Initiation of pharmacological therapy in Parkinson's disease: when, why, and how

Rob M A de Bie, Carl E Clarke, Alberto J Espay, Susan H Fox, Anthony E Lang

Lancet Neurol 2020; 19: 452–61

Published Online March 12, 2020 https://doi.org/10.1016/S1474-4422(20)30036-3

See Comment page 376

Amsterdam University Medical Centers, University of Amsterdam, Department of Neurology, Amsterdam Neuroscience, Amsterdam, Netherlands (Prof R M A de Bie MD); **Department of Neurology, City Hospital, Sandwell and West Birmingham NHS Trust, Birmingham, UK** (Prof C E Clarke MD); **Institute for Applied Health Research, University of Birmingham, Birmingham, UK** (Prof C E Clarke); **UC Gardner Neuroscience Institute and James J and Joan A Gardner Family Center for Parkinson's Disease and Movement Disorders, Department of Neurology, University of Cincinnati, Cincinnati, OH, USA** (Prof A J Espay MD); **Edmond J Safra Program in Parkinson's Disease and the Morton and Gloria Shulman Movement Disorders Clinic, Toronto Western Hospital, UHN, Division of Neurology, University of Toronto, Toronto, ON, Canada** (Prof S H Fox MRCP, Prof A E Lang MD)

Correspondence to: Prof A E Lang, Edmond J Safra Program in Parkinson's Disease and the Morton and Gloria Shulman Movement Disorders Clinic, Toronto Western Hospital, UHN, Division of Neurology, University of Toronto, Toronto, ON M5T 2S8, Canada
anthony.lang@uhnresearch.ca

Debate is ongoing regarding when, why, and how to initiate pharmacotherapy for Parkinson's disease. Early initiation of dopaminergic therapies does not convey disease-modifying effects but does reduce disability. Concerns about the development of motor complications arising from the early initiation of levodopa, which led to misconceived levodopa-sparing strategies, have been largely mitigated by the outcomes of the PD MED and Levodopa in Early Parkinson's Disease (LEAP) studies. The LEAP study also showed the potential for early improvement in quality of life, even when disability is negligible. Until more effective methods of providing stable dopamine concentrations are developed, current evidence supports the use of levodopa as initial symptomatic treatment in most patients with Parkinson's disease, starting with low doses and titrating to therapeutic threshold. Monoamine oxidase-B inhibitors and dopamine agonists can be reserved as potential adjunct treatments later in the disease course. Future research will need to establish effective disease-modifying treatments, address whether patients' quality of life is substantially improved with early initiation of treatment rather than a wait and watch strategy, and establish whether new levodopa formulations will delay onset of dyskinesia.

Introduction

Clinical equipoise surrounds medication choices for patients with early Parkinson's disease. Here, we review the evidence for and against various early treatment alternatives, including the potential for levodopa and other dopaminergic drugs to have disease-modifying effects. We discuss data for and against a wait and watch approach, which is often taken for patients with mild symptoms, and review the risk factors for the development of dyskinesia, the most frequent justification for delaying levodopa. We discuss the evidence against levodopa-sparing strategies as it relates to differential efficacy compared with levodopa and the adverse side-effect profile of dopamine agonists. Particular side-effects of dopamine agonists include impulse control disorders and a narcotic-like withdrawal syndrome when reduced or discontinued. Finally, we attempt to provide a viewpoint on the relevant literature as it relates to when, why, and how drug therapy should be initiated, and conclude with implications for both clinical practice and future research on the initiation of treatment in Parkinson's disease.

Is there a therapy that shows disease-modifying effects?

The development of a neuroprotective treatment is the goal for any neurodegenerative disease. Disease modification is defined as a change in the natural course of a disease by an intervention, and it could be argued that pharmacologically correcting striatal dopamine, although considered symptomatic, addresses an important aspect of the underlying biology of Parkinson's disease. For the purpose of this Review, we will apply the restrictive view of disease modification to interventions with a direct effect on the underlying disease pathogenesis that slows or halts neuronal cell death. A major difference between symptomatic and disease-modifying interventions is that disease-modifying interventions have a longer durability of effect than expected from their known pharmacological effects.

Many studies have not been able to distinguish a disease-modifying effect from a known or unknown symptomatic effect because of the absence of biomarkers linking the mechanisms of action of the interventions to the pathophysiology of the targeted populations, as well as the difficulties with measuring the effects on the underlying disease.[1] Table 1 highlights the various trial designs, endpoints, limitations, and challenges to the study of disease-modifying therapies in Parkinson's disease. Unfortunately, beginning with the first large neuroprotective trial, Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism (DATATOP),[3] multiple studies of putative disease-modifying therapies, using various designs and outcome measures,[36] have not shown a difference between the therapy and placebo.

Levodopa is the most widely used and effective drug for the treatment of Parkinson's disease. However, concern persists about the potential for dopamine (and thus levodopa) to accelerate disease progression by mediating mitochondrial and lysosomal dysfunction[37] and increasing concentrations of potentially toxic α-synuclein oligomers.[38] Concerns about levodopa potentially causing a toxic effect by inducing oxidative stress provided the incentive for the Earlier versus Later Levodopa Therapy in Parkinson Disease (ELLDOPA) study,[31] in which 361 patients with early Parkinson's disease were randomly allocated to placebo or 150 mg, 300 mg, or 600 mg of levodopa per day. After 40 weeks, a 2–4 week levodopa washout did not lead to a deterioration of motor function, as measured by the Unified Parkinson's Disease Rating Scale (UPDRS), to the same level as in the placebo group, suggesting a disease-modifying effect. By contrast, the dopamine transporter SPECT endpoint, obtained in a subgroup of patients, showed a reduction in dopamine transporter after levodopa washout, suggesting that either levodopa accelerated the loss of dopamine nerve terminals or that levodopa modified the function of the striatal dopamine transporter. Taken together, these data left

	Intervention* tested	Limitations	Comments
Parallel group design			
Time until need for initiation of symptomatic therapy	CEP-1347,[2] tocopherols,[3] riluzole,[4] paliroden (NCT00228150), selegiline,[3,5,6] lazabemide[7]	Inconsistent reasons for initiating treatment (patient and physician specific)	All studies with this design are strongly influenced by possible symptomatic effects of the study drug
Time until development of motor complications from levodopa	Isradipine[8]	Late endpoint; other influencing factors	Not clear that delaying motor complications truly implies disease modification
Time until development of a disease milestone (eg, gait dysfunction, postural instability, cognitive decline)	..	Late endpoint; other symptomatic therapies have been initiated	Not known if milestone is pathogenically related to the mechanism of the intervention of interest
Change in mean UPDRS motor scores, other scores, or dynamics of progression (slope analysis of change of scores over time)	Ubidecarenone (coenzyme Q10),[9-11] mitoquinone (NCT00329056), creatine,[12-14] inosine,[15] isradipine,[8] riluzole,[16] GPI-1485,[10] pioglitazone,[17] GDNF,[18-20] paliroden (NCT00228150), PYM50028 (NCT01060878), selegiline,[21,22] rasagiline[23]	Changes in these rating scales are small in early stages of disease, so that trials over many years are needed for statistical significance	..
Long-term randomised controlled study: composite of clinical and other features (typically resistance to dopaminergic therapy)	Creatine[12-14]	Long-term trial; important effect of other symptomatic therapies, intercurrent or concurrent diseases, etc	Gait, cognitive, quality of life and other composite endpoints tend to emerge late in follow-up and have multifactorial causes
Imaging and other biomarkers	Paliroden (NCT00228150), pramipexole,[24,25] ropinirole,[26] levodopa,[25,26] α-dihydroergocryptine[27]	Potential unexpected influence of treatment on the biomarker and not necessarily on the disease process	No imaging or other biomarkers have been validated to measure disease progression
Washout design			
Change in mean UPDRS motor scores or other scores, typically in untreated patients; one variation of this design has been used in patients with later-stage fluctuating disease to evaluate scores in the morning after an overnight withdrawal of symptomatic drugs[28]	TCH346,[29] exenatide,[28] nicotine,[30] levodopa[31]	Limited by duration of double-blind period before patients require other symptomatic therapy	Less potential influence of symptomatic effects of the therapy depending on how long patients remain off study and symptomatic therapy and depending on duration of action of any symptomatic effects of the intervention
Futility (non-superiority) design			
Change in disease-related features (usually motor scores) over time; goal is to establish that treatment is futile as opposed to efficacious	Minocycline,[13] ubidecarenone,[9-11] creatine[12-14]	Reliability depends heavily on the stability of the disease behaviour and reliability of the rating scale used; substantial bias can occur from using historical placebo-treated patient cohorts from previous randomised controlled trials	Design can more rapidly identify drugs that should not be candidates for larger, more expensive phase 3 trials and can minimise costs and sample size
Delayed-start design (early start *vs* delayed start)			
Placebo-controlled period 1 followed by active treatment in both groups in period 2; endpoint is change in rating scale scores: differential outcomes at the end of period 2 combined with diverging slope of change in period 1 (ie, difference between groups is increasing over time) and slopes of scores in period 2 are not converging	Rasagiline,[32] pramipexole,[24] levodopa[33]	Sensitive to differential dropout rate (ie, more patients in delayed-start group requiring symptomatic therapy than in the early-start group); limitations in duration of placebo-controlled phase	Potentially more precise in separating symptomatic from disease-modifying effects; additional comments on the rasagiline results in the ADAGIO study: possible positive effects with 1 mg of rasagiline were not seen with 2 mg, and naturalistic follow-up showed no long-term benefits of early start rasagiline treatment in terms of UPDRS total or subscales scores (including dyskinesia) or falls, freezing, or cognitive decline[34]

ADAGIO=Attenuation of Disease Progression with Azilect Given Once-daily. MAO-B=monoamine oxidase-B. UPDRS=Unified Parkinson's Disease Rating Scale. *The mechanisms of the interventions are: CEP-1347 and minocycline are anti-apoptotic; tocopherols are antioxidant; riluzole is a glutamate antagonist; paliroden stimulates production of nerve growth factor; selegiline, rasagiline, and lazabemide are MAO-B inhibitors and propargylamines, which inhibit glyceraldehyde-3-phosphate and are anti-apoptotic; TCH346 is a propargylamine without MAO-B inhibition effect; ubidecarenone is an electron acceptor for Complexes I and II; mitoquinone has 1000 times the potency of ubidecarenone; inosine is a pro-uric acid antioxidant; isradipine is a calcium channel blocker; GPI-1485 is a neuroimmunophilin ligand; pioglitazone is a peroxisome proliferator-activated receptor gamma agonist; GDNF is glial cell-derived neurotrophic factor; PYM50028 modulates GDNF and brain-derived neurotrophic factor; pramipexole, ropinirole, and α-dihydroergo-cryptine are dopamine agonists with various potential direct and indirect neuroprotective effects; exenatide is a glucagon-like peptide-1 receptor agonist with various potential neuroprotective effects.

Table 1: **Endpoints of different clinical trial designs[35] to test disease modification in Parkinson's disease**

uncertainty about the net effect of levodopa on disease progression.

In an attempt to resolve this issue, the Levodopa in Early Parkinson's Disease (LEAP) study[33] used a delayed-start design to evaluate if levodopa had a disease-modifying effect. 445 patients with early Parkinson's disease were randomly assigned to receive levodopa 300 mg per day (early-start) for 40 weeks or placebo (delayed-start). Both groups then received the same dose of levodopa for another 40 weeks. At 80 weeks, the end of the trial, symptom severity did not differ between the two groups, nor did the level of disability, Mini-Mental State Examination score, depression, or disease-related quality of life. The incidence of levodopa-related motor fluctuations and dyskinesia also did not differ between the groups. These findings indicate that levodopa probably has no

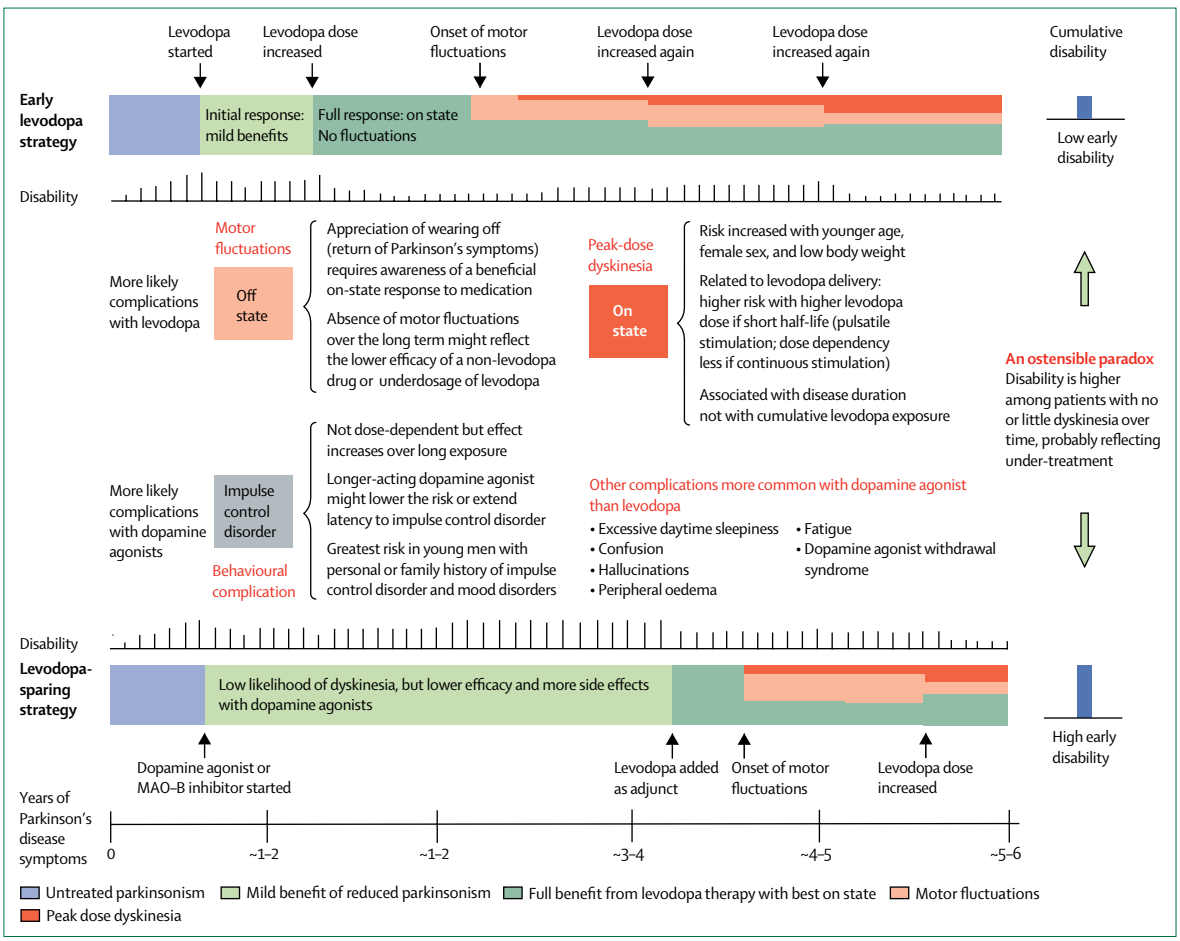

Figure: **The differences between early levodopa versus levodopa-sparing strategies**
The awareness of wearing off requires an appreciation of the on state (maximum benefit), a rare feature of non-levodopa medications. Once levodopa is added (as happens in almost all patients) the effect of delaying motor complications is lost. MAO-B=monoamine oxidase-B.

disease-modifying effect, either beneficial or detrimental, in Parkinson's disease.

In summary, clinical trials have not shown convincing evidence of disease-modifying effects with any of the drugs evaluated, including symptomatic medications—ie, levodopa, dopamine agonists, and monoamine oxidase-B (MAO-B) inhibitors. For this reason, the early initiation of these drugs might be justified to improve quality of life by reducing motor disability but not on the assumption that they might modify the disease course or slow the underlying neurodegeneration.[39]

How do early treatments compare regarding efficacy?

Levodopa has been the most effective (gold standard) treatment for Parkinson's disease for more than 50 years. Despite a symptomatic efficacy superior to that of all other oral pharmacotherapies, the capacity of levodopa to induce motor fluctuations and dyskinesia is the most common justification for delaying its use in favour of alternative medications in early treatment of Parkinson's disease.[40] Various factors that predispose patients to the development of dyskinesia and strategies that have been used in the hope of avoiding or delaying these factors are summarised in the figure.

The crucial effect of disease severity and levodopa dose on dyskinesia development was highlighted by a intriguing study evaluating patients in Ghana and Italy.[41] 91 untreated patients with Parkinson's disease from Ghana were matched with an Italian cohort for sex, age, and disease duration at the first assessment. Levodopa was initiated later in Ghana (mean disease duration 4·2 years in Ghana versus 2·4 years in Italy; p=0·001). Despite this difference, disease duration at the occurrence of motor fluctuations and dyskinesia was similar in the two populations—ie, patients in Ghana did not develop complications any later because levodopa had been delayed. The authors concluded that motor fluctuations and dyskinesia are not associated with the duration of levodopa therapy, but rather with longer disease duration and higher levodopa daily dose. Thus, additional dyskinesia-free time is not necessarily gained by delaying

levodopa, and this delay could come at the expense of more disability in the early treatment-free period.

Few studies have directly compared the longer-term effect of initial treatment choices in Parkinson's disease. The ongoing PD MED trial[42] is a pragmatic, open-label, randomised trial in early Parkinson's disease in which patients were randomly assigned to receive levodopa, a dopamine agonist, or an MAO-B inhibitor. In this trial, levodopa was added when required and switching from the allocated group was allowed if clinically indicated. 1620 patients were enrolled from 91 neurology and geriatrics units, and the median follow-up was 3 years (range 0–9). The 39-item patient-rated Parkinson's Disease Questionnaire (PDQ-39) mobility score and summary index,[43] EuroQol EQ-5D utility measure,[44] and Hoehn and Yahr disease[45] stage score were all significantly better with levodopa than with levodopa-sparing therapy (dopamine agonist and MAO-B inhibitor groups combined), despite the earlier development of dyskinesia in the levodopa group (hazard ratio [HR] 1·52, 95% CI 1·16–2·00; p=0·003) and the similar incidence of motor fluctuations in all groups (1·11, 0·90–1·37; p=0·3; table 2).[42] The differences in PDQ-39 scores were below levels detectable by patients according to the minimum clinically important difference and the effect size methods.[46,47] However, these differences were persistent, and their potential accumulation over time and effect on institutionalisation, dementia, and death, are still being examined in this ongoing trial (final report expected in 2020). One important caveat regarding the PD MED trial is that few patients under the age of 60 years were enrolled and age is an important factor that influences motor complications such as dyskinesia.

Pragmatic, open-label follow-up of patients participating in studies comparing initial levodopa with alternative therapies have tried to address whether early advantages of levodopa-sparing approaches (the intent of which was to reduce the incidence of dyskinesia) provide longer-term benefits. This question is especially relevant given the different side-effect profiles of dopamine agonists (discussed in the next section) and because the delay in onset of dyskinesia shown in these studies applies to the first few years when higher doses of levodopa are usually not required and when dyskinesias are often not even evident to the patient. Table 3 summarises the open-label, long-term follow-up studies of randomised controlled trials comparing levodopa with dopamine agonists. Overall, after many years of follow-up, when patient disability requires optimisation with levodopa (the most effective symptomatic therapy) as well as adjunctive medications, little evidence exists for differences in the features of parkinsonism or of the motor side-effect profile, independent of how the treatment was initiated.

Thus, accumulating evidence supports better motor function and quality of life with initial levodopa therapy, despite an earlier onset of dyskinesia and motor fluctuations. Further, these events are not different in early versus later levodopa treatment groups on long-term follow-up. These data are now a part of the UK National Institute for Health and Care Excellence (NICE) guidelines, which in the 2017 update recommended: "Offer levodopa to people in the early stages of Parkinson's disease whose motor symptoms impact on their quality of life."[54] Despite the evidence, initial dopamine agonist and MAO-B inhibitor treatment has remained entrenched in many centres. To assess this issue, we reviewed the initial treatment choices for 424 patients in North America participating in the Parkinson Progression Markers Initiative (PPMI) who were medication-naive at baseline. 259 (61%) of the 424 patients were started on a levodopa-sparing therapy, with 190 (45%) on dopamine agonists before levodopa and only 145 (34%) on levodopa as the first treatment. Separately, data collected from the Parkinson's Foundation Quality Improvement Initiative registry showed that in 2017, 1142 (39·4%) of 2900 patients initially used a dopamine agonist, and this frequency was unchanged when compared with 2717 patients in 2010 (adjusted odds ratio [OR] 0·91, 95% CI 0·80–1·03; p=0·1172).[55] These practice preferences, despite the evidence, might be a consequence of patient concerns and an absence of physician education or knowledge, as well as marketing strategies used by the pharmaceutical industry.

	Point estimate (95% CI)	p value
PDQ-39 mobility score	1·8 (0·5–3·0)	0·005
PDQ-39 summary index	1·0 (0·3–1·7)	0·008
EuroQol EQ-5D utility measure	0·03 (0·01–0·05)	0·0002
Hoehn and Yahr disease stage score	0·07 (0·03–0·12)	0·0009

Positive point estimates favour levodopa. PDQ-39=Parkinson's Disease Questionnaire 39 (scores are 0–100, higher scores indicate lower disease-related quality of life). Point estimates are estimated mean differences between levodopa and levodopa-sparing groups.

Table 2: **Results of the PD MED trial comparison of levodopa versus levodopa-sparing therapies[42]**

How do the side-effects of early treatments compare?

The previous section reviewed evidence related to early, intermediate, and long-term efficacy as well as motor and some non-motor complications of early treatments. Here, we discuss comparisons of non-motor side-effect profiles of early symptomatic treatments that might determine treatment options. The overall conclusions from evidence-based medicine recommendations are that the number of side-effects and the proportion of patients withdrawing from treatment because of poor tolerability are higher with dopamine agonists than with MAO-B inhibitors or levodopa in early Parkinson's disease. In a meta-analysis of nine randomised controlled trials evaluating early symptomatic therapy trials, withdrawal due to tolerability issues was significantly higher with dopamine agonists

	Trial characteristics	Number of patients	Duration of follow-up*	Comparison of efficacy between groups	Comparison of adverse effects between groups
CALM-PD[48]	Pramipexole *vs* levodopa (1:1),[49] follow-up at 23·5 months for the primary outcome	222 of original 301	Mean 6 years	There was no difference between mean UPDRS motor scores (difference −2·7, 95% CI −5·9 to 0·6),† UPDRS ADL (−1·3, −2·7 to 0·1), or quality of life scores on PDQUALIF (−0·2, −3·3 to 2·9)	Motor complications were more common in the levodopa-first group (OR 2·1, 95% CI 1·2 to 3·7) but dyskinesia was generally mild (2·6, 1·4 to 4·8) and the prevalence of moderately and severely disabling dyskinesia was similarly low in both groups (pramipexole 3 [3%] of 108 and levodopa 4 [4%] of 114); excessive daytime sleepiness (0·4, 0·2 to 0·7) and oedema (0·5, 0·2 to 1·0) were more common in the pramipexole-first group
056 trial[50]	Ropinirole *vs* levodopa (2:1),[51] follow-up at 5 years for the primary outcome	48 of original 268	10 years	There was no difference between mean UPDRS motor scores (difference −3·2, 95% CI −12·1 to 5·6),† UPDRS ADL (−0·6, −5·2 to 4·0), or PDQ-39 scores (2·8, −4·7 to 10·3)	There was a lower incidence of dyskinesia in the ropinirole-first group (OR 0·3, 95% CI 0·1 to 1·0)
PDRG-UK trial[52]	Bromocriptine, levodopa, or levodopa plus selegiline (1:1:1),[53] first interim analysis after follow-up at 3 years	166 of original 782	Median follow-up 14 years	Disability scores were better in the levodopa arm than in the bromocriptine arm (Webster: 16·6 *vs* 19·8; p=0·03, Northwestern University Disability: 34·3 *vs* 30·0; p=0·05); physical functioning (difference 20·8, 95% CI 10·0 to 31·6) and physical summary scores (5·2, 0·7 to 9·7) on the 36-item short-form health survey were also superior on levodopa	A pre-planned interim analysis showed higher mortality in the levodopa plus selegiline group, leading to discontinuation of that group;[53] there were no differences in mortality, prevalence of dyskinesia (5·3%, 95% CI −15 to 25),† motor fluctuations (−5·1%, −25 to 15), or dementia between bromocriptine-first and levodopa-first

ADL=activity of daily living. OR=odds ratio. PDQ-39=Parkinson's Disease Questionnaire 39. PDQUALIF=Parkinson's Disease Quality of Life Scale. UPDRS=Unified Parkinson's Disease Rating Scale. *From randomisation to last assessment. †A negative score means a difference in favour of levodopa.

Table 3: **Comparison of levodopa and dopamine agonists in long-term follow-up studies of randomised controlled trials**

versus levodopa (OR 2·46, 95% CI 1·44–4·20).[56] The latest Cochrane review of 29 trials comparing dopamine agonists with levodopa in more than 2000 patients with early Parkinson's disease reported that participants treated with dopamine agonists were significantly more likely to discontinue treatment because of adverse events (2·49, 2·08–2·98; p<0·0001).[57] The Cochrane review of dopamine agonist versus MAO-B inhibitor trials (only two eligible randomised controlled trials) concluded that the proportion of patients withdrawing from treatment was lower with MAO-B inhibitors than with dopamine agonists (0·11, 0·01–0·99).[58] In the PD MED study, 179 (28%) of 632 patients allocated to receive dopamine agonists and 104 (23%) of 460 patients allocated to receive a MAO-B inhibitor discontinued treatment because of side-effects, compared with 11 (2%) of 528 patients on levodopa (p<0·0001).[42] The proportion of patients who had discontinued treatment by 7 years because of a combination of side-effects and absence of efficacy was 72% for a MAO-B inhibitor, 50% for dopamine agonists, and 7% for levodopa (p<0·0001).

Levodopa and dopamine agonists

Here, we deal exclusively with complications related to levodopa and non-ergot dopamine agonists because the use of ergot-derived dopamine agonists (ie, bromocriptine, pergolide, and cabergoline) has markedly declined or been discontinued in many countries because of uncommon but important fibrotic reactions, such as pleural and retroperitoneal fibrosis and cardiac valvulopathy.[59–61]

On first exposure to any dopaminergic agents, nausea, vomiting, and light-headedness can occur. The Cochrane review of dopamine agonists in early Parkinson's disease reported increased risks of nausea (OR 1·32, 95% CI 1·05–1·66; p=0·02) and dizziness (1·45, 1·09–1·92; p=0·01) with dopamine agonists versus levodopa.[57] The relative risk (RR) of nausea was similar with ropinirole (RR 2·25, 95% CI 1·85–2·74), pramipexole (2·28, 1·54–3·37), and rotigotine (2·08, 1·30–3·34) versus placebo.[62]

Although first recognised as a late side-effect of dopamine agonist use, leg oedema can occur soon after starting treatment, and was reported in 22 (10%) of 221 patients treated with pramipexole in the Pramipexole in Patients with Early Parkinson's Disease (PROUD) study.[24] Peripheral oedema typically occurs after several months of dopamine agonist use and can lead to drug discontinuation (OR 3·68, 95% CI 2·62–5·18; p<0.0001).[57]

Sleep disorders, such as excessive daytime sleepiness, subjective sleepiness, and insomnia, are more common in patients with Parkinson's disease than in age-matched controls. However, the differential effect of disease versus medications is unclear.[63] The treatment of Parkinson's disease might exacerbate or induce sleep disorders, with the risk of somnolence significantly higher with dopamine agonist treatment than with levodopa (OR 1·49,

95% CI 1·12–2·00; p=0·007).[57] Serious consequences, such as falling asleep while driving, have been reported with dopamine agonists; however, some studies do not support a link and the risk might be similar regardless of the dopaminergic medication used.[63]

Hallucinations can occur even in early Parkinson's disease (OR 1·69, 95% CI 1·13–2·52; p=0·01).[57] In the PD MED study, cognitive problems, including psychosis, confusion, and depression, were reported as the reason for discontinuing dopamine agonists in 76 (12%) of 632 patients, versus 42 (9%) of 460 patients taking MAO-B inhibitors and 3 (1%) of 528 patients taking levodopa.[42]

The most problematic adverse effect of using dopamine agonists is the potential for developing impulse control disorders, which has led to important changes in recommendations for dopamine agonist use in the treatment of early Parkinson's disease.[64] Impulse control disorders are behavioural symptoms, occurring individually or in combination, and can range from mild impulsivity to conditions that fulfil Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria, such as pathological gambling, compulsive shopping, binge eating, and hypersexuality. The risk of impulse control disorders has consistently been shown to be (up to 4 times) higher in patients with Parkinson's disease who are taking a dopamine agonist compared with levodopa alone. However, very few studies have addressed the occurrence of impulse control disorders in early Parkinson's disease. In the Drug Interaction with Genes in Parkinson's Disease (DIGPD) study of 306 patients with early Parkinson's disease (treated for less than 5 years), the 5-year cumulative impulse control disorder incidence was 46·1% (95% CI 37·4–55·7) and the risk was significantly associated with dopamine agonist use (prevalence ratio 4·23, 95% CI 1·78–10·09) but not levodopa use.[65] The risk increases with time of treatment exposure. In 300 de novo patients participating in the PPMI study, the cumulative incidence of impulse control disorder symptoms was 8% in year one, 18% in year two, and 25% in year three, although a similar proportion of participants were taking levodopa and dopamine agonists at years one and two.[66] The panel summarises the factors that influence the development of this important adverse effect. Although a dose effect has been inconsistent in the literature,[65,67] simply lowering the dose of the causative dopamine agonist might result in only partial or no symptom resolution, and complete drug withdrawal might be the only method of resolving the impulse control disorder.

Dopamine agonist withdrawal syndrome is a related challenge, which occurs in patients who are reducing or discontinuing a dopamine agonist. The characteristics of this syndrome include severe psychiatric features of agitation, anxiety, and irritability, as well as autonomic symptoms of diaphoresis and orthostasis, that do not respond to levodopa (distinguishing these from non-motor symptoms related to the off state).[72] Although typically occurring in patients with later-stage Parkinson's disease, physicians should be aware of dopamine agonist withdrawal syndrome when selecting an initial therapy. Retrospective cohort studies of patients withdrawing from dopamine agonists have reported a 15–20% incidence of dopamine agonist withdrawal syndrome, although mild impulse control disorder-like behaviours might be under reported.[73] The main risk factor for dopamine agonist withdrawal syndrome is the presence of impulse control disorders;[72–75] however, this syndrome can also occur in patients who discontinue dopamine agonists for other reasons. Other risk factors might include low motor disability and high overall dopaminergic medication doses.[76] Managing dopamine agonist withdrawal syndrome often requires restarting the dopamine agonist, but at a lower dose, and then down-titrating again at a much slower pace.

***Panel*: Risks and influencing factors of impulse control disorders**

Drug profile

- Duration of exposure[66]
- Inconsistent dose effect[65,67]
- Stimulation of dopamine receptor subtype
  - D3 stimulation: all commonly used oral dopamine agonists have mixed D2 and D3 agonist properties[68]
  - No consistent differences in impulse control disorder risk with different dopamine agonists[69]
- Once-per-day or transdermal formulations versus shorter duration dopamine agonists; more continuous stimulation proposed to provide lower risk; inconsistent evidence[70]

Patient profile (predisposing factors)[66,67,69]

- Male sex
- Younger age and younger age at disease onset
- History of impulse control disorders
- Positive family history of impulse control disorders or addiction
- History of mood disorders; depression predisposes patients to development of impulse control disorders and this risk is magnified by dopamine agonists[71]
- Cultural factors: no consistent association

Monoamine oxidase inhibitors

A unique problem with using MAO inhibitors compared with dopamine agonists or levodopa in early Parkinson's disease is the potential for drug–drug interactions. The most substantial concern relates to the potential development of serotonin syndrome with use of non-selective MAO inhibitors and co-treatment with serotonergic and other monoaminergic-acting drugs, such as selective serotonin-reuptake inhibitors, serotonin–norepinephrine-reuptake inhibitors, tricyclic drugs classed as antidepressants, and stimulants. However, this occurrence is extremely rare with selective MAO-B inhibitor use in early Parkinson's disease. In one survey of 4568 patients

with Parkinson's disease, only 11 (0·24%) patients developed symptoms possibly consistent with the serotonin syndrome (only 2 [0·4%] considered serious),[77] and no serotonin syndrome was reported in a phase 4, retrospective, multicentre cohort of 1504 patients with Parkinson's disease using stricter criteria for defining the syndrome.[78] The use of lower doses of some drugs classed as antidepressants was shown to be safe in the Attenuation of Disease Progression with Azilect Given Once Daily (ADAGIO; rasagiline) trial, with no cases of serotonin syndrome (191 patients out of >1000 were taking amitriptyline, 50 mg or less; trazodone, 100 mg or less; citalopram, 20 mg or less; sertraline, 100 mg or less; paroxetine, 30 mg or less; and escitalopram, 10 mg or less).[32]

When should symptomatic treatment be started?

Before symptoms are perceived as causing disability, most physicians and patients are comfortable with a wait and watch approach to initiating pharmacotherapy. Although earlier treatment has not been shown to improve long-term outcomes,[79] delaying therapy could have short-term negative effects on patients' quality of life. Two studies reported different results: one showed clear quality of life advantages to early treatment,[80] whereas the other showed no significant change in PDQ-39 scores in either the treated or untreated group, despite a striking 12-point difference in motor scores of the UPDRS[45] between the two groups.[81]

The LEAP study included patients who had been diagnosed with Parkinson's disease within the previous 2 years and who had not had any disability.[33] The primary outcome was the effect on disease severity measured with the UPDRS. The study also assessed effects on functioning in daily life with the Academic Medical Center linear disability scale (ALDS)[82] and health-related quality of life with the PDQ-39. Because patients had insufficient disability to warrant treatment with anti-parkinsonian medication at the time of inclusion, they could not have expected to improve much in this domain; the ALDS score was maximal. Nevertheless, as well as less severe parkinsonism (ie, lower UPDRS scores) in the first 40 weeks, the early-start group had a better disease-related quality of life at 22 weeks than the delayed-start group. By that time, 47 (21%) of the 223 patients in the delayed-start group transitioned to active levodopa therapy because disability-involving activities of daily living had developed, and symptomatic treatment was considered necessary. Thus, although almost 80% of the delayed-start group did not require treatment for emergent disability, the PDQ-39 summary index differed between the two groups in favour of the early-start group. These findings are a hint that patients without apparent disability or very bothersome symptoms might still have a quality of life benefit from levodopa in a low dose. This issue requires further study, including a comparison to therapy with non-pharmacological measures.

Conclusion and future directions

The clinical relevance of laboratory studies showing a role of dopamine in potentiating various mechanisms of neuronal damage is uncertain. Although early initiation of dopaminergic therapies does not convey disease-modifying effects, it reduces disability. The accumulated evidence and experience of the authors suggest that levodopa strikes the best balance between efficacy and side-effects, with improvements in quality of life, possibly even in the early clinical stages when disability might be negligible. Concerns about the development of motor complications arising from the early initiation of levodopa, which led to the emphasis on levodopa-sparing strategies, have been largely dispelled by the outcomes of the PD MED[42] and LEAP[33] trials. The LEAP trial showed a similar prevalence and severity of motor complications in patients allocated to early-start and delayed-start groups. Importantly, the LEAP trial results largely dismissed concerns about potential toxic effects of levodopa on dopaminergic neurons, which had inspired the ELLDOPA[31] study. Furthermore, there seems to be no advantage to delaying levodopa when symptoms warrant therapy; this delay might only result in longer time with untreated disability and a shorter period free of motor complications (figure). With PD MED as the only long-term naturalistic study, and extrapolated evidence from a few short-term comparative studies, for most patients, the weight of evidence supports initiating symptomatic therapy with levodopa at a low dose, titrated until reaching the therapeutic threshold, reserving the use of MAO-B inhibitors and dopamine agonists as potential adjunct treatments later in the disease. Despite substantial risk concerns, dopamine agonists remain commonly prescribed for early treatment. Young age of Parkinson's disease onset, the strongest risk factor for the early development of motor complications with levodopa, is an important factor in considering alternatives, such as initiating dopaminergic therapy with a dopamine agonist. However, this decision needs to be balanced with the potential for lower efficacy and important complications compared with levodopa in the long term (eg, impulse control disorders) and close and careful clinical follow-up is required should this treatment be chosen. Randomised controlled trials in patients with early Parkinson's disease have not addressed the effects on efficacy and side-effect profile of the variability in clinical phenotype, which can range from a mixture of motor features, including tremor with little bradykinesia, to predominant postural instability and gait dysfunction, to non-motor issues such as depression. Future research will need to aim at establishing effective disease-modifying treatments, possibly more likely in subgroups of patients identified through subtype-specific biomarkers.[83]

Future studies will also need to settle the equivocal data on whether patients' quality of life is significantly improved with the earlier initiation of treatment rather than a wait and watch strategy. Research is also needed to establish

Search strategy and selection criteria

We searched MEDLINE (Ovid MEDLINE® ALL) on April 11, 2019. We searched for randomised controlled trials investigating disease modification capabilities of drugs for Parkinson's disease without date restrictions. For the efficacy of pharmacological treatment in early Parkinson's disease and adverse events of pharmacological treatment in early Parkinson's disease, we searched for systematic review publications up to Dec 31, 2012 and randomised controlled trials from Jan 1, 2013 onwards. For details of the specific search terms please see the appendix.

whether newer, more effective methods of providing stable levodopa plasma concentrations (eg, new levodopa formulations or longer-acting catechol-O-methyltransferase inhibitors),[84] initiated soon after diagnosis, will delay the onset of dyskinesia. Pharmacogenomic studies will need to extend preliminary observations that patient-specific differences influence response to some drugs (eg, rasagiline[85] and entacapone[86,87]) and might better inform how to initiate therapy. Another crucial area in this regard is the establishment of a definitive genetic risk guide to important treatment complications such as impulse control disorders[88,89] with dopamine agonists or early severe dyskinesia[90,91] with levodopa.

Contributors

RMADB and CEC screened the results of the literature searches for relevant articles. All authors equally contributed to the writing of the manuscript.

Declaration of interests

RMADB has received research grants from ZonMw, Parkinson Vereniging, Stichting Parkinsonfonds, Stichting Parkinson Nederland, and unrestricted research grants from GE Healthcare and Medtronic. CEC has received personal compensation as a consultant and scientific advisory board member for BIAL and Teva/Lundbeck. SHF receives research grant funding from the National Institutes of Health (NIH), Parkinson Canada, Dystonia Medical Research Foundation, and Michael J Fox Foundation for Parkinson Research; honoraria from American Academy of Neurology and International Parkinson and Movement Disorder Society; consultancy and advisory board funding from Atuka, Arcadia, CHDI Foundation, Sunovion, Paladin, and Teva; and royalties from Oxford University Press. AJE receives grant support from the NIH and the Michael J Fox Foundation for Parkinson Research; personal compensation as a consultant and scientific advisory board member for AbbVie, Adamas, Acadia, Acorda, Neuroderm, Impax, Sunovion, Lundbeck, Osmotica Pharmaceutical, and USWorldMeds; publishing royalties from Lippincott Williams & Wilkins, Cambridge University Press, and Springer; and honoraria from USWorldMeds, Lundbeck, Acadia, and Sunovion. AEL has received grants from Brain Canada, Canadian Institutes of Health Research, Corticobasal Degeneration Solutions, Edmond J Safra Philanthropic Foundation, Michael J Fox Foundation for Parkinson Research, the Ontario Brain Institute, Parkinson Foundation, Parkinson Canada, and W Garfield Weston Foundation; personal compensation for consultancy work from AbbVie, Acorda, AFFiRis, Biogen, Bristol-Myers Squibb, Intracellular, Janssen, Jazz, Lilly, Lundbeck, Merck, Ono, Paladin, PhotoPharmics, Roche, SPARC, Sunovion, Seelos, Syneos, Sun Pharma, Theravance, and Corticobasal Degeneration Solutions; honoraria from Sun Pharma, AbbVie, and Sunovion; and publishing royalties from Elsevier, Saunders, Wiley-Blackwell, Johns Hopkins Press, and Cambridge University Press.

References

1 Espay AJ, Schwarzschild MA, Tanner CM, et al. Biomarker-driven phenotyping in Parkinson's disease: a translational missing link in disease-modifying clinical trials. *Mov Disord* 2017; **32:** 319–24.

2 Parkinson Study Group PRECEPT Investigators. Mixed lineage kinase inhibitor CEP-1347 fails to delay disability in early Parkinson disease. *Neurology* 2007; **69:** 1480–90.

3 Parkinson Study Group. Effects of tocopherol and deprenyl on the progression of disability in early Parkinson's disease. *N Engl J Med* 1993; **328:** 176–83.

4 Rascol O, Olanow CW, Brooks D, Koch G, Truffinet P, Bejuit R. A 2-year, multicenter, placebo-controlled, double-blind, parallel-group study of the effect of riluzole on Parkinson's disease progression. *Mov Disord* 2002; **17** (suppl 5)**:** S39.

5 Tetrud JW, Langston JW. The effect of deprenyl (selegiline) on the natural history of Parkinson's disease. *Science* 1989; **245:** 519–22.

6 Pålhagen S, Heinonen EH, Hägglund J, et al. Selegiline delays the onset of disability in de novo parkinsonian patients. *Neurology* 1998; **51:** 520–25.

7 Kieburtz. Effect of lazabemide on the progression of disability in early Parkinson's disease. *Ann Neurol* 1996; **40:** 99–107.

8 Simuni T. A phase 3 study of isradipine as a disease-modifying agent in patients with early Parkinson's disease (STEADY-PD III): final study results. 2019 American Academy of Neurology Annual Meeting; Philadelphia, PA; May 4–10, 2019.

9 Shults CW, Oakes D, Kieburtz K, et al. Effects of coenzyme Q10 in early Parkinson disease: evidence of slowing of the functional decline. *Arch Neurol* 2002; **59:** 1541–50.

10 NINDS NET-PD Investigators. A randomized clinical trial of coenzyme Q10 and GPI-1485 in early Parkinson disease. *Neurology* 2007; **68:** 20–28.

11 Beal MF, Oakes D, Shoulson I, et al. A randomized clinical trial of high-dosage coenzyme Q10 in early Parkinson disease: no evidence of benefit. *JAMA Neurol* 2014; **71:** 543–52.

12 Bender A, Koch W, Elstner M, et al. Creatine supplementation in Parkinson disease: a placebo-controlled randomized pilot trial. *Neurology* 2006; **67:** 1262–64.

13 NINDS NET-PD Investigators. A randomized, double-blind, futility clinical trial of creatine and minocycline in early Parkinson disease. *Neurology* 2006; **66:** 664–71.

14 Kieburtz K, Tilley BC, Elm JJ, et al. Effect of creatine monohydrate on clinical progression in patients with Parkinson disease: a randomized clinical trial. *JAMA* 2015; **313:** 584–93.

15 Dolhun R. Parkinson's inosine trial ending early. Dec 10, 2018. https://www.michaeljfox.org/news/parkinsons-inosine-trial-ending-early (accessed Jan 4, 2020).

16 Jankovic J, Hunter C. A double-blind, placebo-controlled and longitudinal study of riluzole in early Parkinson's disease. *Parkinsonism Relat Disord* 2002; **8:** 271–76.

17 NINDS Exploratory Trials in Parkinson Disease (NET-PD) FS-ZONE Investigators. Pioglitazone in early Parkinson's disease: a phase 2, multicentre, double-blind, randomised trial. *Lancet Neurol* 2015; **14:** 795–803.

18 Nutt JG, Burchiel KJ, Comella CL, et al. Randomized, double-blind trial of glial cell line-derived neurotrophic factor (GDNF) in PD. *Neurology* 2003; **60:** 69–73.

19 Lang AE, Gill S, Patel NK, et al. Randomized controlled trial of intraputamenal glial cell line-derived neurotrophic factor infusion in Parkinson disease. *Ann Neurol* 2006; **59:** 459–66.

20 Whone A, Luz M, Boca M, et al. Randomized trial of intermittent intraputamenal glial cell line-derived neurotrophic factor in Parkinson's disease. *Brain* 2019; **142:** 512–25.

21 Olanow CW, Hauser RA, Gauger L, et al. The effect of deprenyl and levodopa on the progression of Parkinson's disease. *Ann Neurol* 1995; **38:** 771–77.

22 Larsen JP, Boas J, Erdal JE. Does selegiline modify the progression of early Parkinson's disease? Results from a five-year study. *Eur J Neurol* 1999; **6:** 539–47.

23 Parkinson Study Group. A controlled, randomized, delayed-start study of rasagiline in early Parkinson disease. *Arch Neurol* 2004; **61:** 561–66.

24 Schapira AH, McDermott MP, Barone P, et al. Pramipexole in patients with early Parkinson's disease (PROUD): a randomised delayed-start trial. *Lancet Neurol* 2013; **12:** 747–55.

See **Online** for appendix

25 Parkinson Study Group. Dopamine transporter brain imaging to assess the effects of pramipexole vs levodopa on Parkinson disease progression. *JAMA* 2002; **287:** 1653–61.

26 Whone AL, Watts RL, Stoessl AJ, et al. Slower progression of Parkinson's disease with ropinirole versus levodopa: the REAL-PET study. *Ann Neurol* 2003; **54:** 93–101.

27 Pöpperl G, Tatsch K, Ruzicka E, Storch A, Gasser T, Schwarz J. Comparison of alpha-dihydroergocryptine and levodopa monotherapy in Parkinson's disease: assessment of changes in DAT binding with [123I]IPT SPECT. *J Neural Transm* 2004; **111:** 1041–52.

28 Athauda D, Maclagan K, Skene SS, et al. Exenatide once weekly versus placebo in Parkinson's disease: a randomised, double-blind, placebo-controlled trial. *Lancet* 2017; **390:** 1664–75.

29 Olanow CW, Schapira AH, LeWitt PA, et al. TCH346 as a neuroprotective drug in Parkinson's disease: a double-blind, randomised, controlled trial. *Lancet Neurol* 2006; **5:** 1013–20.

30 Villafane G, Thiriez C, Audureau E, et al. High-dose transdermal nicotine in Parkinson's disease patients: a randomized, open-label, blinded-endpoint evaluation phase 2 study. *Eur J Neurol* 2018; **25:** 120–27.

31 Fahn S, Oakes D, Shoulson I, et al. Levodopa and the progression of Parkinson's disease. *N Engl J Med* 2004; **351:** 2498–508.

32 Olanow CW, Rascol O, Hauser R, et al. A double-blind, delayed-start trial of rasagiline in Parkinson's disease. *N Engl J Med* 2009; **361:** 1268–78.

33 Verschuur CVM, Suwijn SR, Boel JA, et al. Randomized delayed-start trial of levodopa in Parkinson's disease. *N Engl J Med* 2019; **380:** 315–24.

34 Hauser RA, Lew MF, Hurtig HI, Ondo WG, Wojcieszek J, Fitzer-Attas CJ. Long-term outcome of early versus delayed rasagiline treatment in early Parkinson's disease. *Mov Disord* 2009; **24:** 564–73.

35 Lang AE, Melamed E, Poewe W, Rascol O. Trial designs used to study neuroprotective therapy in Parkinson's disease. *Mov Disord* 2013; **28:** 86–95.

36 Kieburtz K, Olanow CW. Advances in clinical trials for movement disorders. *Mov Disord* 2015; **30:** 1580–87.

37 Burbulla LF, Song P, Mazzulli JR, et al. Dopamine oxidation mediates mitochondrial and lysosomal dysfunction in Parkinson's disease. *Science* 2017; **357:** 1255–61.

38 Mor DE, Tsika E, Mazzulli JR, et al. Dopamine induces soluble α-synuclein oligomers and nigrostriatal degeneration. *Nat Neurosci* 2017; **20:** 1560–68.

39 Espay AJ. The Final nail in the coffin of disease modification for dopaminergic therapies: the LEAP trial. *JAMA Neurol* 2019; **76:** 747–48.

40 Olanow CW. Levodopa: effect on cell death and the natural history of Parkinson's disease. *Mov Disord* 2015; **30:** 37–44.

41 Cilia R, Akpalu A, Sarfo FS, et al. The modern pre-levodopa era of Parkinson's disease: insights into motor complications from sub-Saharan Africa. *Brain* 2014; **137:** 2731–42.

42 Gray R, Ives N, Rick C, et al. Long-term effectiveness of dopamine agonists and monoamine oxidase B inhibitors compared with levodopa as initial treatment for Parkinson's disease (PD MED): a large, open-label, pragmatic randomised trial. *Lancet* 2014; **384:** 1196–205.

43 Jenkinson C, Fitzpatrick R, Peto V, Greenhall R, Hyman N. The Parkinson's Disease Questionnaire (PDQ-39): development and validation of a Parkinson's disease summary index score. *Age Ageing* 1997; **26:** 353–57.

44 Schrag A, Selai C, Jahanshahi M, Quinn NP. The EQ-5D—a generic quality of life measure—is a useful instrument to measure quality of life in patients with Parkinson's disease. *J Neurol Neurosurg Psychiatry* 2000; **69:** 67–73.

45 Fahn S, Elton RL. The Unified Parkinson's Disease Rating Scale. In: Fahn S, Marsden CD, Calne DB, Goldstein M, eds. Recent developments in Parkinson's disease. Florham Park, NJ: Macmillan Healthcare Information, 1987: 153–63, 293–304.

46 Peto V, Jenkinson C, Fitzpatrick R. Determining minimally important differences for the PDQ-39 Parkinson's disease questionnaire. *Age Ageing* 2001; **30:** 299–302.

47 Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. *Med Care* 2003; **41:** 582–92.

48 Parkinson Study Group CALM Cohort Investigators. Long-term effect of initiating pramipexole vs levodopa in early Parkinson disease. *Arch Neurol* 2009; **66:** 563–70.

49 Parkinson Study Group. Pramipexole vs levodopa as initial treatment for Parkinson disease: a randomized controlled trial. *JAMA* 2000; **284:** 1931–38.

50 Hauser RA, Rascol O, Korczyn AD, et al. Ten-year follow-up of Parkinson's disease patients randomized to initial therapy with ropinirole or levodopa. *Mov Disord* 2007; **22:** 2409–17.

51 Rakshi JS, Pavese N, Uema T, et al. A comparison of the progression of early Parkinson's disease in patients started on ropinirole or L-dopa: an 18F-dopa PET study. *J Neural Transm* 2002; **109:** 1433–43.

52 Katzenschlager R, Head J, Schrag A, Ben-Shlomo Y, Evans A, Lees AJ. Fourteen-year final report of the randomized PDRG-UK trial comparing three initial treatments in PD. *Neurology* 2008; **71:** 474–80.

53 Lees AJ. Comparison of therapeutic effects and mortality data of levodopa and levodopa combined with selegiline in patients with early, mild Parkinson's disease. *BMJ* 1995; **311:** 1602–07.

54 National Institute for Health and Care Excellence. Parkinson's disease in adults: diagnosis and management. National Institute for Health and Care Excellence: London, 2017.

55 Dubaz OM, Wu S, Cubillos F, Miao G, Simuni T. Changes in prescribing practices of dopaminergic medications in individuals with Parkinson's disease by expert care centers from 2010 to 2017: the Parkinson's Foundation quality improvement initiative. *Mov Disord Clin Pract* 2019; **6:** 687–92.

56 Baker WL, Silver D, White CM, et al. Dopamine agonists in the treatment of early Parkinson's disease: a meta-analysis. *Parkinsonism Relat Disord* 2009; 15: 287–94.

57 Stowe RL, Ives NJ, Clarke C, et al. Dopamine agonist therapy in early Parkinson's disease. *Cochrane Database Syst Rev* 2008; **2:** CD006564.

58 Caslake R, Macleod A, Ives N, Stowe R, Counsell C. Monoamine oxidase B inhibitors versus other dopaminergic agents in early Parkinson's disease. *Cochrane Database Syst Rev* 2009; **4:** CD006661.

59 Simonis G, Fuhrmann JT, Strasser RH. Meta-analysis of heart valve abnormalities in Parkinson's disease patients treated with dopamine agonists. *Mov Disord* 2007; **22:** 1936–42.

60 Antonini A, Poewe W. Fibrotic heart-valve reactions to dopamine-agonist treatment in Parkinson's disease. *Lancet Neurol* 2007; **6:** 826–29.

61 Alberti C. Drug-induced retroperitoneal fibrosis: short aetiopathogenetic note, from the past times of ergot-derivatives large use to currently applied bio-pharmacology. *G Chir* 2015; **36:** 187–91.

62 Kulisevsky J, Pagonabarraga J. Tolerability and safety of ropinirole versus other dopamine agonists and levodopa in the treatment of Parkinson's disease: meta-analysis of randomized controlled trials. *Drug Saf* 2010; **1:** 147–61.

63 Chahine LM, Amara AW, Videnovic A. A systematic review of the literature on disorders of sleep and wakefulness in Parkinson's disease from 2005 to 2015. *Sleep Med Rev* 2017; **35:** 33–50.

64 Fox SH, Katzenschlager R, Lim SY, et al. International Parkinson and movement disorder society evidence-based medicine review: update on treatments for the motor symptoms of Parkinson's disease. *Mov Disord* 2018; **33:** 1248–66.

65 Corvol JC, Artaud F, Cormier-Dequaire F, et al. Longitudinal analysis of impulse control disorders in Parkinson disease. *Neurology* 2018; **91:** e189–201.

66 Smith KM, Xie SX, Weintraub D. Incident impulse control disorder symptoms and dopamine transporter imaging in Parkinson disease. *J Neurol Neurosurg Psychiatry* 2016; **87:** 8–70.

67 Antonini A, Barone P, Bonuccelli U, Annoni K, Asgharnejad M, Stanzione P. ICARUS study: prevalence and clinical features of impulse control disorders in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 2017; **88:** 317–24.

68 Gerlach M, Double K, Arzberger T, Leblhuber F, Tatschner T, Riederer P. Dopamine receptor agonists in current clinical use: comparative dopamine receptor binding profiles defined in the human striatum. *J Neural Transm* 2003; **110:** 1119–27.

69 Gatto EM, Aldinio V. Impulse control disorders in Parkinson's disease. A brief and comprehensive review. *Front Neurol* 2019; **10:** 351.

70 Voon V, Napier TC, Frank MJ, et al. Impulse control disorders and levodopa-induced dyskinesias in Parkinson's disease: an update. *Lancet Neurol* 2017; **16:** 238–50.

71 Marín-Lahoz J, Sampedro F, Martinez-Horta S, Pagonabarraga J, Kulisevsky J. Depression as a risk factor for impulse control disorders in Parkinson disease. *Ann Neurol* 2019; **86:** 762–69.

72 Rabinak CA, Nirenberg MJ. Dopamine agonist withdrawal syndrome in Parkinson disease. *Arch Neurol* 2010; **67:** 58–63.

73 Patel S, Garcia X, Mohammad ME, et al. Dopamine agonist withdrawal syndrome (DAWS) in a tertiary Parkinson disease treatment center. *J Neurol Sci* 2017; **379:** 308–11.

74 Cunnington AL, White L, Hood K. Identification of possible risk factors for the development of dopamine agonist withdrawal syndrome in Parkinson's disease. *Parkinsonism Relat Disord* 2012; **18:** 1051–52.

75 Pondal M, Marras C, Miyasaki J, et al. Clinical features of dopamine agonist withdrawal syndrome in a movement disorders clinic. *J Neurol Neurosurg Psychiatry* 2013; **84:** 130–35.

76 Yu XX, Fernandez HH. Dopamine agonist withdrawal syndrome: A comprehensive review. *J Neurol Sci* 2017; **374:** 53–55.

77 Richard IH, Kurlan R, Tanner C, et al. Serotonin syndrome and the combined use of deprenyl and an antidepressant in Parkinson's disease. *Neurology* 1997; **48:** 1070–77.

78 Panisset M, Chen JJ, Rhyee SH, Conner J, Mathena J. Serotonin toxicity association with concomitant antidepressants and rasagiline treatment: retrospective study (STACCATO). *Pharmacotherapy* 2014; **34:** 1250–58.

79 Schneider RB, Lu X, Biglan K, McDermott MP. Earlier dopaminergic treatment in Parkinson's disease is not associated with improved outcomes. *Mov Disord Clin Pract* 2019; **6:** 222–26.

80 Grosset D, Taurah L, Burn DJ, et al. A multicentre longitudinal observational study of changes in self reported health status in people with Parkinson's disease left untreated at diagnosis. *J Neurol Neurosurg Psychiatry* 2007; **78:** 465–69.

81 Asimakopoulos P, Caslake R, Harris CE, Gordon JC, Taylor KS, Counsell C. Changes in quality of life in people with Parkinson's disease left untreated at diagnosis. *J Neurol Neurosurg Psychiatry* 2008; **79:** 716–18.

82 Weisscher N, Post B, de Haan RJ, Glas CA, Speelman JD, Vermeulen M. The AMC Linear Disability Score in patients with newly diagnosed Parkinson disease. *Neurology* 2007; **69:** 2155–61.

83 Lang AE, Espay AJ. Disease modification in Parkinson's disease: current approaches, challenges, and future considerations. *Mov Disord* 2018; **33:** 660–77.

84 Fabbri M, Ferreira JJ, Lees A, et al. Opicapone for the treatment of Parkinson's disease: a review of a new licensed medicine. *Mov Disord* 2018; **33:** 1528–39.

85 Masellis M, Collinson S, Freeman N, et al. Dopamine D2 receptor gene variants and response to rasagiline in early Parkinson's disease: a pharmacogenetic study. *Brain* 2016; **139:** 2050–62.

86 Trenkwalder C, Kuoppamäki M, Vahteristo M, Müller T, Ellmén J. Increased dose of opa with levodopa and entacapone improves "off" time in a randomized trial. *Neurology* 2019; **92:** e1487–96.

87 Corvol JC, Bonnet C, Charbonnier-Beaupel F, et al. The COMT Val158Met polymorphism affects the response to entacapone in Parkinson's disease: a randomized crossover clinical trial. *Ann Neurol* 2011; **69:** 111–18.

88 Cormier-Dequaire F, Bekadar S, Anheim M, et al. Suggestive association between OPRM1 and impulse control disorders in Parkinson's disease. *Mov Disord* 2018; **33:** 1878–86.

89 Castro-Martínez XH, García-Ruiz PJ, Martínez-García C, et al. Behavioral addictions in early-onset Parkinson disease are associated with DRD3 variants. *Parkinsonism Relat Disord* 2018; **49:** 100–03.

90 Purcaro C, Vanacore N, Moret F, et al. DAT gene polymorphisms (rs28363170, rs393795) and levodopa-induced dyskinesias in Parkinson's disease. *Neurosci Lett* 2019; **690:** 83–88.

91 Sampaio TF, Dos Santos EUD, de Lima GDC, et al. MAO-B and COMT genetic variations associated with levodopa treatment response in patients with Parkinson's disease. *J Clin Pharmacol* 2018; **58:** 920–26.