodopa: 2.7 (SE 0.5) NS

			Delay to reaching wearing-off from diagnosis Bromocriptine + levodopa: 7.9 (SE 1.0) Levodopa: 6.2 (SE 0.9) NS **Delay to reaching wearing-off from first treatment** Bromocriptine + levodopa: 4.5 (SE 0.6) Levodopa: 2.7 (SE 0.5) $p<0.01$ **Delay to reaching wearing-off from levodopa** Bromocriptine + levodopa: 2.1 (SE 0.5) Levodopa: 2.9 (SE 0.6) NS **Hallucinations or confusion before the occurrence of motor complications** Bromocriptine + levodopa: 5/25 Levodopa: 2/29 RD: -13.1% (95% CI -32.9% to 5.6%) **UPDRS motor score at 5 years** Bromocriptine + levodopa: 10.6 (SE 1.1; SD 5.5) Levodopa: 11.0 (SE 1.5; SD 8.1) NS RMD: 0.4 (95% CI -3.3 to 4.1)

Weiner 1993 Early combination therapy (bromocriptine and levodopa) does not prevent motor fluctuations in PD	Triple-masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than 2 primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class rating
	Yes	No	Unclear	Primary outcome not specified	No	Yes	III
	Population N Trial length	Intervention and comparator	Outcomes				
	PD patients not previously treated with levodopa or bromocriptine N=22	Bromocriptine monotherapy, up to 30 mg/d. Mean dose 18 mg. (n=6)	Motor examination: modified version of the Columbia University Scale Bromocriptine monotherapy: score decreased maximally by 1 month, but the degree of this improvement was not significant when compared with baseline. After this initial modest improvement, motor score became progressively worse despite increasing bromocriptine doses and				

	4 years	Levodopa monotherapy, up to 1200 mg/d. Mean dose 417 mg. (n=9) Bromocriptine levodopa combination therapy, up to 18 mg bromocriptine, 1200 mg levodopa, mean dose bromocriptine 14 mg, mean dose levodopa 386 mg (n=7)	exceeded baseline scores after 15 months. At no time did bromocriptine monotherapy result in significant improvement of motor examination scores. Levodopa monotherapy: achieved statistically significant improvement at 3 months (p<0.03) and peak improvement at 6 months (p<0.0001). Motor examination score remained consistently below that of the baseline throughout the study. Combination therapy: reached peak improvement in motor examination score at 3 months, but the degree of improvement never reached significance compared with baseline. One-way ANOVA revealed no significant difference between the three groups at any time. Late complications of therapy (no difference between groups except for dystonia) **Motor fluctuations** Bromocriptine: 1/6 Levodopa: 3/9 RD levodopa vs bromocriptine: 16.7% (95% CI -28.4% to 50.8%) Combination: 5/7 RD levodopa vs combination: -38.1% (95% CI -67.5% to 9.2%) **Dystonia** Bromocriptine: 2/6 Levodopa: 9/9 RD levodopa vs bromocriptine: 66.7% (95% CI 19.3%–90.3%) Combination: 5/7 RD levodopa vs combination: 28.6% (95% CI -7.6% to 64.1%) **Chorea** Bromocriptine: 1/6 Levodopa: 5/9 RD levodopa vs bromocriptine: 38.9% (95% CI -10.2% to 67.9%) Combination: 4/7

			RD levodopa vs combination: -1.59% (95% CI -41.2% to 39.5%) **Freezing** Bromocriptine: 5/6 Levodopa: 2/9 RD levodopa vs bromocriptine: 5.6% (95% CI -37.2% to 40.8%) Combination: 4/7 RD levodopa vs combination: -34.9% (95% CI -66.3% to 10.8%)

Bakheit 1990 Long-term double-masked trial of early treatment with levodopa plus bromocriptine vs levodopa alone in PD. Interim results.	Triple-masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than 2 primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class rating
	Yes, masked evaluator and patient	Yes	Unclear	Primary outcome not stated	Yes	Yes	II
	Population N Trial length	Intervention and comparator	Outcomes				
	Early PD, under treatment with levodopa <750 mg for less than 2 years N=31 One-year results	Levodopa maximum dose 750 mg/d plus bromocriptine 10 mg three times a day n=16 Levodopa maximum dose 750 mg per day plus placebo n=15	**Mean dose of levodopa at 12 months** Levodopa plus bromocriptine: 136 mg/d Levodopa plus placebo: 361 mg/d $p<0.01$ **North Western University Disability rating scale at 12 months** Levodopa plus bromocriptine: 46.0 Levodopa plus placebo: 45.5 $p=0.04$ **Withdrawal due to side effects** Levodopa plus bromocriptine: 3/16 Levodopa plus placebo: 0/15 RD levodopa vs combination: -18.8% (95% CI -43% to 5%)				

Gimenez-Roldan 1997	Triple-masked or objective	Baseline characteristics	Concealed allocation	No more than 2 primary	Inclusion exclusion	Minimum 80%	Class rating

Early combination of bromocriptine and levodopa in PD: a prospective randomized study of two parallel groups over a total follow-up period of 44 months including an initial 8-month double-blind stage	outcome rating	presented and equivalent		outcomes specified	criteria defined	completion rate	
	Double-blind placebo-controlled stage (8 months) plus open-label stage	Yes	Unclear	Not stated	Yes	Yes for placebo-controlled stage No for open-label stage	II for placebo-controlled stage, IV for open-label stage
	Population N Trial length	Intervention and comparator	Outcomes				
	PD between 40–70, maximum H&Y III, response to levodopa introduced 2–6 months before entering study N=57 8 months double-blind; 44 months open label	Levodopa plus bromocriptine (maximum 30 mg/d) n=27 for 8 months, n=21 for 44 months Levodopa plus placebo n=23 for 8 months, n=19 for 44 months Attempts were made to lower levodopa dosage once target bromocriptine dosage reached	**Mean daily levodopa dosage at end of double-blind period (8 months)** Levodopa plus bromocriptine: 464.8 (SD 296 mg/d) Levodopa plus placebo: 507.6 (SD 164 mg/d) (non-significant) Bromocriptine dose: 15 mg/d **Mean daily levodopa dosage at end of open label period (44 months)** Levodopa plus bromocriptine: 515.4 (SD 240 mg/d) Levodopa plus placebo: 725.6 (SD 230 mg/d) $p<0.01$ Bromocriptine dose: 24.2 (SD 5.7 mg/d) **Number of patients reporting response oscillations at 44 months** Levodopa plus bromocriptine: 14.2% (3/21) Levodopa plus placebo: 47.3% (9/19) RD levodopa vs combination: 33.1% (95% CI 4.5%–56%) **Number of patients reporting choreic dyskinesias at 44 months** Levodopa plus bromocriptine: 9.5% (2/21) Levodopa plus placebo: 36.8% (7/19) RD levodopa vs combination: 27.3% (95% CI 1.1%–50.5%) **Mean UPDRS motor subscale scores, baseline vs 44 months** Levodopa plus bromocriptine: 17.0 (SD 11.0) baseline, 10.3 (SD 14.1) endpoint, change -6.7 (SD 17.9)			

			Levodopa plus placebo 19.4 (SD 9.6) baseline, 22.6 (SD 14.3) endpoint, change 3.2 (SD 20.0) RMD change: 9.9 (95% CI -1.9 to 21.7)

Przuntek 1992 Primary combination therapy of early PD. **Pruntek 1996** Early institution of bromocriptine in PD inhibits the emergence of levodopa-associated motor side effects. Long-term results of the PRADO study.	Triple-masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than 2 primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class rating
	No	Yes	Unclear	Yes	Yes	No	IV
	Population N Trial length	Intervention and comparator	Outcomes				
	Drug-naïve de novo PD patients, H&Y stage I to IV N=587 4 years	Levodopa/ benserazide n=302 Mean dose at 4 years 439 mg (SD 169) Levodopa/ benserazide plus bromocriptine n=285 Mean dose at 4 years 308 mg (SD 136) levodopa plus 13.8 mg (SD 7.1) bromocriptine Study started with 3 months of levodopa monotherapy for both groups, followed by gradual substitution of levodopa up to 30%–50% by bromocriptine	Primary endpoints: time of onset of the first manifestation of any motor side effect and the cumulative sum score covering all assessments during the study. **AE-related discontinuation** Levodopa: 15/302 Levodopa plus bromocriptine: 40/285 RD: -9.1% (95% CI -14.0 to -4.4%) **Motor side effects** Levodopa: 87/302 (28.8%) Levodopa plus bromocriptine: 57/285 (20%) *p*=0.008 RD: 8.8% (95% CI 1.8%–15.6%) **Cumulative probability of experiencing motor side effects** Levodopa: 0.43 Levodopa plus bromocriptine: 0.28 *p*=0.0252 **Mean time until first occurrence of some motor side effect** Levodopa: 3.18 (SE 0.08) years Levodopa plus bromocriptine: 3.43 (SE 0.08) years The cumulative probability of experiencing the first motor side effect within 4 years decreased with the amount of substitution of levodopa by bromocriptine. **Hallucinations** Levodopa: 19/302			

		in the bromocriptine group between the third and sixth month of the study.	Levodopa plus bromocriptine: 15/285 RD: 1.0% (95% CI -2.9% to 4.9%)

PD Med Collaborative Group 2014 Long-term effectiveness of DAs and MAO-B inhibitors compared with levodopa as initial treatment for PD: a large open-label pragmatic randomized trial	Triple-masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than 2 primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class rating
	No, open label randomized trial. Three randomization options: 1. levodopa vs DA vs MAO-B inhibitors (n=1058) 2. levodopa vs DA (n=348) 3. DA vs MAO-B inhibitors (n=214)	No, patients assigned only to DAs and MAO-B inhibitors had less severe disease and were younger	Yes	Yes	Yes	Yes	IV
	Population N Trial length	Intervention and comparator	Outcomes				
	Early PD, untreated or treated for less than 6 months N=1620 3-year median follow-up (range 0–9 years)	DA n=632 MAO-B inhibitor n=460 Levodopa n=528	Primary outcomes were the mobility dimension on the 39-item patient rated PD questionnaire quality of life scale PDQ-39, and cost-effectiveness **Discontinuation of allocated drug over 7 years** MAO-B inhibitors: 72% (331/460) DAs: 50% (316/632) Levodopa: 7% (37/528) *p*<0.0001 RD levodopa vs MAO-B inhibitors: -65% (95% CI -69.3% to -60.0%) RD levodopa vs DA: -43% (95% CI -47.3% to -38.4%) **AE-related discontinuation** MAO-B inhibitors: 104/460				

			DAs: 179/632 Levodopa: 11/528 *p*<0.0001 RD levodopa vs MAO-B inhibitor: -20.5% (95% CI -24.7% to -16.6%) RD levodopa vs DA: -26.2% (95% CI -30.0% to -22.5%) **2-year probability of requiring a drug from another class added to their treatment** MAO-B inhibitors: 64% DAs: 40% Levodopa: 20% **Mean daily levodopa dosage at 1 year** MAO-B inhibitor: 131 mg/d (SD 172) DA: 96 mg/d (SD 157) Levodopa: 347 mg/d (SD 139) **Mean daily levodopa dosage at 7 years** MAO-B inhibitor: 489 mg/d (SD 246) DA: 526 mg/d (SD 266) Levodopa: 531 mg/d (SD 229) **PDQ-39 mobility scores** did not differ significantly between the levodopa group and levodopa-sparing group at any follow-up assessment. However, the average score during the first 7 years of follow up was 1.8 points (95% CI 0.5–3.0; *p*=0.005) better with levodopa than with levodopa-sparing therapy. PDQ-39 mobility scores averaged 1.4 points (95% CI 0.0–2.9, *p*=0.05) better in patients initiating therapy with MAO-B inhibitors than DAs. **H&Y disease stage scores** were on average 0.07 (95% CI 0.03–0.12; *p*=0.0009) points better with levodopa than with levodopa-sparing therapy. Patients in the levodopa group were more likely to develop **dyskinesia** than those in the levodopa-sparing group (HR 1.52, 95% CI 1.16–2.00, *p*=0.003) Levodopa: 109/528 Levodopa sparing: 121/878 RD: 6.9% (95% CI 2.8%–11.1%)

			Rates of dyskinesia were similar (HR 0.85, 95% CI 0.6–1.22; *p*=0.4) in the DA and MAO-B inhibitor groups. DA: 62/459 Levodopa vs DA: RD 7.1% (95% CI 2.4%–11.8%) MAO-B inhibitor: 63/460 Levodopa vs MAO-B inhibitor: RD 7% (95% CI 2.2%–11.6%) There was no difference in **motor fluctuations** (HR 1.11, 95% CI 0.90–1.37; *p*=0.3) between levodopa and levodopa-sparing groups. Motor fluctuations were higher in the DA group than in the MAO-B inhibitor group (HR 1.32, 95% CI 1.01–1.72; *p*=0.04). Levodopa: 150/528 DA: 125/459 Levodopa vs DA: RD 1.2% (95% CI -4.5%–6.7%) MAO-B inhibitor: 101/460 Levodopa vs MAO-B inhibitor: RD 6.5% (95% CI 1%–11.8%)

Italian Parkinson Study Group 1992 A multicenter Italian randomized study on early treatment of PD: comparison of L-dopa, l-deprenyl, and dopaminoagonists. Study design and short-term results. **Caraceni 2001** Levodopa or dopamine agonists, or deprenyl as initial treatment for PD. A randomized multicenter study.	Triple-masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than 2 primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class rating
	No, randomized open trial	Yes	Yes	Yes	Yes	Yes	IV
	Population N Trial length	Intervention and comparator	Outcomes				
	Idiopathic PD mean duration of symptom onset 17 months N=475 2 months (IPSG) 3 years (Carceni)	Levodopa (max dose 750 mg) DA (lisuride 3 mg max or bromocriptine 60 mg max) Deprenyl (max dose 10 mg) Those assigned to	Primary outcome: occurrence of motor fluctuations and dyskinesias **Mean difference on UPDRS motor score between baseline and two-month follow-up visit** Levodopa: -3.4 (SE 0.39) Bromocriptine: -2.3 (SE 0.55) Lisuride: -3.2 (SE 0.44) Deprenyl: -2.4 (SE 0.38) *p*<0.0001 for all comparisons to baseline no difference between treatments **Mean difference on H&Y between baseline and two-month follow-up visit** Levodopa: -0.1 (SE 0.03)				

		DAs or deprenyl originally could add levodopa whenever required.	Bromocriptine: -0.1 (SE 0.06) Lisuride: -0.2 (SE 0.04) Deprenyl: -0.1 (SE 0.04) $p<0.0001$ for all comparisons to baseline no difference between treatments **Presence of motor fluctuations at 3 years** Levodopa: 46/156 (29.7%) DA: 27/162 (16.7%) Deprenyl: 29/155 (18.7%) RD levodopa vs DA: 12.8% (95% CI 3.6%–21.9%) RD levodopa vs deprenyl: 10.8% (95% 1.3%–20.1%) RD DA vs deprenyl: -2.0% (95% CI -10.5% to 6.4%) OR levodopa vs DA: 2.09 (95% CI 1.22–3.56) OR levodopa vs deprenyl: 1.82 (95% CI 1.07–3.07) OR DA vs deprenyl: 0.87 (95% CI 0.49–1.54) **Mean time to development of motor fluctuations** Levodopa: 26 months (SE 2.3) DA: 23 (SE 3.2) Deprenyl: 29 (SE 3.2) **Presence of dyskinesia at 3 years** Levodopa: 42/156 (27.1%) DA: 24/162 (14.8%) Deprenyl: 32/155 (20.6%) RD levodopa vs DA: 12.1% (95% CI 3.2%–20.9%) RD levodopa vs deprenyl: 6.3% (95% CI -3.2% to 15.6%) RD DA vs deprenyl: -5.8% (95% CI -14.3% to 2.6%) OR levodopa vs DA: 2.12 (95% CI 1.21–3.69) OR levodopa vs deprenyl: 1.42 (95% CI 0.84–2.39) OR DA vs deprenyl: 0.67 (95% CI 0.38–1.19) **Mean time to development of dyskinesia** Levodopa: 26 months (SE 2.3) DA: 18 (SE 2.9) Deprenyl: 21 (SE 2.6) **Motor score equal or worse than before treatment at 3 years** Levodopa: 43/156 (27.7%) DA: 60/162 (37.0%) Deprenyl: 51/155 (32.9%) RD levodopa vs DA: -9.5% (95% CI -19.5% to 0.1%)

			RD levodopa vs deprenyl: -5.3% (95% CI -15.4% to 4.9%) RD DA vs deprenyl: 4.1% (95% CI -6.3% to 14.4%) OR levodopa vs DA: 0.65 (95% CI 0.40–1.04) OR levodopa vs deprenyl: 0.78 (95% CI 0.48–1.26) OR DA vs deprenyl: 1.20 (95% CI 0.76–1.90) **Treatment withdrawal** Levodopa: 10/156 (6.4%) DA: 53/162 (32.7%) Deprenyl: 30/155 (19.4%) RD levodopa vs DA: -26.3% (95% CI -34.4% to -17.9%) RD levodopa vs deprenyl: -12.9% (95% CI -20.5% to -5.6%) RD DA vs deprenyl: 13.4% (95% CI 3.7%–22.7%) **Add-on therapy** Levodopa: 20/156 (12.9%) DA: 66/162 (40.7%) Deprenyl: 99/155 (63.9%) RD levodopa vs DA: -27.9% (95% CI -36.8% to -18.4%) RD levodopa vs deprenyl: -51.1% (95% CI -59.4% to -41.1%) RD DA vs deprenyl: -23.1% (95% CI -33.3% to -12.2%) OR levodopa vs DA: 0.21 (95% CI 0.12–0.38) OR levodopa vs deprenyl: 0.08 (95% CI 0.05–0.15) OR DA vs deprenyl: 0.39 (95% CI 0.25–0.61)

Parkinson's Study Group 2000 Pramipexole vs levodopa as initial treatment for PD.	Triple-masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than 2 primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class rating
	Yes	Yes	Yes	Yes	Yes	Yes	I
	Population N Trial length	Intervention and comparator	Outcomes				
	PD patients, H&Y stage I to III, requiring dopaminergic therapy at the	Pramipexole, up to 4.5 mg Average dose 2.78 mg/d n=151	Primary outcome: time from randomization until the first occurrence of any of 3 specified dopaminergic complications: wearing-off, dyskinesia, or on-off fluctuations.				

	time of enrollment N=301 2 years	Levodopa up to 600 mg Average dose 406 mg/d n=150 Open label levodopa could be prescribed to both groups as needed	**Proportion of subjects requiring supplemental levodopa** Pramipexole: 53% Levodopa: 39% HR: 1.54 (95% CI 1.09–2.17; *p*=0.02) **First dopaminergic complications** (proportion of subjects who reached the primary endpoint by 2 years) Pramipexole: 42/151 (28%) Levodopa: 76/150 (51%) HR: 0.45 (95% CI 0.30–0.66; *p*<0.001) RD levodopa vs pramipexole: 22.9% (95% CI 11.9%–33.1%) **Wearing-off** Pramipexole: 36/151 (24%) Levodopa: 57/150 (38%) HR: 0.57 (95% CI 0.37–0.88; *p*=0.01) RD levodopa vs pramipexole: 14.2% (95% CI 3.7%–24.2%) **Dyskinesia** Pramipexole: 15/151 (10%) Levodopa: 46/150 (31%) HR: 0.33 (95% CI 0.18–0.60; *p*<0.001) RD levodopa vs pramipexole: 20.7% (95% CI 11.8%–29.4%) **On-off fluctuations** Pramipexole: 2/151 (1%) Levodopa: 8/150 (5%) HR: 0.27 (95% CI 0.06–1.32; *p*=0.11) RD levodopa vs pramipexole: 4.0% (95% CI -0.3% to 8.9%) **Mean change from baseline to 2 years in UPDRS scores** Motor Pramipexole: -3.4 (SD 8.6) Levodopa: -7.3 (SD 8.6) Difference: -3.9 (95% CI -5.7 to -2.1; *p*<0.001) ADL Pramipexole: 1.1 (SD 4.5) Levodopa: 2.2 (SD 3.2) Difference: -1.4 (95% CI -2.2 to -0.5; *p*=0.001) **AE-related discontinuation**

			Pramipexole: 17/151 Levodopa: 10/150 RD levodopa vs pramipexole: -4.6% (95% CI -11.3% to 2.0%) **Hallucinations** Pramipexole: 14/151 Sinemet: 5/150 RD levodopa vs pramipexole: -5.9% (95% CI -11.9% to -0.3%)

Parkinson Study Group (Holloway) 2004 Pramipexole vs levodopa as initial treatment for PD Extension of trial above.	Triple-masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than 2 primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class rating
	Yes	Yes	Yes	Yes	Yes	No	II
	Population N Trial length	Intervention and comparator	Outcomes				
	PD H&Y stage I–III N=301 4 years	Pramipexole n=151 Levodopa n=150 Open label levodopa could be prescribed to both groups as needed.	Primary outcome: Time from randomization until the first occurrence of any of 3 specified dopaminergic complications—wearing-off, dyskinesia, or on-off fluctuations **Proportion of subjects requiring open-label levodopa** Pramipexole: 109/151 Levodopa: 89/150 **Mean total daily levodopa dosage** Pramipexole: 434 (SD 498 mg/d) Levodopa: 702 (SD 442 mg/d) Mean dose pramipexole: 2.78 (SD 1.1 mg/d) **Percentage of subjects reaching the primary end point of dyskinesia, wearing-off, or on-off fluctuations** Pramipexole: 78/151 (51.7%) Levodopa: 111/150 (74%) HR: 0.48 (95% CI 0.35–0.66; $p<0.0001$) RD levodopa vs pramipexole: 22.3% (95% CI 11.5%–32.5%) **Percentage of subjects reaching the primary end point of wearing-off**				

			Pramipexole: 71/151 (47%) Levodopa: 94/150 (62.7%) HR: 0.68 (0.49–0.93; *p*=0.02) RD: 15.7% (95% CI 4.4%–26.3%) **Percentage of subjects reaching the primary end point of dyskinesia** Pramipexole: 37/151 (24.5%) Levodopa: 81/150 (54%) HR: 0.37 (95% CI 0.25–0.56; *p*<0.001) RD: 29.5% (95% CI 18.6%–39.4%) **Percentage of subjects reaching the primary end point of on-off fluctuations** Pramipexole: 10/151 (6.6%) Levodopa: 12/150 (8%) HR: 0.64 (95% CI 0.26–1.59; *p*=0.34) RD: 1.4% (95% CI -4.8% to 7.6%) **Percentage of subjects with freezing** Pramipexole: 56/151 (37.1%) Levodopa: 38/150 (25.3%) HR: 1.7 (95% CI 1.11–2.59; *p*<0.0001) RD: -11.8% (95% CI -21.9 to -1.3%) **Mean change from baseline to month 48 in UPDRS** Motor Score Pramipexole: 1.3 (SD 13.3) Levodopa: -3.4 (SD 12.3) Treatment effect: -4.9 (95% CI -1.9 to -7.8; *p*=0.001) **Proportion of patients experiencing hallucinations** Pramipexole: 22/151 Levodopa: 12/150 RD: -6.6 (95% CI -13.9 to 0.7%)

Parkinson Study Group CALM Cohort Investigators 2009 Long-term effect of initiating	Triple-masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than 2 primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class rating
	No	Presented but not equivalent	Yes	Yes	Yes	No	IV
	Population N	Intervention and comparator	Outcomes				

pramipexole vs levodopa in early PD	Trial length		
	PD H&Y stage I–III. N=301 6 years	Pramipexole 108 entered cohort Levodopa 114 entered cohort Open label levodopa could be prescribed to both groups as needed.	Primary outcome variable: the time-weighted average of self-reported disability scores in the "on" and "off" states as measured by the Schwab and England Activities of Daily Living Scale **Proportion of patients on levodopa at final visit** Pramipexole: 98/108 (91%) Levodopa: 106/114 (93%) **Any dopaminergic complication at final visit** Pramipexole: 54/108 (50%) Levodopa: 78/114 (68%) RD levodopa vs pramipexole: 18.4% (95% CI 5.5%–30.5%) **Dyskinesia at final visit** Pramipexole: 22/108 (20%) Levodopa: 42/114 (37%) RD: 16.5% (95% CI 4.6%–27.7%) **Wearing-off at final visit** Pramipexole: 48/108 (44%) Levodopa: 67/114 (59%) RD: 14.3% (95% CI 1.2%–26.8%) **UPDRS motor score change from baseline visit** Pramipexole: 1.0 (SD 12.2) Levodopa: -1.2 (SD 12.9) Treatment effect: -2.7 (95% CI -5.9 to 0.6; *p*=0.1) Only 7 subjects (3/108 in the initial pramipexole group and 4/114 in the initial levodopa group) reported dyskinesia that was at least moderately disabling, and only 10 subjects (6 in the initial pramipexole group and 4 in the initial levodopa group) reported having painful dyskinesia at the final visit. RD: 0.7% (95% CI -4.8 to 6.2)

Rascol 2000 A 5-year study of the incidence of dyskinesias in patients	Triple-masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than 2 primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class rating
	Yes	Yes	Yes	Yes	Yes	No	II

with early PD who were treated with ropinirole or levodopa	Population N Trial length	Intervention and comparator	Outcomes
	PD, H&Y stage 1–3, requiring dopaminergic therapy N=268 5 years	Ropinirole, up to 24 mg per day n=179, 85 completed study Levodopa, up to 1200 mg per day n=89, 45 completed study	Primary outcome: incidence of dyskinesia Mean daily doses at study completion: 16.5 mg (SD 6.6 mg) ropinirole plus 427 mg (SD 221 mg) of open label levodopa supplementation, and 753 mg (SD 398 mg) of levodopa **Risk of dyskinesia** HR for remaining free of dyskinesia in ropinirole group compared to levodopa group: HR 2.82 (95% CI 1.78–4.44; *p*<0.001) **Proportion of patients developing dyskinesia** Ropinirole: 36/177 Levodopa: 40/88 RD levodopa vs ropinirole: 25.1% (95% CI 13.2%–36.8%) **HR** for remaining free of disabling dyskinesia in the ropinirole group compared with the levodopa group: HR 3.02 (95% CI 1.52–6.02; *p*=0.002) **Proportion of patients with disabling dyskinesia** Ropinirole: 14/179 Levodopa: 20/89 RD: 14.7% (95% CI 5.8%–24.8%) **Length of time until dyskinesia developed in 25% of patients remaining in study** Ropinirole: 214 weeks Levodopa: 104 weeks **Mean decrease from baseline in UPDRS part III motor score** (patients who completed study) Ropinirole: -0.8 (SD 10.1) (slight improvement) Levodopa: -4.8 (SD 8.3) Difference in mean scores, significant in favor of levodopa: -4.48 (95% CI -7.72 to -1.25; *p*=0.008) **Length of time until 25% of patients remaining in study first had an increase in the wearing-off effect** Ropinirole: 199 weeks

			Levodopa: 145 weeks **Proportion of patients who had an increase in symptoms due to wearing-off of the drugs during the study** Ropinirole: 39/172 Levodopa: 29/85 RD: 11.4% (95% CI 0% to 23.4%) **Withdrawal from study due to lack of efficacy** Ropinirole: 14/179 Levodopa: 5/89 RD: -2.2 (95% CI -8.0% to 5.3%) **AE-related early study withdrawal** Ropinirole: 48/179 Levodopa: 29/89 RD: 5.8% (95% CI -5.5% to 17.7%) **Neuropsychiatric adverse effects** Ropinirole: 43/179 Levodopa: 15/89 RD: -7.2% (95% CI -16.5% to 3.6%) **Hallucinations** Ropinirole: 31/179 Levodopa: 5/89 RD: -11.7% (95% CI -18.7% to -3.3%) **Dyskinesia (reported as an AE)** Ropinirole: 16/179 Levodopa: 23/89 RD: 16.9% (95% CI 7.5%–27.4%)

Hauser 2007 Ten-year follow-up of PD patients randomized to initial therapy with ropinirole or levodopa	Triple-masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than 2 primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class rating
	No, open-label extension study	Yes	Yes	No	Yes	No	IV
	Population N Trial length	Intervention and comparator	Outcomes				

	PD, H&Y stage 1–3, requiring dopaminergic therapy N=69 10 years	Ropinirole, up to 24 mg/d n=42, 28 completed study Levodopa, up to 1200 mg/d n=27, 20 completed study	**Levodopa dosage at final visit (month 120)** Ropinirole: 631.7 (SD 262.1) mg Levodopa: 800.2 (SD 397.3) mg **Mean LEDD** Ropinirole: 786.6 (SD 352.7) mg Levodopa: 862.5 (SD 518.5) mg **Adjusted mean change in UPDRS motor scores** Ropinirole: 9.5 (SE 2.8) Levodopa: 6.3 (SE 3.5) NS Treatment difference: -3.2 (95% CI -12.1 to 5.6; *p*=0.46) **Presence of dyskinesia** Ropinirole: 22/42 Levodopa: 21/27 Adjusted OR: 0.3 (95% CI 0.1 to 1.0; *p*=0.046) RD: 25.4% (95% CI 2.0%–44.1%) **Median time to dyskinesia** Ropinirole: 3156 days (8.6 years) Levodopa: 2563 days (7 years) Adjusted HR: 0.4 (95% CI 0.2–0.8; *p*=0.007) **Odds of exhibiting at least mildly disabling dyskinesia** Ropinirole: 6/42 Levodopa: 7/27 OR: 0.5 (95% CI 0.2–1.5; *p*=0.21) RD: 11.6% (95% CI -7% to 31.9%) **At least mild wearing-off** Ropinirole: 25/42 Levodopa: 18/27 Adjusted OR: 0.8 (95% CI 0.23–2.39; *p*=0.63) RD: 7.1% (95% CI -16% to 28.2%) **At least moderate wearing-off** Ropinirole: 8/42 Levodopa: 12/27 Adjusted OR: 0.3 (95% CI 0.09–0.90; *p*=0.03) RD: 25.4% (95% CI 3.3%–45.8%)

Whone 2003	Triple-masked or objective	Baseline characteristics	Concealed allocation	No more than 2 primary	Inclusion exclusion	Minimum 80%	Class rating

Slower progression of PD with ropinirole vs levodopa: the REAL-PET study	outcome rating	presented and equivalent		outcomes specified	criteria defined	completion rate	
	Yes	Yes	Yes	Yes	Yes	Yes	I
	Population N Trial length	Intervention and comparator	Outcomes				
	PD patients aged 30–75, H&Y stage I-2.5, symptom duration <2 years. Not previously treated with levodopa or DAs and determined to require such therapy. N=162 2 years	Ropinirole, max 24 mg/d n=87 Mean dose at 2 years 12.2 mg/d Levodopa, max 1000 mg/d n=75 Mean dose at 2 years 558.7 mg/d	Primary outcome: mean percentage reduction in side to side averaged putamen 18F-dopa uptake **Adjusted mean change in "on" UPDRS motor score from baseline to endpoint (2 years)** Ropinirole: + 0.70 (SE 0.97, SD 9.0) Levodopa: – 5.64 (SE 1.05, SD 9.1) Motor function was superior with levodopa compared with ropinirole (95% CI 3.54–9.14) RMD: -6.34 (95% CI -9.14 to -3.54) **Incidence of dyskinesia** Ropinirole: 3/87 Levodopa: 20/75 OR: 0.09 (95% CI 0.02–0.29; *p*<0.001) RD levodopa vs ropinirole: 23.2% (95% CI 12.5–34.4) **Time to develop dyskinesia (in favor of ropinirole)** HR: 8.28 (95% CI 2.46–27.93; *p*<0.001) **Hallucinations** Ropinirole: 6/87 Levodopa: 1/75 RD: -5.5% (95% CI -13% to 1.4%) **AE-related discontinuation** Ropinirole: 13/87 Levodopa: 4/75 RD: -9.6% (95% CI -19% to 0.001%)				

Watts 2010 Onset of dyskinesia with adjunct ropinirole prolonged-release or additional	Triple-masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than 2 primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class rating
	Yes	Yes	Yes	Yes	Yes	No	II
	Population N Trial length	Intervention and comparator	Outcomes				

levodopa in early PD	Idiopathic PD ages 30–70, H&Y stage I–III, on levodopa maximum dose 600 mg, not longer than 3 years, suboptimal symptom control, mild wearing-off and simple motor fluctuations. No DA use within 6 weeks of screening. N=208 104 weeks	Ropinirole PR, up to 24 mg/d. Mean dose 10 mg. n=105 Levodopa, up to 1000 mg/d of additional levodopa (added to patient's baseline levodopa dosage) Mean dose added 284 mg. n=104	Primary endpoint: time to onset of dyskinesia measured by the investigators assessment of the presence of dyskinesia at each visit by indicating if dyskinesia was present by observation or by history on at least 2 study visits. **Number of patients developing dyskinesia** Ropinirole PR: 3/105 Levodopa: 18/104 OR: 0.14 (95% CI 0.04–0.48) RD: 14.4% (95% CI 6.5%–23.1%) There was a significant delay in the time to onset of dyskinesia for subjects treated with ropinirole PR compared with levodopa (HR 6.46; $p<0.001$). **Mean change in UPDRS motor score from baseline to week 28** (no significant difference) Ropinirole PR: -3.7 (SD 9.3) (n=83) Levodopa: -3.5 (SD 7.0) (n=81) RMD: 0.20 (95% CI -2.32 to 2.72) Standardized mean difference (SMD): 0.02 (95% CI -0.28 to 0.33) **Adverse effect–related withdrawal** Ropinirole: 15/105 Levodopa: 9/104 RD: -5.6% (95% CI -14.6% to 3.2%)

Bracco 2004 The long-acting dopamine receptor agonist cabergoline in early PD. Final results of a 5-year double-blind levodopa-controlled study	Triple-masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than 2 primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class rating
	Yes	Yes	Yes	Yes	Yes	No	II
	Population N Trial length	Intervention and comparator	Outcomes				
	Levodopa, DA, and selegiline naïve patients with newly diagnosed PD N=419	Cabergoline, flexible dose, up to 4 mg, average dose 2.8–2.9 mg. Levodopa could be	Primary efficacy endpoint was the development of motor complications confirmed at 2 consecutive 3-monthly visits. **AE-related premature discontinuation from the study** Cabergoline: 42/211 Levodopa: 29/208 RD: -5.9% (95% CI -13.1% to 1.3%)				

	Until confirmed development of motor complications, or up to a minimum of 3 years and maximum of 5 years	added if necessary. n=211 Levodopa, flexible dose, up to 600 mg n=209	**Mean levodopa dosage at 5 years** Cabergoline: 431 mg Levodopa: 784 mg **Dyskinesia at 5 years** Cabergoline: 20/211 Levodopa: 44/208 RD: 11.7% (95% CI 4.8%–18.5%) OR: 0.39 (95% CI 0.22–0.69) **End of dose failures at 5 years** Cabergoline: 34/211 Levodopa: 46/208 RD: 6% (95% CI -1.6% to 13.5%) OR: 0.67 (95% CI 0.42–1.10) **Unpredictable fluctuations at 5 years** Cabergoline: 5/211 Levodopa: 6/208 RD: 0.5% (95% CI -0.03% to 0.04%) OR: 0.82 (95% CI 0.25–2.64) **More than 1 motor complication at 5 years** Cabergoline: 47/211 Levodopa: 70/208 RD: 11.4% (95% CI 2.8%–19.8%) OR: 0.57 (95% CI 0.37–0.87) Addition of levodopa more than doubled the risk of developing motor complications in both treatment groups. **Motor disability** Mean UPDRS section III scores over time were statistically significantly lower ($p<0.01$) in the levodopa group than in the cabergoline group, with mean values of 13.8 vs 12.9 in the cabergoline vs levodopa arm at 1 year, 18.6 vs 17.2 at 3 years, and 19.2 vs 16.3 at 5 years. RMD at 5 years: 2.9 (95% CI 0.7–5.1) SMD at 5 years: 0.25 (95% CI 0.06–0.44) Satisfactory clinical improvements in motor disability (defined as a >30% decrease in mean UPDRS section III score vs baseline) were seen in 81.4% of patients in the cabergoline group vs 86.6% of patients in the levodopa group at 1 year, 58.9% vs 75.6% at 3 years, and 46.4% vs 67.9% at 5 years. Between-treatment differences for these

			values were statistically significant at 3 years (p<0.01) and 4 years (p<0.05). **Adverse effects** The cabergoline treated group had a slightly higher frequency of nausea, vomiting, dyspepsia, and gastritis (37.4% vs 32.2% in the levodopa group). Dizziness and postural hypotension were also slightly more common in the cabergoline treated group (31.3% vs 24%). Peripheral oedema was more common in the cabergoline-treated group than in the levodopa group and was the only AE showing a significantly higher risk of frequency in cabergoline-treated patients compared with levodopa-treated patients (16.1% vs 3.4%, p<0.0001). Hallucination occurred in 4.3% of patients in the cabergoline group, a frequency comparable to that in the levodopa group (4.8%). **Hallucinations** Levodopa: 9/209 Cabergoline: 10/211 RD: -0.4% (95% CI -4.7 to 3.8)

Rinne 1998 Early treatment of PD with cabergoline delays the onset of motor complications	Triple-masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than 2 primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class rating
	Yes	Yes	Unclear	Yes	Yes	Unclear	II
	Population N Trial length	Intervention and comparator	Outcomes				
	Previously untreated PD patients, H&Y stage I to III N=412 3 years	Cabergoline, maximum 4 mg/d. Median dose 3 mg. n=208 Levodopa, maximum 600 mg/d. Median dose 500 mg. n=204	Primary endpoint: onset of motor complications confirmed at 2 subsequent visits **Study endpoint** (development of motor complications confirmed at two consecutive 3-month visits) Cabergoline: 47/208 (22%) Levodopa: 70/204 (34%) RD: 11.7% (95% CI 3.0%–20.2%) OR: 0.56 (95% CI 0.36–0.86) **Peak dose dyskinesia** Cabergoline: 12/208 Levodopa: 28/204				

		Open-label levodopa could be added in both treatment arms	RD: 8.0% (95% CI 2.2%–13.9%) OR: 0.38 (95% CI 0.19–0.78) Time to onset of motor complications was significantly different between two groups (p<0.02)—lower for cabergoline group than levodopa group. Relative risk of developing motor complications with cabergoline was more than 50% lower than with levodopa. Cabergoline treated patients requiring the addition of levodopa were at the same risk of developing motor complications as those on a stable levodopa dose. **UPDRS part III scores** After 4 years, levodopa recipients showed an average 30% improvement in motor disability and cabergoline treated patients there was a 22% to 23% improvement vs baseline. **Treatment withdrawal** Cabergoline: 16% (33/208) Levodopa: 13% (27/204) RD: -2.6% (95% CI -9.5 to 4.3)

Utsumi 2012 Long-term effects of cabergoline and levodopa in Japanese patients with early PD: a 5-year prospective study	Triple-masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than 2 primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class rating
	No	Yes	Unclear	Yes	Yes	No	IV
	Population N Trial length	Intervention and comparator	Outcomes				
	PD patients 40–70 years, H&Y stage I–III. Never treated with DAs or levodopa. N=98 5 years	Cabergoline, up to 6 mg/d. Mean dose 2.9 mg. n=49 Mean levodopa dose 325 mg. Levodopa, up to 600 mg/d. Mean dose 336 mg.	Primary endpoint: Development of motor complications—dyskinesia, wearing-off, or on-off motor fluctuations **AE-related discontinuation** Cabergoline: 11/49 Levodopa: 2/49 RD: -18.4% (95% CI -4.9% to -32.1%) **Motor complications** Cabergoline: 4/49 Levodopa: 11/49 RD: 14.3% (95% CI -0.2% to 28.6%) OR: 0.31 (95% CI 0.10–1.02)				

		n=49 Mean cabergoline dose 1.6 mg. If necessary to start additional therapy for PD, levodopa and cabergoline could be added to treatment.	Estimated cumulative incidence of motor complications was 17% (95% CI 0%–33%) in the initial cabergoline group and 34% (95% CI 15%–49%) in the initial levodopa group. HR was 0.57 (95% CI 0.18–1.81; *p*=0.347). UPDRS motor score: changes from baseline to 5 years were not significantly different between the initial cabergoline and levodopa groups.

Oertel 2006 Pergolide vs levodopa monotherapy in early PD patients: The PELMOPET study.	Triple-masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than 2 primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class rating
	Yes	Yes	Unclear	No	Yes	No	III
	Population N Trial length	Intervention and comparator	Outcomes				
	Dopamine naïve patients with early PD (H&Y 1–2.5), ages 30 to 75 years, within 2 years of diagnosis of PD. N=294 3 years	Pergolide monotherapy, maximum 5mg/d n=147 Mean daily dose at 3 years: 3.23 (SD 1.36 mg) Levodopa monotherapy, maximum 1200 mg/d n=146 Mean daily dose at 3 years (504 SD 213 mg)	Primary outcome measures were clinical efficacy, severity and time to onset of motor complications, and disease progression. **Symptomatic improvement at 1 year** Mean change from baseline on UPDRS part III motor examination Pergolide: -3.2 Levodopa: -5.2 RMD: -1.92 (95% CI -3.4 to -0.43; *p*=0.006) SMD: 0.30 (95% CI 0.07–0.53; *p*=0.01) **Symptomatic improvement at three years** Mean change from baseline on UPDRS part II motor aspects of experiences of daily living Pergolide: 2.3 (SD 4.9) Levodopa: -0.6 (SD 3.7) RMD: -2.9 (95% CI -3.9 to -1.9; *p*<0.0001) SMD: 0.66 (95% CI 0.43–0.90; *p*<0.0001)				

			Mean change from baseline on UPDRS part III motor examination Pergolide: 2.8 (SD 9.8) Levodopa: -2.8 (SD 7.8) RMD: -5.6 (95% CI -7.6 to -3.6; *p*<0.0001) SMD: 0.64 (95% CI 0.41–0.88; *p*<0.0001) **Motor complications** UPDRS part IVa (complications of therapy: dyskinesia) Mean change from baseline Pergolide: 0.18 (SD 0.94) Levodopa: 0.51 (SD 1.24) RMD: 0.33 (95% CI 0.08–0.58; *p*=0.01) SMD: 0.30 (95% CI 0.07–0.53) UPDRS part IVb (Complications of therapy: fluctuations, wearing-off) Mean change from baseline Pergolide: 0.24 (SD 0.79) Levodopa: 0.32 (SD 0.83) RMD: 0.08 (95% CI -0.11 to 0.27) SMD: 0.10 (95% CI -0.13 to 0.33) **Incidence of dyskinesia** Pergolide: 12/147 (8.2%) Levodopa: 38/146 (26%) RD: 17.9% (95% CI 9.4%–26.3%) OR: 0.25 (95% CI 0.13–0.51) **Incidence of motor complications** Pergolide: 45/147 (30.6%) Levodopa: 64/146 (43.8%) RD: 13.2% (95% CI 2.2%–23.9%) OR: 0.57 (95% CI 0.35–0.91) Time to onset of motor complications, defined by the first positive UPDRS IVa or b score, was not significantly different between the groups after 3 years. HR for developing motor complications for patients in the pergolide group vs levodopa was 0.69 (95% CI 0.47–1.03). Time to onset of dyskinesia, defined by the first positive UPDRS IVa score, was longer in the pergolide group compared with that in the levodopa group. HR for developing dyskinesias for patients in the pergolide

			group vs the levodopa group was 0.48 (95% CI 0.29–0.80). **AE-related discontinuation** Pergolide: 26/147 Levodopa: 16/146 RD: -6.7% (95% CI -14.8% to 1.4%) **Hallucinations** Pergolide: 5/147 Levodopa: 0/146 RD: -3.4% (95% CI -0.2% to -7.7%)

Zhao 2006 Effect of pergolide and madopar as initial treatment on the prognosis of patients with PD	Triple-masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than 2 primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class rating
	Unclear	No	Unclear	Yes	Yes	Yes	IV
	Population N Trial length	Intervention and comparator	Outcomes				
	PD patients ages 50–70 years, H&Y stage I or II N=36 10 months	Artane 0.2 mg n=12 Madopar 500 mg (levodopa/ benserazide) n=12 Pergolide 0.2 mg n=12	Primary outcomes: 1. Dopamine transporter imaging, 2. Change in UPDRS scores before and after treatment **UPDRS Score** Before treatment Artane: 14.18 (SD 7.56) Madopar: 15.5 (SD 8.68) Pergolide: 15.8 (SD 6.75) At 10 months Artane: 14.14 (SD 9.8) Madopar: 6.4 (SD 9.05) Pergolide: 10.36 (SD 8.3) RMD (Pergolide vs Madopar): 3.96 (95% CI -2.99 to 10.91)				

Levodopa vs levodopa plus lisuride

Allain 2000 Five-year follow-up of early lisuride	Triple-masked or objective	Baseline characteristics presented and equivalent	Concealed allocation	No more than 2 primary	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class rating

and levodopa combination therapy versus levodopa monotherapy in de novo PD	outcome rating			outcomes specified			
	Yes, for first year; open study for years 2–5	Yes	Unclear	Yes	Yes	No	Class IV
	Population N Trial length	Intervention and comparator	Outcomes				
	Idiopathic PD, mean H&Y 1.43 (SD 0.5) levodopa, 1.59 (SD 0.4) levodopa plus lisuride N=82 5 years	Levodopa (Modopar; levodopa plus benserazide) + placebo vs. Levodopa + lisuride Selegiline 10 mg added to both groups after 1 year	Primary outcomes: progression of levodopa dosage and scores on UPDRS **Levodopa dosage at 5 years** Levodopa plus placebo: 446.7 mg (SD 139.5) Levodopa plus lisuride: 387.5 mg (SD 156.2) RMD: 59.2 mg (95% CI -4.9 to 123.3) **UPDRS part III motor examination score at 5 years** (data extrapolated from graph) Levodopa plus placebo: 26 (95% CI 24–28.8) Levodopa plus lisuride: 18 (95% CI 16–19.2) Disease progression evaluated with H&Y remained unchanged in both groups with no significant difference between groups. The average score never reached 3 (no further data given). **UPDRS part IV dyskinesia, fluctuations, other complications score at 5 years** Levodopa plus placebo: 0.96 (SD 1.3) Levodopa plus lisuride: 0.73 (SD 1.1) RMD: 0.23 (95% CI -0.29 to 0.75) **Dyskinesia observed** Levodopa plus placebo: 14/41 (34.1%) Levodopa plus lisuride: 8/41 (19.5%) RD: 14.6% (95% CI -4.6% to 32.5%) **Clinical fluctuations** Levodopa plus placebo: 6/41 (14.6%) Levodopa plus lisuride: 9/41 (22%) RD: -7.3% (95% CI -24% to 9.7%)			

			Patients treated with lisuride had a higher rate of psychiatric events, insomnia, and gastrointestinal disorders.

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* (including motor complications) of **different formulations of DAs**?

Thomas 2006 End of dose deterioration in non ergolinic dopamine agonist monotherapy of PD	Triple-masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than 2 primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class rating
	Assessor-blinded	Yes	Unclear	Yes	Yes	No	II
	Population N Trial length	Intervention and comparator	Outcomes				
	De novo PD, previously untreated, H&Y stage I–II N=52 2 years	Ropinirole, up to 24 mg n=27 Pramipexole, up to 4.2 mg n=25	Primary outcome: Self-reported wearing-off periods confirmed by a 30% worsening in the UPDRS motor score during the 5 hours after a DA dose Proportion of patients experiencing wearing-off periods over course of study Ropinirole: 10/27 Pramipexole: 8/25 No significant difference between groups. RR: 1.14 (95% CI 0.72–1.82, *p*=0.58) RD: 5% (95% CI -20% to 28.9%) No difference in UPDRS motor scores between groups throughout the study. Inadequate data in article to calculate RMD between ropinirole and pramipexole.				

Hauser 2010 Randomized, double-blind, multicenter evaluation of pramipexole extended release once	Triple-masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than 2 primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class rating
	Yes	Yes, more males in pramipexole group, but	Yes	Yes	Yes	Yes	I

daily in early PD		males do worse so bias in favor of null hypothesis					
	Population N Trial length	Intervention and comparator	Outcomes				
	PD, H&Y stage I to III, in need of dopaminergic treatment, not previously treated with levodopa N=259 18 weeks	Placebo (n=50) Pramipexole ER mean dose 3.05 mg (n=102) Pramipexole IR mean dose 3.03 mg (n=101) Open label levodopa rescue allowed during maintenance phase, if required—given to 7 patients in placebo group, 3 in ER group, 1 in IR group	Primary efficacy endpoint: change from baseline to week 18 in the sum of parts II and III of the UPDRS **UPDRS parts II and III score, adjusted mean change, with levodopa data censored** Placebo: -2.7 (SE 1.3) Pramipexole ER: -7.4 (SE 1.1, SD 11.1; *p*=0.001) vs placebo Pramipexole IR: -7.5 (SE 1.1, SD 11.1; *p*=0.0006) vs placebo RMD ER vs IR: 0.1 (95% CI -3.0 to 3.2) **UPDRS part III score, adjusted mean change, with levodopa data censored** Placebo: -2.7 (SE 1.0) Pramipexole ER: -5.9 (SE 0.9, SD 9.1; *p*=0.0039) vs placebo Pramipexole IR: -5.9 (SE 0.8, SD 8.0; *p*=0.0038) vs placebo RMD ER vs IR: 0 (95% CI -2.4 to 2.4) **AE-related discontinuation** Placebo: 2/50 Pramipexole ER: 11/106 Pramipexole IR: 8/103 RD ER vs IR: 2.6% (95% CI -5.6 to 10.8) **ICDs** Placebo: 0/50 Pramipexole ER: 2/106 Pramipexole IR: 2/103 RD ER vs IR: -0.05% (95% CI -5.1 to 4.9)				

Poewe 2011 ER pramipexole in early PD	Triple-masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than 2 primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class rating

	Yes	Yes	Yes	Yes	Yes	Yes	I
	Population N Trial length	Intervention and comparator	Outcomes				
	PD patients, H&Y stage 1–3 N=539 33 weeks	Pramipexole ER (up to 4.5 mg, mean dose 2.9 mg) n=223 full analysis set, 189 per protocol set Pramipexole IR (up to 4.5 mg, mean dose 2.9 mg) n=213 full analysis set, 183 per protocol set Placebo n=103 full analysis set, 71 per protocol set	Primary outcome: change from baseline to week 33 in combined score on part II (ADLs) and part III (motor function) on the UPDRS. **Proportion of patients requiring levodopa rescue by 33 weeks** Pramipexole ER: 15/213 Pramipexole IR: 9/207 Placebo: 22/103 $p<0.0001$ both comparisons with placebo **ER non-inferiority to IR** Adjusted mean decrease in UPDRS II+III score at 33 weeks was -8.2 for ER and -8.7 for IR. The resultant treatment difference of -0.5 had a 95% CI of -2.3 to 1.3. In the per protocol set, the adjusted mean decreases were -8.5 for ER and -9.4 for IR, a difference of -0.9 (95% CI -2.7 to 0.9). In neither of these analyses did the lower bound of the 95% CI exceed the predefined margin of -3 and were therefore within the limit establishing noninferiority of pramipexole ER vs IR. Adjusted mean change in UPDRS part III (motor function) score at week 33 Placebo: -1.1 (95% CI -2.5 to 0.3) Pramipexole ER: -6.1 (95% CI -7.1 to -5.1; $p<0.0001$) Pramipexole IR: -6.4 (95% CI -7.4 to -5.4; $p<0.0001$) **AE-related discontinuation** Placebo: 4/103 (3.9%) Pramipexole ER: 24/223 (10.8%) Pramipexole IR: 20/213 (9.4%) RD ER vs IR: 1.4% (95% CI -4.4 to 7.1) New development of ICD during the study Placebo: 1/103 Pramipexole ER: 4/223 Pramipexole IR: 3/213 RD ER vs IR: 0.4% (95% CI -2.5 to 3.3)				

Hauser 2014 Long-term safety and sustained efficacy of extended-release pramipexole in early and advanced PD Only early PD patient data extracted Extension of above study (Poewe)	Triple-masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than 2 primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class rating
	No, open-label extension study of double-blind trial	Baseline characteristics presented. no control group	Not applicable	Yes	Yes	No	IV
	Population N Trial length	Intervention and comparator	Outcomes				
	Early PD: PD at H&Y stage 1–3 N=368 74 weeks	ER pramipexole, dosage range 0.375 to 4.5 mg	Primary outcome: sustained pramipexole efficacy, UPDRS parts II and III Of 292 early-PD patients from the preceding 33-week DB trial (excluding 76 placebo recipients), 6.2% were taking levodopa at open-label baseline. On UPDRS parts II and III amongst 234 observed cases, mean changes in the ex-DB-ER and ex-DB-IR groups (adjusted for country, DB treatment and DB baseline) were 6.6 and 6.3 from DB baseline and +3.1 and +3.9 from OL baseline. Of 143 early-PD patients from the preceding 11- to 13-week DB trial, 53.8% were taking levodopa at OL baseline. Amongst 113 observed cases, adjusted mean UPDRS parts II and III changes from DB baseline (at least 3 months after pramipexole initiation) were +0.5 in the ex-DB-ER group and 1.0 in the ex-DB-IR group. Mean changes from OL baseline were +2.6 and +0.2. AE leading to discontinuation: 50/511 Hallucinations: 19/511 Dyskinesia: 2/511 ICDs identified by mMIDI: 4/511 ICDs identified by questioning: 9/511				

Parkinson's study group PramiBID Investigators 2011	Triple-masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than 2 primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class rating
	Yes	Yes	Yes	Yes	Yes	Yes	I

Twice-daily low dose pramipexole in early PD: a randomized placebo-controlled trial	Population N Trial length	Intervention and comparator	Outcomes
	PD, H&Y<3 N=311 12 weeks	Pramipexole 0.5 mg three times a day n=80 Pramipexole 0.75 mg twice a day n=73 Pramipexole 0.5 mg twice a day n=81 Placebo n=77	Primary outcome: change in the total score on the UPDRS from baseline to week 12 **Total UPDRS—Treatment effect relative to placebo** Pramipexole 0.5 mg twice a day mean difference: 4.4 (95% CI 2.3–6.5; p<0.0001) Pramipexole 0.75 mg twice a day mean difference: 4.7 (95% CI 2.5–6.9; p<0.0001) Pramipexole 0.5 mg three times a day mean difference: 4.4 (95% CI 2.3–6.5; p<0.0001) **Motor UPDRS—Treatment effect relative to placebo** Pramipexole 0.5 mg twice a day mean difference: 3.2 (95% CI 1.5–4.9; SD 7.8; p=0.0002) Pramipexole 0.75 mg twice a day mean difference: 3.4 (95% CI 1.6–5.1; p=0.0002) Pramipexole 0.5 mg three times a day mean difference: 3.3 (95% CI 1.7–5.0; SD 7.5; p=0.0001) RMD twice a day vs three times a day: -0.1 (95% CI -2.46 to 2.26) In the combined pramipexole groups, 6 more participants screened positive for ICDs than at baseline. **AE-related discontinuation** Pramipexole 0.5 mg twice a day: 9/81 Pramipexole 0.75 mg twice a day: 10/73 Pramipexole 0.5 mg three times a day: 8/80 RD pramipexole 0.5 mg twice a day vs three times a day: 1.1% (95% CI -8.8% to 11.1%)

Stocchi 2008 Ropinirole 24-hour prolonged release and ropinirole immediate release in early PD: a	Triple-masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than 2 primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class rating
	Yes	Yes	Unclear	Yes	Yes	No	Class II
	Population N Trial length	Intervention and comparator	Outcomes				

randomized double-blind non-inferiority crossover study	PD, H&Y stage I to III requiring dopaminergic therapy. N=161 36 weeks	IR ropinirole 0.75–24 mg/d PR ropinirole 2–24 mg/d Patients were randomized to 1 of 4 formulation sequences -IR-IR-PR -IR-PR-PR -PR-PR-IR -PR-IR-IR	Primary outcome: mean change between period baseline and endpoint in the UPDRS total motor score, as assessed at the end of each maintenance period **Mean change in UPDRS total motor score from period baseline** (adjusted for period, carryover effect, and period baseline score) Ropinirole PR: -0.1 (SE 0.28; SD 3.53) Ropinirole IR: 0.6 (SE 0.30; SD 3.81) RMD: 0.7 (95% CI -0.1 to 1.5) Upper limit of 95% CI for the adjusted mean treatment difference was less than the predefined threshold of 3 points; ropinirole PR was demonstrated to be non-inferior to ropinirole IR. When patients switched formulation of ropinirole, their mean UPDRS score was maintained, indicating similar doses of each formulation had similar efficacy. **Mean change in UPDRS motor score from study baseline to week 12 for the up-titration period** Ropinirole PR: -10.4 (SD 6.06) Ropinirole IR: -8.9 (SD 5.90) **Hallucinations causing withdrawal of treatment** Ropinirole PR: 3/140 Ropinirole IR: 1/149

Korczyn 1998 Ropinirole versus bromocriptine in the treatment of early PD: a 6-month interim report of a 3-year study. **Korczyn 1999**	Triple-masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than 2 primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class rating
	Yes	Yes	Unclear	No	Yes	Yes for 6-month interim analysis No for 3-year analysis	II (6-month data) III (3-year data)
	Population N Trial length	Intervention and comparator	Outcomes				

A 3-year randomized trial of ropinirole and bromocriptine in early PD.	Early PD (H&Y stage I to III) with limited or no previous dopaminergic therapy. Selegiline use permitted; randomization stratified for use. N=335 3 years	Ropinirole n=168 Mean dose at 6 months 8.3 mg; mean dose at 3 years 12.0 mg Bromocriptine n=167 Mean dose at 6 months 16.8 mg; mean dose at 3 years 24.1 mg	**6-month interim analysis results** *UPDRS total motor examination scores at baseline* Ropinirole (no selegiline): 23.9 (SD 9.6) Bromocriptine (no selegiline): 22.2 (SD 10.6) Ropinirole (plus selegiline): 22.9 (SD 12.6) Bromocriptine (plus selegiline): 23.4 (SD 11.0) *UPDRS total motor scores at 6 months* Ropinirole (no selegiline): 15.9 (SD 8.8) (34% improvement) Bromocriptine (no selegiline): 18.6 (SD 10.3) (20% improvement) Difference: 14% (95% CI 6.0%–21.1%) RMD: -2.7 (95% CI -5.2 to -0.2) Ropinirole (plus selegiline): 14.6 (SD 11.9) (34% improvement) Bromocriptine (plus selegiline): 15.0 (SD 9.3) (37% improvement) Difference: -3% (95% CI -7.2% to 13.3%) RMD: -0.4 (95% CI -4.4 to 3.6) *Proportion of patients with psychiatric AEs* (impaired concentration, confusion, hallucinations, and delusions) Ropinirole: 11/168 Bromocriptine: 9/167 RD: 1.2% (95% CI -4.2% to 6.6%) *Proportion of patients with AE-related discontinuation* Ropinirole: 9/168 Bromocriptine: 17/167 RD: -4.8% (95% CI -10.9% to 1.0%) **3-year results** *Proportion of patients with AE-related discontinuation* Ropinirole: 34/168 Bromocriptine: 33/167 RD: 0.5% (95% CI -8.1% to 9.1%) *Use of supplementary levodopa during the study* Ropinirole: 57/168 Bromocriptine: 70/167 RD: -8.0% (95% CI -18.1% to 2.4%) OR: 0.71 (95% CI 0.46–1.11)

			UPDRS motor score at year 3 (patients who completed the study) Ropinirole (n=102): 15.57 (SD 10.0) Bromocriptine (n=112): 17.55 (SD 10.6) RMD: -1.98 (95% CI -4.74 to 0.78) *Motor score improvement* Ropinirole: 31% (SE 12.6) Bromocriptine: 22% (SE 12.5) Difference: 9% (95% CI -1% to 19%) *Dyskinesia* Ropinirole: 13/168 Bromocriptine: 12/167 RD: 0.5% (95% CI -5.3% to 6.4%) *Psychiatric AEs* Ropinirole: 27/168 Bromocriptine: 23/167 RD: 2.3% (95% CI -5.4% to 10.0%)

Giladi 2007 Rotigotine transdermal patch in early PD: a randomized, double-blind controlled study versus placebo and ropinirole Non-inferiority criteria: -Authors explicitly state the clinically meaningful difference to be excluded by defining the threshold	Triple-masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than 2 primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class rating
	Yes	Yes	Yes	Yes	Yes	No	II
	Population N Trial length	Intervention and comparator	Outcomes				
	PD patients with mild to moderate disease, H&Y stage 3 or less, >80% of patients stage 1&2, not taking levodopa N=561 37 weeks	Treatments titrated to optimal effective dose or maximal permitted dose Rotigotine max dose 8mg, 92% reached maximum dose n=215	Primary endpoint: proportion of patients with a minimum of 20% decrease in the combined UPDRS part II and part III scores **Proportion of patients with a minimum of 20% decrease in the combined UPDRS part II and part III scores** Rotigotine: 52%; 112/215 (p<0.0001 vs placebo) Placebo: 30%; 35/118 Ropinirole: 68%; 155/228 (p<0.0001 vs placebo) OR: 0.51 (95% CI 0.35–0.75) **Decrease from baseline in UPDRS subtotal score from baseline to end of treatment** Rotigotine: -7.2 (SD 9.9; p<0.0001 vs placebo) Placebo: -2.2 (SD 10.2)				

for noninferiority (-0.15) -Standard treatment is substantially similar to previous studies -Inclusion & exclusion criteria and outcomes comparable to previous studies -per protocol analysis		Ropinirole max dose 24 mg, 26% reached maximum dose, median dose 14.1 mg/d n=228 Placebo n=118	Ropinirole: -11.0 (SD 10.5; p<0.0001 vs placebo) RMD (rotigotine vs ropinirole): 3.8 (95% CI 1.9–5.7) The difference between the rotigotine transdermal patch and ropinirole for the primary efficacy parameters did not show non-inferiority. No further data given. **AE-related discontinuation** Placebo: 5% Rotigotine: 17% (37/215) Ropinirole: 13% (30/228) RD (rotigotine vs ropinirole): 4.1% (95% CI -2.7 to 10.8)

Mannen 1991 A multicenter, double-blind study on SR bromocriptine in the treatment of PD *only data for de novo group of patients included here	Triple-masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than 2 primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class rating
	Yes	Yes	Unclear	No	Yes	Yes	II
	Population N Trial length	Intervention and comparator	Outcomes				
	De novo PD patients N=60 8 weeks	SR bromocriptine twice daily 14.2 mg/d n=25 Bromocriptine three times daily 13.5 mg/d n=35	Global improvement rating: No significant differences noted between SR and regular bromocriptine. **SR bromocriptine** Marked improvement: 0/25 Moderate improvement: 11/25 Mild improvement: 4/25 **Bromocriptine** Marked improvement: 1/35 Moderate improvement: 9/35 Mild improvement: 17/35 Safety rating: No significant differences noted between SR and regular bromocriptine **No side effects**				

			SR bromocriptine: 8/25 Bromocriptine: 17/35 RD: -16.6% (95% CI -38.3% to 8.5%)

Castro-Caldas 2005 The Parkinson-Control study: A 1-year randomized double blind trial comparing piribedil (150 mg/d) with bromocriptine (25 mg/d) in early combination with levodopa in PD	Triple-masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than 2 primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class rating
	Yes	Yes	Unclear	Yes	Yes	No	II
	Population N Trial length	Intervention and comparator	Outcomes				
	PD, mean H&Y stage 2, receiving levodopa for more than 3 months but less than 5 years. Motor symptoms had to be insufficiently controlled, requiring therapeutic adaptation. N= 425 1 year	Piribedil (up to 150 mg/d) plus levodopa n=210 Bromocriptine (up to 25 mg/d) plus levodopa n=215	Primary outcome: improvement in UPDRS part III score from baseline to 12-month follow-up **UPDRS part III decrease from baseline** Piribedil (n=209): -7.9 (SD 9.7) Bromocriptine (n=215): -8.0 (SD 9.5) *p*=0.94 RMD: 0.1 (95% CI -1.73 to 1.93) **Change in levodopa dose over 12 months** Piribedil: 7.6 mg (SD 121.9) Bromocriptine: 16.7 mg (SD 91.3) **AE-related discontinuation** Piribedil: 41/209 Bromocriptine: 33/215 RD: 4.3% (95% CI -3.0% to 11.5%) **Dyskinesia** Piribedil: 6/210 Bromocriptine: 10/215 RD: -1.8% (95% CI -5.8% to 2.1%) **Hallucinations** Piribedil: 17/210 Bromocriptine: 6/215 RD: 5.3% (95% CI 1.0%–10.0%)				

5. In people with early PD what is the comparative efficacy of **sustained-release or long-acting levodopa (including levodopa plus entacapone) vs IR levodopa** for motor symptoms?
Treatment

6. In people with early PD, what is the comparative risk of adverse effects (including motor complications) of **sustained-release (including levodopa plus entacapone) vs IR levodopa**?
Treatment

Levodopa IR vs levodopa sustained release

Koller 1999 Immediate-release and controlled-release carbidopa/levodopa in PD: a 5-year randomized multicenter study	Triple-masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than 2 primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class rating
	Yes	No	Yes	Yes	Yes	No	IV
	Population N Trial length	Intervention and comparator	Outcomes				
	PD patients H&Y stage I–III, levodopa naïve N=618 5 years	Levodopa IR n=306 Levodopa CR n=312	Primary endpoint: progression of disease to the onset of motor fluctuations Mean dose of IR after 5 years: 426 (SD 205) mg/d Mean bioequivalent dose (based on 70% absorption) of CR after 5 years: 510 (SD 224) mg/d *p*=0.02 RMD: -84.0 (95% CI -117.8 to -50.2) Probability of reaching endpoint (motor fluctuations or dyskinesia) was estimated at 5 years to be 20.6% for the IR group and 21.8% for the CR group. 16% of both the IR and CR group had changes in motor response. No significant differences between groups. **AEs** *Hallucinations* IR: 15/306 CR: 12/312 RD: 1.1% (95% CI -2.3 to 4.5) *Dyskinesia* IR: 25/306 CR: 31/312 RD: -1.8 (95% CI -6.4 to 2.8) *Depression* IR: 5/306 CR: 9/312					

			RD: -1.3 (95% CI -3.9 to 1.3)

Dupont 1996 Sustained release Madopar HBS compared with standard Madopar in the long-term treatment of de novo parkinsonian patients	Triple-masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than 2 primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class rating
	Yes	Yes	Unclear	Not stated	Yes	No	III
	Population N Trial length	Intervention and comparator	Outcomes				
	PD, H&Y stage I–III, previously untreated with levodopa and DAs N=134 5 years	Madopar HBS Mean daily dose at year 5: 638 mg. 4.3 doses/d n=65 Madopar Mean daily dose at year 5: 719 mg. 4.6 doses/d. n=69	AE-related discontinuation Madopar HBS: 4/65 Madopar: 9/69 RD: -6.9% (95% CI -17.5% to 3.6%) Webster mean score: no significant difference between groups (p=0.53) Madopar Baseline: 10.9 (SD 4.2) Year 1: 5.2 (SD 3) Year 5: 11.2 (SD 6) Madopar HBS Baseline: 10.4 (SD 3.8) Year 1: 4.1 (SD 2.7) Year 5: 9.3 (SD 5.5) RMD at year 5: 1.9 (95% CI -0.94 to 4.74) UPDRS - no significant difference between groups (p=0.53) Madopar Year 2: 18.9 (SD 13.4) Year 5: 29.9 (SD 15.1) Madopar HBS Year 2: 15.8 (SD 10.4) Year 5: 26 (SD 15.9) RMD at year 5: 3.9 (95% CI -3.71 to 11.51) **Proportion of patients with fluctuations and on-phenomena at 5 years** Madopar: 17/29				

			Madopar HBS: 20/35 RD: 1.5% (95% CI -21.8% to 24.2%) **Proportion of patients with dyskinesia at 5 years** Madopar: 12/29 Madopar HBS: 12/35 RD: 7.1% (95% CI -15.8% to 29.5%)

Levodopa vs Levodopa plus Entacapone

Fung 2009 Quality of life in early PD treated with levodopa/carbidopa /entacapone	Triple-masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than 2 primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class rating
	Yes	Yes	Yes	Yes	Yes	Yes	I
	Population N Trial length	Intervention and comparator	Outcomes				
	Idiopathic PD, H&Y stages 1–2.5, 0–3 hours of nondisabling off-time over a consecutive 48-hour period, taking 3–4 equal doses of levodopa with a total daily dose of 300–800 mg per day N=184 12 weeks	LCE n=93 vs LC n=91	Primary outcome: change from baseline to week 12 in the total PDQ-8 score (validated HRQOL measure for PD) **UPDRS part III motor scores** improved from baseline at week 4 and week 12 in both treatment groups with the difference in mean change approaching but not reaching statistical significance at week 4 (p=0.059) and at Week 12 (p=0.087). Data presented graphically only. **Mean UPDRS part IV scores** were very low at baseline and did not change significantly over the 12-week treatment period. **Wearing-off card** Percentage of patients who reported at least one wearing-off symptom in the LCE group was 78.5% at baseline, 69.8% at 4 weeks, and 61.8% at 12 weeks. Percentage of patients who reported a least one wearing-off symptom in the LC group was 84.6% at baseline, 61.5% at 4 weeks, and 61.5% at 12 weeks. There was no significant difference between groups. **AE-related discontinuation** LCE: 6/93 LC: 4/91 RD LC vs LCE: -2.1% (95% CI -9.5% to 5.2%)				

			Dyskinesia LCE: 5/93 LC: 1/91 RD LC vs LCE: -4.3% (95% CI -10.9% to 1.5%)

Hauser 2009 Double-blind trial of levodopa/carbidopa /entacapone versus levodopa/carbidopa in early PD	Triple-masked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than 2 primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class rating
	Yes	Presented, but more males in LCE group	No, unclear	Yes	Yes	Yes	III
	Population N Trial length	Intervention and comparator	Outcomes				
	PD, H&Y stage 1–2.5, not previously treated with levodopa N=423 39 weeks	LCE 100/25/200 mg three times a day LC 100/25 mg three times a day Additional levodopa up to total dose of 750 mg/d could be added if required. If this occurred, the last-observed measures before the introduction of levodopa were carried forward.	Primary outcome was the change from baseline to week 39 in total UPDRS (parts II and III) scores **Change in total UPDRS from baseline to week 39** LCE: 10.0 (SD 9.64) LC: 8.5 SD (9.08) Adjusted mean difference LC vs LCE: -1.7 (SE 0.84; 95% CI -0.34 to -3.32; *p*=0.045) Mean difference adjusted for gender: 1.9 (SE 0.83; 95% CI 0.27–3.55; *p*=0.023) **Mean change from baseline in UPDRS part III motor** LCE: 7.0 (SD 7.47) LC: 6.2 (SD 7.19) RMD LC vs LCE: -0.8 (95% CI -2.2 to 0.6) **Incidence of dyskinesia** LCE: 11/208 LC: 16/215 RD LC vs LCE: 2.2% (95% CI -2.7 to 7.0) **Incidence of wearing-off** LCE: 29/208 LC: 43/215 RD LC vs LCE: 6.1% (95% CI -1.1% to 13.2%) **AE-related discontinuation** LCE: 24/208 LC: 18/215				

			RD: -3.2% (95% CI -9.1% to 2.6%)

Stocchi 2010 Initiating levodopa/carbidopa therapy with and without entacapone in early PD. The STRIDE-PD study. **Olanow 2013** Factors predictive of the development of levodopa induced dyskinesia and wearing-off in PD	Triple-asked or objective outcome rating	Baseline characteristics presented and equivalent	Concealed allocation	No more than 2 primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class rating
	Yes	Yes	Yes	Yes	Yes	No	II
	Population N Trial length	Intervention and comparator	Outcomes				
	PD patients requiring initiation of levodopa; disease duration less than 5 years, could be taking stable doses of DAs. 58% of patients in each group were taking a DA. N=747 134 weeks	LC n=372 Mean dose at the end of titraition period 306.8 mg/d LCE n=373 Mean dose at end of titration period 305.2 mg/d. Pharmacokinetic studies show that addition of entacapone causes a 1.32 to 1.39-fold increase in plasma levodopa levels. Medications given 4 times daily at 3.5-hour intervals	Primary endpoint: time to onset of dyskinesia **AE-related discontinuation** LC: 24/372 LCE: 38/373 RD: -3.7% (95% CI -7.8% to 0.3%) Patients treated with LCE had an increased risk of developing dyskinesia compared to those receiving LC, Cox proportional HR 1.29 (95% CI 1.0–1.65; *p*=0.038.) Survival time estimates for the first quartile of patients were 90.7 weeks (95% CI 65.3–104.0) for the LCE group and 117.1 weeks (95% CI 92.1–132.6) for LC treated patients. Primary endpoint stratified for DA exposure at baseline In patients receiving DAs, LCE treated patients had a greater risk of dyskinesia (HR 1.55, 95% CI 1.13–2.13; *p*=0.006). The estimated first quartile time to onset of dyskinesia was 78.9 weeks for the LCE group and 117.4 weeks for the LC group. Among patients who were not receiving DAs at baseline, those randomized to LCE did not have a greater risk of developing dyskinesia than those receiving LC. Patients treated with DAs at baseline were significantly younger and had a significantly longer disease duration than those without DA exposure. Dyskinesia RD -7.4% (95% CI -13% to 0%) **UPDRS parts II and III, change from baseline to week 130** LCE: 8.4				

			LC: 7.2 *p*=0.18 (standard deviation not provided) **Frequency of wearing-off at 130 weeks** LCE: 139/373, 45.6% LC: 161/372, 48.3% RD: -6.0% (96 % CI -13.0% to 1.0%) **Data from Olanow paper:** *Dyskinesia* Risk of dyskinesia increased in a dose-dependent manner (*p*<0.001). The frequency of dyskinesia at study termination by nominal levodopa dosage was: <400 mg/d: 12.1% 400 mg/d: 36.8% 401–600 mg/d: 45.3% >600 mg/d: 55.8% Predictive factors for the emergence of dyskinesia in stepwise Cox proportional hazards model (in order of importance): young age at PD onset, nominal levodopa dose, lower weight, region (North America), treatment allocation to LCE, female gender, and baseline UPDRS motor ADL score. *Wearing-off* The risk of developing wearing-off increased in a dose-dependent manner (*p*<0.001). The frequency of wearing-off was: <400 mg/d: 27.2% 400 mg/d: 48% 401–600 mg/d: 59.3% >600 mg/d: 72.6% Predictive factors for wearing-off in stepwise Cox proportional hazards model (in order of importance): young age at PD onset, baseline UPDRS motor ADL score, region (North America), nominal levodopa dose, female gender, and baseline UPDRS motor exam score.

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

Antonini 2017 ICARUS study	Cohort study with prospective data collection	All relevant confounding characteristics presented and equivalent, or	Outcome measurement is objective or determined without	No more than 2 primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class rating

		there is appropriate statistical adjustment	knowledge of risk factor status, or is a patient reported outcome				
	Yes	Yes	Patient reported outcome	Yes	Yes	Yes	III
	Population N Length of follow-up	Risk factors assessed	Outcomes				
	Adults with probable idiopathic PD who had been treated with clinical benefit for at least 6 months with any approved pharmacological PD treatment N=1069 2 years	Prevalence of ICDs by PD therapy (levodopa, DAs, or combination)	Primary objective: prospectively assess the presence of ICD behaviors and their subtypes. Used the QUIP. Baseline prevalence of ICDs: 306/1069 (28.6%) 1 year: 292/995 (29.3%) 2 years: 245/925 (26.5%) A higher proportion of males (32.5%) screened positive for ICDs at baseline vs females (21.7%). ICD-positive patients were younger, younger at PD onset, and had longer disease duration. At baseline, the prevalence of ICDs in patients receiving ongoing levodopa or DAs was comparable, while prevalence was numerically higher in patients receiving a combination of levodopa and DAs. **Baseline** Levodopa: 26.5% (56/211) DAs: 26.7% (64/240) RD levodopa vs DAs:0.13% (95% CI -8.21% to 8.1%) Combination levodopa and DAs: 30.1% (179/594) RD levodopa vs levodopa and DAs: -3.59% (95% CI -10.3% to 3.7%) **Year 1** Levodopa: 23.6% (51/216) DAs: 22.9% (40/175) RD levodopa vs DAs: 0.62% (95% CI -7.92% to 8.92%) Combination levodopa and DAs: 33.2% (195/587)			

			RD levodopa vs levodopa and DAs: -9.61 (95% CI -16.1 to -2.48) **Year 2** Levodopa: 19.3% (40/207) DAs: 20% (25/125) RD levodopa vs DAs:0.68% (95% CI -9.9 to 7.8) Combination levodopa and DAs: 30.5% (178/584) RD levodopa vs levodopa and DAs: -11.2% (95% CI -17.3 to -4.23)

Erga 2017 Impulsive and compulsive behaviors in PD: The Norwegian ParkWest Study	Cohort study with prospective data collection	All relevant confounding characteristics presented and equivalent, or there is appropriate statistical adjustment	Outcome measurement is objective or determined without knowledge of risk factor status or is a patient reported outcome	No more than 2 primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class rating
	Yes	Yes	Patient reported outcome	Not stated	Yes	Unclear	III
	Population N Length of follow-up	Risk factors assessed	Outcomes				
	Participants derived from the Norwegian ParkWest project, a population-based longitudinal study of PD. Patients with newly diagnosed PD and normal controls were	Prevalence of ICDs by PD therapy (levodopa, DAs, or combination)	Used the QUIP **Prevalence of ICDs** PD: 20.8% (26/125) Controls: 5.7% (9/159) OR: 4.4 (95% CI 2.0–9.7) The highest frequency of ICBs was observed among patients using DAs only (9/18, 50%), followed by those on both DAs and levodopa (23/60, 38.3%), and patients taking levodopa (6/43, 13.9%). Compared to controls, the corresponding odds ratios were 7.4 (95% CI 2.6–20.9) for those on DAs only and 4.6 (95% CI 2.3–9.3) for combination users. Patients using levodopa only had no increased odds of ICBs compared to controls (OR 1.2, 95% CI 0.5–3.2).				

	recruited from 4 counties in Norway and followed prospectively. N=314 5 years		RD levodopa vs DAs: 36.1% (95% CI -58.3 to -11.2) RD levodopa vs levodopa plus DAs: -24.4% (95% CI -39 to -7) In multivariable models, DA treatment and depressive symptoms were significant predictors of ICB status.

Bastiaens 2013 Prospective cohort study of impulse control disorders in PD	Cohort study with prospective data collection	All relevant confounding characteristics presented and equivalent, or there is appropriate statistical adjustment	Outcome measurement is objective or determined without knowledge of risk factor status or is a patient reported outcome	No more than 2 primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class rating
	Yes	Yes	No	Not stated	Yes	Unclear	IV
	Population N Length of follow-up	Risk factors assessed	Outcomes				
	Cohort of nondemented outpatients with idiopathic PD N=164 Subjects were followed until they reached the first of the following predetermined endpoints: new onset ICDs; discontinuation of DAA	Demographic and clinical characteristics	Of 164 cohort subjects, data on ICDs was only discussed for the 46 subjects who were treated with DAs. 18 of 46 subjects developed new onset ICDs, a cumulative frequency of 39.1% after median DA treatment duration of 21 months. Compared to subjects on DAs without ICDs, those with ICDs had a significantly higher lifetime prevalence of cigarette smoking and caffeine use, a greater prevalence of motor complications, and higher peak DA dosages.				

	therapy; death or loss to follow-up, or June 30, 2011		

Joutsa 2012 Effects of dopamine agonist dose and gender on the prognosis of impulse control disorders in PD	Cohort study with prospective data collection	All relevant confounding characteristics presented and equivalent, or there is appropriate statistical adjustment	Outcome measurement is objective or determined without knowledge of risk factor status or is a patient reported outcome	No more than 2 primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class rating
	Yes	Yes	Yes	Not stated	No	No	III
	Population N Length of follow-up	Risk Factors Assessed	Outcomes				
	Individuals with PD who participated in 2 surveys about ICD 15 months apart N=290	Demographic and clinical characteristics	Used the QUIP ICDs and related behaviors present At baseline: 119/280, 42.5% At follow-up: 108/279, 38.7% Male gender (OR 6.10; 95% CI 2.16–17.18) and higher DA dose (for 100 mg LEDD increase OR 2.25; 95% CI 1.29–3.91) at baseline were the only factors significantly associated with ICD outcome at follow-up among patients with ICDs at baseline. The optimal LEDD cut off for predicting poor ICD outcome was >161 mg LEDD, corresponding to 1.6 mg of pramipexole or 8 mg ropinirole. In patients with no ICDs at baseline, an increase in depressive symptoms on the BDI score between baseline and follow-up (for 1 point increase, OR 1.095, 95% CI 1.004–1.195) was the only factor significantly associated with ICDs at follow-up.				

Smith 2015 Incident impulse control disorder	Cohort study with prospective data collection	All relevant confounding characteristics presented and equivalent, or there is	Outcome measurement is objective or determined without	No more than 2 primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class rating

symptoms and dopamine transporter imaging in PD		appropriate statistical adjustment	knowledge of risk factor status or is a patient reported outcome				
	Yes	Yes	Yes	No	Yes	No	III
	Population N Length of follow-up	Risk actors assessed	Outcomes				
	Patients enrolled in the PPMI cohort study of newly diagnosed, untreated (at enrolment) patients with PD and healthy controls. N=320 Up to 3 years	Dopamine replacement therapy, clinical and demographic factors	**Cumulative rate of incident ICD behaviours** 1 year: 7.8% 2 years: 18.1% 3 years: 25.1% **Observed cumulative rate of incident ICD symptoms by dopamine replacement therapy use** (no significant difference between groups at any time point) *On DRT* 1 year: 9.3% (17/183) 2 years: 14.9% (28/188) 3 years: 18.8% (16/85) *Not on DRT* 1 year: 6.9% (7/101) 2 years: 3.7% (1/29) 3 years: 0% (0/11) Younger age at baseline was significantly associated with higher risk of incident ICD symptoms (OR 0.97; *p*=0.02)				

Corvol 2018 Longitudinal analysis of impulse control disorders in Parkinson disease	Cohort study with prospective data collection	All relevant confounding characteristics presented and equivalent, or there is appropriate statistical adjustment	Outcome measurement is objective or determined without knowledge of risk factor status (can be patient reported)	No more than 2 primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class rating
	Yes	Yes	No	No	Yes	No	IV
	Population N Trial length	Intervention and comparator	Outcomes				

	Multicenter longitudinal cohort of patients with PD (H&Y 2 or less in 87%, mean disease duration 2.6 years) followed annually for 5 years for the development of ICDs N=411	Calculated incidence of ICDs according to DA use	At baseline 81/411 (19.7%) had ICDs. Compared to patients without ICDs at baseline, those with ICDs were younger and had longer disease duration. After adjustment for age and disease duration, those with ICDs were more likely to be obese, regular coffee drinkers, and to have higher scores on the UPDRS parts I and IV. They used DAs more frequently (93% vs 69%) and at higher doses (mean levodopa equivalent dose 211 mg vs 145 mg). Frequency of use and dose of levodopa were similar in the two groups. 43% of patients had an ICD at one or more visits. ICD prevalence increased from 19.7% at baseline to 32.8% at 5 years. Of 306 (46 never DA users, 260 ever DA users) patients without ICDs at baseline with at least one additional visit, 94 (4 never DA users, 90 ever DA users) developed ICDs, corresponding to a 5-year cumulative incidence of 46.1% (95% CI 37.4–55.7). In never users, this was 12.4% (95% CI 4.8–30). In ever users, this was 51.5% (95% CI 41.8–62.1). Men developed ICDs more frequently than women over time; younger patients had a higher prevalence of ICDs at all visits. DA use in the past 12 months was associated with a 2.23-fold higher ICD prevalence. Analysis of ever users shows a 39% higher prevalence of ICDs per 1-SD increase in cumulative duration of use, and a 32% higher prevalence of ICDs per 1-SD increase in dose. After discontinuation of DAs, ICDs progressively resolved.

Kon 2018 The factors associated with impulse control behaviours in PD: A 2-year longitudinal retrospective cohort study	Cohort study with prospective data collection	All relevant confounding characteristics presented and equivalent, or there is appropriate statistical adjustment	Outcome measurement is objective or determined without knowledge of risk factor status (can be patient reported)	No more than 2 primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class rating
	Yes	Yes	Yes (patient reported outcome, QUIP)	No	Yes	Yes	III

	Population N Trial length	Intervention and comparator	Outcomes
	Patients with PD followed for at least 2 years at Aomori Hospital Movement Disorder Clinic N=148 2 years	Compared characteristics of patients with and without ICBs.	30/141 (21%) had at least one ICB at baseline. 12/30 had persistence of their ICB at two-year follow-up. DA use was higher at baseline in patients with ICBs (20/30, 67%), compared to those without ICBs (46/111, 41%; p=0.01). Pergolide use was higher in patients with ICBs at baseline than those without ICB (23% vs 5.4%, p=0.0003). ICB persisters had more pergolide use (p=0.0005) than ICB remitters. In patients without ICBs at baseline who developed ICBs over the two-year study (14/111), 57% (8/14) had DA treatment initiated, compared to 29% (28/97) of those without ICBs (p=0.04).

Marin-Lahoz 2019 Depression as a risk factor for impulse control disorders in PD	Cohort study with prospective data collection	All relevant confounding characteristics presented and equivalent, or there is appropriate statistical adjustment	Outcome measurement is objective or determined without knowledge of risk factor status (can be patient reported)	No more than 2 primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class rating
	Yes	Yes	Yes (patient reported outcome, QUIP)	Yes	Yes	No	III
	Population N Trial length	Intervention and comparator	Outcomes				
	Data obtained from the PPMI. Included patients with PD who did not have ICDs at baseline. N=354 Mean follow up 4 years	Evaluated the effect of depression on the development of ICDs Calculated HR for development	Presence of ICD evaluated at baseline and follow-up visits using the QUIP. The incidence rate of ICDs was 19.38 cases per 100 patient years for depressed patients and 10.3 cases for nondepressed patients. Proportional hazards analysis for depression showed an increased risk of ICDs in patients depressed at baseline (HR=1.96, 95% CI 1.32–2.9; p<0.001). The use of DAs also carried an increased risk of ICD development (HR=1.74, 95% CI 1.22–2.5; p=0.002).				

		of ICDs with DA use	The model including the 2 predictors showed they both maintained similar effects on ICD risk and depressed patients had a higher risk of ICDs when on DAs. The relationship between depression and ICD development was significant for both symptomatic depression and treated depression. The association between baseline depression and longitudinal ICD development remained significant after adjusting for age, sex, time since PD diagnosis, motor score, genetic status, anxiety, apathy, and RBD. Both depression and DA use remained significant in a model including all the above mentioned potential confounders.

Markovic 2020 Dynamics of impulsive-compulsive behaviours in early PD: a prospective study	Cohort study with prospective data collection	All relevant confounding characteristics presented and equivalent, or there is appropriate statistical adjustment	Outcome measurement is objective or determined without knowledge of risk factor status (can be patient reported)	No more than 2 primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class rating
	Yes	Yes	Yes (patient reported outcome, QUIP)	Yes	Yes	Yes for data collection at 1, 2, and 3 years, but not at 5 years	III
	Population N Trial length	Intervention and comparator	Outcomes				
	PD in stage 1 H&Y and healthy controls N=106 PD, 125 controls 5-year follow-up	Compared the rate of ICBs at baseline and at follow up in patients with PD and healthy controls; evaluated risk factors	At baseline, ICBs present in 21/106 PD patients and 13/125 controls. PD-ICBs were more frequently males and were more often treated with DAs than PD-no ICBs. **ICBs at follow up in PD patients** 1 year: 19/92 (21%) 2 years: 19/86 (22%) 3 years: 22/85 (26%) 5 years: 21/73 (29%) PD-ICBs had higher DA doses than PD-no ICBs.				

		including use of DAs	Logistic regression models for the presence and occurrence of any ICB showed that the use of DAs at baseline was a predictor for the presence or occurrence of any ICB (OR 4.92, 95% CI 2.01–12.02).

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

Haaxma 2015 Risk of disabling response fluctuations and dyskinesias for dopamine agonists versus levodopa in PD	Cohort study with prospective data collection	All relevant confounding characteristics presented and equivalent, or there is appropriate statistical adjustment	Outcome measurement is objective or determined without knowledge of risk factor status	No more than 2 primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class rating
	Yes	No	No	No	Yes	No	IV
	Population N Length of follow-up	Risk factors assessed	Outcomes				
	Cohort study of all consecutive de novo PD patients starting on levodopa or DAs. N=127; 77 on levodopa, 50 on DAs Median follow-up 8.1 years		The primary endpoints were the onset of response fluctuations, dyskinesia, and the moment when these complications became disabling. Levodopa starters were older with more severe PD compared to DA starters. Median duration of monotherapy of all DA therapy starters was 2.5 years (95% CI 1.9–3.1). Dyskinesia occurred in 74% of levodopa starters after a median of 3.9 years (95% CI 3.3–4.4), and in 50% of the DA starters after a median of 6.4 years (95% CI 4.0–8.8) with an HR of 2.04 (95% CI 1.26–3.30). Disabling response fluctuations and dyskinesia occurred in 59.7% of levodopa starters after a median of 7.3 years (95 % CI 6.1–8.4) and in 52% of DA starters after a median of 6.1 years (95% CI 4.4–7.9) with an HR of 0.88 (95% CI 0.54–1.44). After adjustment for age and severity of PD at the start of dopaminergic therapy, the statistical conclusions remained unchanged.				

Bjornestad 2016	Cohort study with prospective	All relevant confounding characteristics	Outcome measurement is objective	No more than 2 primary	Inclusion exclusion	Minimum 80%	Class rating

Risk and course of motor complications in a population-based incident PD cohort	data collection	presented and equivalent, or there is appropriate statistical adjustment	or determined without knowledge of risk factor status	outcomes specified	criteria defined	completion rate	
	Yes	Yes	No	Not stated	Yes	Yes	IV
	Population N Length of follow-up	Risk factors assessed	Outcomes				
	Subjects from the Norwegian ParkWest project, a prospective, population-based, multicenter, longitudinal cohort study. Newly diagnosed and untreated PD patients from general population were recruited. N=189 Median follow-up 5 years	Age, gender, time since motor onset, and motor severity at baseline – primary risk factors of interest Initial treatment (levodopa vs DA) and actual levodopa equivalent dose at onset of motor complications.	**Point prevalence of dyskinesia** 1 year: 3.8% 2 years: 4.5% 3 years: 5.2% 4 years: 9.8% 5 years: 12.7% **Cumulative incidence of dyskinesia** 1 year: 6.3% 2 years: 9.5% 3 years: 12.7% 4 years: 18.0% 5 years: 24.3% Independent risk factors for dyskinesia were female gender (HR 2.73, 95% CI 1.49–4.98) and higher baseline UPDRS motor score (HR per unit 1.05, 95% CI 1.02–1.08). A subgroup of patients (36/189) never used levodopa. Among these, 4/36 (11%) had dyskinesia. In comparison, 27.5% of levodopa-treated patients had dyskinesia. In a multivariate Cox regression analysis (with adjustment for baseline age, gender, time since motor onset, and motor severity), initial treatment with levodopa was associated with an increased risk of developing motor fluctuations (HR 1.84, 95% CI 1.09–3.10) but not dyskinesia (HR 0.88, 95% CI 0.42–1.85). Actual levodopa dose was independently associated with both motor fluctuations (HR per 100 mg 1.13, 95% CI 1.01–1.26) and dyskinesia (HR per 100 mg 1.28, 95% CI 1.16–1.42). Few patients rated their dyskinesia as severe (0.6%) or painful (1.8%) within the first 5 years of diagnosis.				

Kelly 2019 Predictors of Motor Complications in Early PD: A Prospective Cohort Study	Cohort study with prospective data collection	All relevant confounding characteristics presented and equivalent, or there is appropriate statistical adjustment	Outcome measurement is objective or determined without knowledge of risk factor status (can be patient reported)	No more than 2 primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class rating
	Yes	N/A	No	Yes	Yes	Yes	IV
	Population N Trial length	Intervention and comparator	Outcomes				
	Oxford PD Centre Discovery Cohort, PD patients within 3.5 years of diagnosis (mean time since diagnosis 1.35 years, 92% H&Y stage 1 or 2), clinical examination every 18 months N=740 Followed up to 10 years	No comparison between levodopa and DAs performed. Evaluated incidence of dyskinesia and motor fluctuations over time and clinical characteristics associated with increased risk.	Presence and intensity of motor complications determined using the MDS-UPDRS IV questions 1 (dyskinesia) and 3 (motor fluctuations). 186/734 (25%) developed dyskinesia; 254/733 (35%) developed motor fluctuations over time. Higher levodopa dose, favorable medication response, younger age at symptom onset, and greater nonmotor symptom burden (anxiety and low mood) were significantly associated with dyskinesia and motor fluctuations. Lower BMI was associated with dyskinesia; higher education level was associated with motor fluctuations.				

Kim 2020 Motor complications in PD: 13-year follow-up of the CamPaiGN cohort	Cohort study with prospective data collection	All relevant confounding characteristics presented and equivalent, or there is appropriate	Outcome measurement is objective or determined without knowledge of	No more than 2 primary outcomes specified	Inclusion exclusion criteria defined	Minimum 80% completion rate	Class rating

		statistical adjustment	risk factor status (can be patient reported)				
	Yes	N/A	No	Yes	Yes	Unclear	IV
	Population N Trial length	Intervention and comparator	Outcomes				
	Incident population-based PD cohort of newly diagnosed cases in the county of Cambridge shire, UK N=141 All cases followed up at 2-year intervals, mean follow-up 7.8 years, maximum follow-up 13 years.	No comparison between patients initially treated with levodopa or DAs.	Analyzed incidence of motor fluctuations and levodopa-induced dyskinesia using UPDRS section 4. Cox regression analysis was used to investigate covariates that might influence development of motor fluctuations and dyskinesia, including LEDD at baseline, and levodopa use at baseline. Levodopa-induced dyskinesia developed in 39 patients with a cumulative incidence of 14.5% at 5 years and 55.7% at 10 years. Median time to dyskinesia was 8.7 years. No association was found between LEDD at baseline, levodopa use at baseline, and levodopa-induced dyskinesia.				

Appendix 5. Evidence synthesis tables

Table 1. Change in UPDRS part III score from baseline to endpoint

Study	**Class**	**Time point**	**RMD (95% CI)**
Watts 2010	II	6 months	0.2 (-2.32 to 2.72)
Conclusion (low confidence): In early PD, levodopa is possibly no more effective than dopamine agonists (with or without levodopa) in improving motor function at six months.			
Oertel 2006	III	1 year	-1.92 (-3.4 to -0.43)
Olanow 1995	II	1 year	-3.2 (-7.5 to 1.1)
Summary effect estimate (random effects meta-analysis)			-2.06 (-3.46 to -0.65)

Conclusion (low confidence): In early PD, levodopa is possibly more effective than dopamine agonists (with or without levodopa) in improving motor function at one year.			
Parkinson Study Group 2000	I	2 years	-3.9 (-5.7 to -2.1)
Whone 2003	I	2 years	-6.34 (-9.14 to -3.54)
Summary effect estimate (random effects meta-analysis)			-4.88 (-7.22 to -2.53)
Conclusion (moderate confidence): In early PD, levodopa is likely more effective than dopamine agonists (with or without levodopa) in improving motor function at two years.			
Oertel 2006	III	3 years	-5.6 (-7.6 to -3.6)
Conclusion (very low confidence): In early PD, there is insufficient evidence to support or refute the effectiveness of levodopa compared to dopamine agonists (with or without levodopa) in improving motor function at 3 years.			
Parkinson Study Group 2004	II	4 years	-4.9 (-7.8 to -1.9)
Conclusion (low confidence): In early PD, levodopa is possibly more effective than dopamine agonists (with or without levodopa) in improving motor function at 4 years.			
Bracco 2004	II	5 years	-2.9 (-5.1 to -0.7)
Rascol 2000	II	5 years	-4.48 (-7.72 to -1.25)
Summary effect estimate (random effects meta-analysis)			-3.4 (-5.22 to -1.58)
Conclusion (moderate confidence): In early PD, levodopa is likely more effective than dopamine agonists (with or without levodopa) in improving motor function at 5 years.			
Parkinson Study Group 2009	IV	6 years	-2.7 (-5.9 to 0.6)
Conclusion (very low confidence): In early PD, there is insufficient evidence to support or refute the effectiveness of levodopa compared to dopamine agonists (with or without levodopa) in improving motor function at 6 years.			
Hauser 2007	IV	10 years	-3.2 (-12.1 to 5.6)
Conclusion (very low confidence): In early PD, there is insufficient evidence to support or refute the effectiveness of levodopa compared to dopamine agonists (with or without levodopa) in improving motor function at 10 years.			

Table 2. Risk of dyskinesia

Study	**Class**	**Time point**	**RD (95% CI)**
Hely 1989	II	2 years	18.8% (2.9%–35.3%)
Parkinson Study Group 2000	I	2 years	20.7% (11.8%–29.4%)
Watts 2010	II	2 years	14.4% (6.5%–23.1%)
Whone 2003	I	2 years	23.2% (12.5%–34.4%)
Summary effect estimate (random effects meta-analysis)			18.7% (13.7%–23.8%)
Conclusion (moderate confidence): In early PD, levodopa is probably more likely than dopamine agonists (with or without levodopa) to induce dyskinesia at two years.			
Caraceni 2001	IV	3 years	12.1% (3.2%–20.9%)
Oertel 2006	III	3 years	17.9% (9.4%–26.3%)
PD Research Group UK 1993	IV	3 years	25% (19.3%–30.9%)
Rinne 1998	II	3 years	8% (2.2%–13.9%)

Summary effect estimate (random effects meta-analysis) (excludes Caraceni 2001 and PD Research Group UK 1993)			12.5% (2.8%–22.1%)
Conclusion (low confidence): In early PD, levodopa is possibly more likely than dopamine agonists (with or without levodopa) to induce dyskinesia at three years.			
Gimenez-Roldan 1997	II	4 years	27.3% (1.1%–50.5%)
Parkinson Study Group 2004	II	4 years	29.5% (18.6%–67.9%)
Weiner 1993	III	4 years	38.9% (-10.2% to 67.9%)
Summary effect estimate (random effects meta-analysis) (excludes Weiner 1993)			29.2% (19.6%–38.8%)
Conclusion (moderate confidence): In early PD, levodopa is probably more likely than dopamine agonists (with or without levodopa) to induce dyskinesia at four years.			
Allain 2000	IV	5 years	14.6% (-4.6% to 32.5%)
Bracco 2004	II	5 years	11.7% (4.8%–18.5%)
Hely 1994	IV	5 years	27.3% (10.1%–42.3%)
Montastruc 1994	IV	5 years	36.3% (11.6%–55.3%)
Rascol 2000	II	5 years	25.1% (13.2%–36.8%)
Summary effect estimate (random effects meta-analysis) (excludes Allain 2000, Hely 1994, and Montastruc 1994)			17.5% (4.5%–30.5%)
Conclusion (low confidence): In early PD, levodopa is possibly more likely than dopamine agonists (with or without levodopa) to induce dyskinesia at five years.			
Parkinson Study Group 2009	IV	6 years	16.5% (4.6%–27.7%)
Conclusion (very low confidence): There is insufficient evidence to determine whether, in early PD, levodopa is more or less likely than dopamine agonists (with or without levodopa) to induce dyskinesia at six years.			
PD Med Collaborative Group 2014	IV	7 years	7.1% (2.4%–11.8%)
Conclusion (very low confidence): There is insufficient evidence to determine whether, in early PD, levodopa is more or less likely than dopamine agonists (with or without levodopa) to induce dyskinesia at seven years.			
Hauser 2007	IV	10 years	25.4% (2%–44.1%)
Lees 2001	IV	10 years	9.2% (0.5%-17.6%)
Summary effect estimate (random effects meta-analysis)			14.3% (-0.4% to 29.1%)
Conclusion (very low confidence): There is insufficient evidence to determine whether, in early PD, levodopa is more or less likely than dopamine agonists (with or without levodopa) to induce dyskinesia at ten years.			
Katzenschlager 2008	IV	14 years	1.6% (-17.3% to 20%)

Conclusion (very low confidence): There is insufficient evidence to determine whether, in early PD, levodopa is more or less likely than dopamine agonists (with or without levodopa) to induce dyskinesia at fourteen years.

Table 3. Risk of hallucinations

Study	Class	Time point	RD (95% CI)
Parkinson Study Group 2000	I	2 years	-5.9% (-11.9% to 0.3%)
Whone 2003	I	2 years	-5.5% (-13% to 1.4%)
Summary effect estimate (random effects meta-analysis)			-5.7% (-10.3% to -1.2%)
Conclusion (low confidence): In early PD, dopamine agonists (with or without levodopa) are possibly more likely than levodopa to induce hallucinations at two years.			
Oertel 2006	III	3 years	-3.4% (-7.7% to -0.2%)
Conclusion (very low confidence): There is insufficient evidence to determine whether, in early PD, levodopa is more or less likely than dopamine agonists (with or without levodopa) to induce hallucinations at three years.			
Parkinson Study Group 2004	II	4 years	-6.6% (-13.9% to 0.7%)
Przuntek 1996	IV	4 years	1% (-2.9% to 4.9%)
Summary effect estimate (random effects meta-analysis) (excludes Przuntek 1996)			-6.6% (-13.9% to 0.7%)
Conclusion (low confidence): In early PD, dopamine agonists (with or without levodopa) are possibly no more likely than levodopa to induce hallucinations at four years.			
Bracco 2004	II	5 years	-0.4% (-4.7% to 3.8%)
Montastruc 1994	IV	5 years	-13.1% (-32.9% to 5.6%)
Rascol 2000	II	5 years	-11.7% (-18.7% to -3.3)
Summary effect estimate (random effects meta-analysis) (excludes Montastruc 1994)			-5.6% (-16.6% to 5.5%)
Conclusion (low confidence): In early PD, dopamine agonists (with or without levodopa) are possibly no more likely than levodopa to induce hallucinations at five years.			

Table 4. Risk of AE-related discontinuation of treatment

Study	Class	Time point	RD (95% CI)
Bakheit 1990	II	1 year	-18.8% (-43% to 5%)

Conclusion (very low confidence): There is insufficient evidence to determine whether, in early PD, levodopa is more or less likely than dopamine agonists (with or without levodopa) to cause medication discontinuation due to adverse effects at one year.			
Parkinson Study Group 2000	I	2 years	-4.6% (-11.3% to 2%)
Watts 2010	II	2 years	-5.6% (-14.6% to 3.2%)
Whone 2003	I	2 years	-9.6% (-19% to 0%)
Summary effect estimate (random effects meta-analysis)			-6.1% (-10.7% to -1.4%)
Conclusion (low confidence): In early PD, dopamine agonists (with or without levodopa) are possibly more likely than levodopa to cause medication discontinuation due to adverse effects at two years.			
Caraceni 2001	IV	3 years	-26.3% (-33.3% to -17.9%)
Oertel 2006	III	3 years	-6.7% (-14.8% to 1.4%)
PD Research Group UK 1993	IV	3 years	-36.7% (-44.3% to -28.3%)
Rinne 1998	II	3 years	-2.6% (-9.5% to 4.3%)
Summary effect estimate (random effects meta-analysis) (excludes Caraceni 2001 and PD Research Group UK 1993)			-4.3% (-9.6% to 0.9%)
Conclusion (low confidence): In early PD, dopamine agonists (with or without levodopa) are possibly no more likely than levodopa to cause medication discontinuation due to adverse effects at three years.			
Przuntek 1996	IV	4 years	-9.1% (-14% to -4.4%)
Conclusion (very low confidence): There is insufficient evidence to determine whether, in early PD, levodopa is more or less likely than dopamine agonists (with or without levodopa) to cause medication discontinuation due to adverse effects at four years.			
Bracco 2004	II	5 years	-5.9% (-13.1% to 1.3%)
Rascol 2000	II	5 years	5.8% (-5.5% to 17.7%)
Utsumi 2012	IV	5 years	-18.4% (-32.1% to -4.9%)
Summary effect estimate (random effects meta-analysis) (excludes Utsumi 2012)			-1% (-12.3% to 10.4%)
Conclusion (moderate confidence): In early PD, dopamine agonists (with or without levodopa) are probably no more likely than levodopa to cause medication discontinuation due to adverse effects at five years.			
PD Med Collaborative Group 2014	IV	7 years	-26.2% (-30% to -22.5%)

Conclusion (very low confidence): There is insufficient evidence to determine whether, in early PD, levodopa is more or less likely than dopamine agonists (with or without levodopa) to cause medication discontinuation due to adverse effects at ten years.

Table 5. Risk of dyskinesia

Study	Class	Time point	RD (95% CI)*
Caraceni 2001	IV	3 years	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 to induce dyskinesia at three years.			
PD Med Collaborative Group 2014	IV	7 years	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 to induce dyskinesia at seven years.			

*Positive values indicate that the risk is higher with levodopa.

Table 6. Risk of AE-related discontinuation of treatment

Study	Class	Time point	RD (95% CI)*
Caraceni 2001	IV	3 years	-12.9% (-20.5% to -5.6%)
Conclusion (very low confidence): There is insufficient evidence to determine whether, in early PD, levodopa is more or less likely than MAO-B inhibitors to cause medication discontinuation due to adverse effects at three years.			
PD Med Collaborative Group 2014	IV	7 years	-20.5% (-24.7% to -16.6%)
Conclusion (very low confidence): There is insufficient evidence to determine whether, in early PD, levodopa is more or less likely than MAO-B inhibitors to cause medication discontinuation due to adverse effects at seven years.			

*Negative values indicate that the risk is higher with MAO-B inhibitors.

Table 5. Change in UPDRS part III score from baseline to endpoint

Study	Class	Comparison	Time point	RMD (95% CI)
Thomas 2006	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 2010	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 2011	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 2011	I	Pramipexole twice daily vs pramipexole three times daily	12 weeks	-0.1 (-2.46 to 2.26)
Conclusion (moderate confidence): In early PD, pramipexole taken three times daily is probably no more effective than pramipexole taken twice daily in improving motor function at 12 weeks.				
Stocchi 2008	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 1999	III	Ropinirole vs bromocriptine	3 years	-1.98 (-4.74–0.78)
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 three years.				
Giladi 2007	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 2006	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 one year.				

Table 6. Risk of dyskinesia

Study	**Class**	**Comparison**	**Time point**	**RD (95% CI)**
Korczyn 1999	III	Ropinirole vs bromocriptine	3 years	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 three years.				

Castro-Caldas 2006	II	Piribedil vs bromocriptine	1 year	-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 one year.				

Table 7. Risk of hallucinations

Study	Class	Comparison	Time point	RD (95% CI)
Castro-Caldas 2006	II	Piribedil vs bromocriptine	1 year	5.3% (1.0%–10.0%)
Conclusion (low confidence): In early PD, piribedil is possibly more likely than bromocriptine to cause hallucinations at one year.				

Table 8. Risk of AE-related discontinuation

Study	Class	Comparison	Time point	RD (95% CI)
Hauser 2010	I	Pramipexole ER vs pramipexole IR	18 weeks	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-related treatment discontinuation at 18 weeks.				
Poewe 2011	I	Pramipexole ER vs pramipexole IR	33 weeks	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 weeks.				
Kieburtz 2011	I	Pramipexole twice daily vs pramipexole three times daily	12 weeks	1.1% (-8.8% to 11.1%)
Conclusion (moderate confidence): In early PD, pramipexole taken three times daily is probably no more likely than pramipexole taken twice daily to cause AE-related treatment discontinuation at 12 weeks.				
Korczyn 1999	III	Ropinirole vs bromocriptine	3 years	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 three years.				
Giladi 2007	II	Rotigotine vs ropinirole	37 weeks	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 weeks.				
Castro-Caldas 2006	II	Piribedil vs bromocriptine	1 year	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 one year.

Table 9. Change in UPDRS part III score from baseline to endpoint

Study	Class	Comparison	Time point	RMD (95% CI)
Dupont 1996	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 2009	III	LC vs LCE	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 LC compared to LCE in improving motor function at 39 weeks.				

Table 10. Risk of dyskinesia

Study	Class	Comparison	Time point	RD (95% CI)
Dupont 1996	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 1999	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 2009	I	LC vs LCE	12 weeks	-4.3 (-10.9 to 1.5)
Conclusion (moderate confidence): In early PD, LC is probably no more likely than LCE to cause dyskinesia at 12 weeks.				
Hauser 2009	III	LC vs LCE	39 weeks	2.2% (-2.7% to 7.0%)
Conclusion (very low confidence): There is insufficient evidence to determine whether, in early PD, LCE is more or less likely than LCE to induce dyskinesia at 39 weeks.				
Stocchi 2010	II	LC vs LCE	2.5 years	-7.4 (-13.0 to 0)
Conclusion (low confidence): In early PD, LCE is possibly no more likely than LC to induce dyskinesia at 2.5 years.				

Table 11. Risk of hallucinations

Study	Class	Comparison	Time point	RD (95%CI)

Koller 1999	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.				

Table 12. Risk of AE-related discontinuation

Study	Class	Comparison	Time point	RD (95%CI)
Dupont 1996	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 adverse effect–related treatment discontinuation at 5 years.				
Fung 2009	I	Levodopa/carbidopa vs levodopa/carbidopa/entacapone	12 weeks	-2.1% (-9.5% to 5.2%)
Conclusion (moderate confidence): In early PD, LC is probably no more likely than LCE to cause AE-related treatment discontinuation at 12 weeks.				
Hauser 2009	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, LC is more or less likely than LCE to cause AE-related treatment discontinuation at 39 weeks.				
Stocchi 2010	II	Levodopa/carbidopa vs levodopa/carbidopa/entacapone	2.5 years	-3.7 (-7.8 to 0.3)
Conclusion (low confidence): In early PD, LCE is possibly no more likely than LC to cause AE-related treatment discontinuation at 2.5 years.				

Appendix 6. Rationale of factors considered in developing the practice recommendations

In this appendix, EVID refers to evidence systematically reviewed; RELA to strong evidence derived from related conditions; PRIN to axiomatic principles of care; and INFER to inferences made from one or more statements in the recommendation rationale.

In the tables that follow, consensus is considered to have been reached if 80% or more of the guideline panel agree on the strength of a given domain. For nonpremise domains, intensity of

shading corresponds to the number of panel members who were in agreement (shading of greater intensity indicates a larger number of panel members who reached agreement). The strength of the recommendation is anchored to the strength of the inference. The recommendation strength can be downgraded for any modifier; it can be upgraded only by one level for a moderate to large benefit relative to harm. In addition, domains include the premises and factors on which the recommendations are based.

Practice recommendations

Levodopa vs DA vs MAO-B inhibitors

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 MAOB-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 two to three 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 five years of follow-up. Initial treatment with levodopa is more likely to induce dyskinesia than initial treatment with DAs for up to five 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 five 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 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]

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).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm > benefit 1	Benefit > harm 0	Benefit >> harm 2	Benefit >>> harm 16	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 9	Critically important 10	Yes
Variation in preferences	Large 1	Moderate 2	Modest 4	Minimal 12	Yes
Feasible	Rarely 0	Occasionally 0	Usually 3	Always 16	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 3	Small 16	Yes
Strength of recommendation	R/U	C	B	A	

1b. In patients with early PD who seek treatment for motor symptoms, clinicians should recommend levodopa as the initial preferential dopaminergic therapy (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm > benefit 1	Benefit > harm 0	Benefit >> harm 6	Benefit >>> harm 6	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 1	Very important 10	Critically important 2	Yes
Variation in preferences	Large 1	Moderate 1	Modest 5	Minimal 6	Yes
Feasible	Rarely 0	Occasionally 0	Usually 2	Always 11	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 3	Small 10	Yes
Strength of recommendation	R/U	C	B	A	

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).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm > benefit 2	Benefit > harm 4	Benefit >> harm 7	Benefit >>> harm 0	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 7	Very important 5	Critically important 1	Yes
Variation in preferences	Large 0	Moderate 6	Modest 5	Minimal 2	Yes
Feasible	Rarely 0	Occasionally 0	Usually 7	Always 6	Yes
Cost relative to net benefit	Very large 0	Large 4	Moderate 8	Small 1	Yes
Strength of recommendation	R/U	C	B	A	

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).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 8	Benefit >>> harm 11	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 11	Critically important 8	Yes
Variation in preferences	Large 0	Moderate 2	Modest 8	Minimal 9	Yes
Feasible	Rarely 0	Occasionally 0	Usually 7	Always 12	Yes
Cost relative to net benefit	Very large 0	Large 1	Moderate 6	Small 12	Yes
Strength of recommendation	R/U	C	B	A	

Prescribing levodopa

Recommendation 2 rationale

The evidence comparing IR levodopa to CR levodopa or LCE 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.

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 LCE 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.

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.

Recommendation 2 statements

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

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 2	Benefit >> harm 8	Benefit >>> harm 3	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 5	Very important 7	Critically important 1	Yes
Variation in preferences	Large 0	Moderate 1	Modest 6	Minimal 6	Yes
Feasible	Rarely 0	Occasionally 0	Usually 4	Always 9	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 3	Small 10	Yes
Strength of recommendation	R/U	C	B	A	

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).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 1	Benefit >> harm 4	Benefit >>> harm 8	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 2	Very important 8	Critically important 3	Yes
Variation in preferences	Large 0	Moderate 2	Modest 4	Minimal 7	Yes
Feasible	Rarely 0	Occasionally 0	Usually 4	Always 9	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 4	Small 9	Yes
Strength of recommendation	R/U	C	B	A	

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).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 3	Benefit >>> harm 13	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 9	Critically important 7	Yes
Variation in preferences	Large 0	Moderate 2	Modest 2	Minimal 12	Yes
Feasible	Rarely 0	Occasionally 0	Usually 7	Always 9	Yes
Cost relative to net benefit	Very large 0	Large 1	Moderate 6	Small 9	Yes
Strength of recommendation	R/U	C	B	A	

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

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm > benefit 1	Benefit > harm 1	Benefit >> harm 8	Benefit >>> harm 9	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 3	Very important 8	Critically important 8	Yes
Variation in preferences	Large 0	Moderate 2	Modest 4	Minimal 13	Yes
Feasible	Rarely 0	Occasionally 0	Usually 3	Always 16	Yes
Cost relative to net benefit	Very large 0	Large 1	Moderate 5	Small 13	Yes
Strength of recommendation	R/U	C	B	A	

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).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 1	Benefit >> harm 7	Benefit >>> harm 8	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 4	Very important 9	Critically important 3	Yes
Variation in preferences	Large 0	Moderate 0	Modest 10	Minimal 6	Yes
Feasible	Rarely 0	Occasionally 0	Usually 5	Always 11	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 6	Small 10	Yes
Strength of recommendation	R/U	C	B	A	

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 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.

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.

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, excessive daytime sleepiness, sudden-onset sleep, nausea, postural hypotension, and hallucinations (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 4	Benefit >>> harm 15	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 6	Critically important 13	Yes
Variation in preferences	Large 0	Moderate 2	Modest 3	Minimal 14	Yes
Feasible	Rarely 0	Occasionally 2	Usually 1	Always 16	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 4	Small 15	Yes
Strength of recommendation	R/U	C	B	A	

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).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 6	Benefit >>> harm 13	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 1	Very important 7	Critically important 11	Yes
Variation in preferences	Large 0	Moderate 0	Modest 7	Minimal 12	Yes
Feasible	Rarely 0	Occasionally 0	Usually 5	Always 14	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 7	Small 12	Yes
Strength of recommendation	R/U	C	B	A	

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).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 5	Benefit >>> harm 14	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 8	Critically important 11	Yes
Variation in preferences	Large 0	Moderate 1	Modest 8	Minimal 10	Yes
Feasible	Rarely 0	Occasionally 0	Usually 5	Always 14	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 5	Small 14	Yes
Strength of recommendation	R/U	C	B	A	

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).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 6	Benefit >>> harm 10	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 11	Critically important 5	Yes
Variation in preferences	Large 0	Moderate 0	Modest 10	Minimal 6	Yes
Feasible	Rarely 0	Occasionally 2	Usually 9	Always 5	Yes
Cost relative to net benefit	Very large 0	Large 1	Moderate 6	Small 9	Yes
Strength of recommendation	R/U	C	B	A	

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.

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 ICBs.[80]

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.

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).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm > benefit 1	Benefit > harm 1	Benefit >> harm 6	Benefit >>> harm 5	Yes
Importance of outcomes	Not important or unknown 1	Mildly Important 3	Very important 6	Critically important 3	No
Variation in preferences	Large 0	Moderate 4	Modest 6	Minimal 3	No
Feasible	Rarely 0	Occasionally 2	Usually 5	Always 6	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 7	Small 6	Yes
Strength of recommendation	R/U	C	B	A	

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 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.[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.

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]

Recommendation 4 statements

4a. Clinicians should integrate patient preferences concerning formulation, mode of administration, and cost when prescribing a DA (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 2	Benefit >> harm 4	Benefit >>> harm 7	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 2	Very important 7	Critically important 4	Yes
Variation in preferences	Large 0	Moderate 2	Modest 4	Minimal 7	Yes
Feasible	Rarely 0	Occasionally 1	Usually 5	Always 7	Yes
Cost relative to net benefit	Very large 0	Large 1	Moderate 7	Small 5	Yes
Strength of recommendation	R/U	C	B	A	

4b. Clinicians should prescribe the lowest dose of DA required to provide therapeutic benefit (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 4	Benefit >>> harm 15	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 12	Critically important 7	Yes
Variation in preferences	Large 0	Moderate 1	Modest 6	Minimal 12	Yes
Feasible	Rarely 0	Occasionally 0	Usually 6	Always 13	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 5	Small 14	Yes
Strength of recommendation	R/U	C	B	A	

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 pharmacological interventions, if appropriate.

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.

Recommendation 5 statements5a. 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).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 1	Benefit >>> harm 12	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 5	Critically important 8	Yes
Variation in preferences	Large 0	Moderate 2	Modest 7	Minimal 4	Yes
Feasible	Rarely 0	Occasionally 0	Usually 3	Always 10	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 5	Small 8	Yes
Strength of recommendation	R/U	C	B	A	

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).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 4	Benefit >>> harm 9	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 7	Critically important 6	Yes
Variation in preferences	Large 0	Moderate 1	Modest 6	Minimal 6	Yes
Feasible	Rarely 0	Occasionally 0	Usually 4	Always 9	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 4	Small 9	Yes
Strength of recommendation	R/U	C	B	A	

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 is more likely to induce dyskinesia than initial treatment with MAO-B inhibitors for up to the first five years of follow-up. Most patients on monotherapy with a MAO-B inhibitor will require additional therapy within two to three 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 the two 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 MAOB-inhibitor and an SSRI.[87-89]

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).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 8	Benefit >>> harm 11	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 1	Very important 17	Critically important 1	Yes
Variation in preferences	Large 0	Moderate 2	Modest 7	Minimal 10	Yes
Feasible	Rarely 0	Occasionally 1	Usually 5	Always 13	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 9	Small 10	Yes
Strength of recommendation	R/U	C	B	A	

6b. Clinicians may prescribe MAO-B inhibitors as the initial dopaminergic therapy for mild motor symptoms in patients with early PD (Level C).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm > benefit 1	Benefit > harm 6	Benefit >> harm 4	Benefit >>> harm 2	No
Importance of outcomes	Not important or unknown 1	Mildly Important 8	Very important 4	Critically important 0	Yes
Variation in preferences	Large 0	Moderate 3	Modest 8	Minimal 2	Yes
Feasible	Rarely 0	Occasionally 1	Usually 6	Always 6	Yes
Cost relative to net benefit	Very large 0	Large 4	Moderate 8	Small 1	Yes
Strength of recommendation	R/U	C	B	A	