Therapies in Parkinson's disease

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Purpose of review
This review examines currently available therapeutic strategies for Parkinson's disease, emphasizing evidence-based data as well as a patient-centered approach to the treatment of motor and nonmotor symptoms.

Recent findings
Although clinical trials of disease-modifying approaches have been thus far disappointing, steady advances are being made in the symptomatic treatment of Parkinson's disease. In this review, we focus on recent studies with monoamine oxidase type B inhibitors (selegiline and rasagiline), coenzyme Q10, creatine, and exercise in early Parkinson's disease. We also discuss the relative merits and disadvantages of delaying the initiation of levodopa therapy, the role of dopamine agonists, particularly ropinirole and pramipexole, and management of motor and behavioral complications, such as fluctuations, dyskinesias and impulse-control disorders. Novel formulations and delivery approaches for conventional and new drugs are also discussed. Finally, we review recent studies of surgical treatments of Parkinson's disease, such as deep brain stimulation.

Summary
Numerous clinical trials have provided evidence that health-related quality of life can be substantially improved with early diagnosis and institution of exercise and other physical measures, appropriate timing of dopaminergic therapy, and strategies to delay and treat levodopa-related motor complications and nonmotor Parkinson's disease-related symptoms.

Keywords
deep brain stimulation, dopamine agonists, dyskinesias, levodopa, Parkinson's disease, treatment

INTRODUCTION

Since the original description by James Parkinson, almost two centuries ago, major strides have been made in our appreciation of the broad spectrum of motor and nonmotor features of Parkinson's disease. Furthermore, extraordinary progress has been made in our understanding of the pathogenesis of the disease, largely fueled by scientific discoveries that are providing new insights into the functional circuitry of the basal ganglia, mechanisms of cell death, genetics, epidemiology, imaging, pharmacology, and neurosurgery. Although some of these advances are gradually being translated into clinical practice and provide rationale for new and emerging therapeutic interventions, true pathogenesis-targeted therapies are still lacking. Development of such therapeutic strategies will require not only better understanding of mechanisms underlying neurodegeneration, but better animal models that more accurately mimic the progressive human disease [1,2]. In addition, there is an urgent need for quantitative tools and biomarkers that reliably measure clinically relevant outcomes and progression.

Although evidence-based medicine has become the 'holy grail' of therapeutics, guiding many important clinical, economic, and regulatory decisions and policies, limitations of randomized, placebo-controlled trials must be acknowledged. It is important to recognize that data generated by placebo-controlled randomized trials, which often involve a relatively homogenous population with prespecified duration of symptoms, age, comorbidities, and concomitant medications, tend to be short-term and are limited by other strict

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KEY POINTS

- Despite growing emphasis on evidence-based medicine, therapy of Parkinson's disease must be individualized and tailored to the needs of the particular patient.
- Currently there are no drugs or other therapeutic interventions that have been found to be neuroprotective or disease modifying.
- Although levodopa is clearly more efficacious than dopamine agonists in controlling the motor symptoms of Parkinson's disease, many parkinsonologists prefer starting symptomatic therapy with dopamine agonists, particularly in patients with young-onset Parkinson's disease.
- Amantadine continues to be the most effective drug for the treatment of levodopa-induced dyskinesias.
- Deep brain stimulation targeting subthalamic nucleus or globus pallidus interna should be reserved for patients with levodopa-responsive Parkinson's disease who have levodopa-related complications that cannot be adequately controlled with medications.

inclusion–exclusion criteria and other protocol restrictions [3]. These constraints are necessary in order to take into account as many potential confounding variables as possible, including a placebo effect. The placebo-related benefit, based on an analysis of 858 patients treated with placebo in 11 clinical trials, is about 16%, but may be as high as 55%, and may persist for 6 months or even longer [4]. Because the findings from placebo-controlled trials may not be always generalizable, as most patients encountered in a clinic would not qualify for the various clinical trials, clinicians must use their own experience and best clinical judgment, coupled with the scientific evidence, in selecting the optimal therapeutic strategy for their own patients. Customized treatment, tailored to the specific needs of each patient, should be the fundamental principle governing patient care.

In addition to evidence-based medicine, there is also growing emphasis on containing the rising cost of Parkinson's disease-related healthcare. In this regard, group visits have been suggested and found to be 'feasible', but they do not improve efficiency, cost, or quality of life (QoL) [5]. One study, based on 138 000 incident Parkinson's disease cases of whom only 58% were cared for by neurologists, showed that Parkinson's disease patients seen by a neurologist were 20% less likely to die over a 6-year period than those seen by a primary care physician [6]. They were also 20% less likely to be placed in a nursing home and 14% less likely to have a broken hip. Thus, Parkinson's disease-related care by neurologists seems to be associated with better outcomes and is less costly than when delivered by primary care physicians.

The goal of this review is to highlight recent studies and provide an evidence-based review of current treatments of Parkinson's disease [7–9]. The review is organized according to the sequence of therapeutic options available and considered appropriate during the course of the disease, from early to advanced Parkinson's disease (Table 1).

DISEASE-MODIFYING STRATEGIES

For neuroprotective or disease-modifying therapy to be effective, it must target and reverse the critical pathogenic mechanisms and be implemented as early as possible. The European Medicines Agency (EMA) issued guidelines for defining neuroprotective therapies and indicated that such an agent must delay disease progression clinically and has to have an effect on the underlying pathophysiologic process [10]. There are many reasons for the lack of success thus far in finding and validating neuroprotective or disease-modifying therapies: first, despite recent advances, there is still paucity of understanding of the various genetic, environmental and other pathogenic mechanisms of Parkinson's disease-related neurodegeneration; second, a lack of animal models showing a progressive phenotype that would be suitable for testing neuroprotective strategies; third, uncertainty about type and dose of drug that would best target the disease-driving pathogenic cellular mechanisms of Parkinson's disease; fourth, limitations of study designs that could be used to test a candidate drug in a controlled, longitudinal, double-blind, placebo-controlled trial; fifth, poor sensitivity of current rating scales to detect clinically meaningful slowing of disease-progression; and finally, lack of sensitive, cost-effective, and clinically and pathologically relevant biomarkers that reliably measure the course of the disease. Although validated biomarkers of progression are not yet available, there are several studies currently under way to explore various blood, cerebrospinal fluid, genetic, imaging and other markers that might be useful in detecting early, perhaps even presymptomatic, phases of the disease and track the progression [11,12].

Pathogenic mechanisms of Parkinson's disease-related neurodegeneration

It is beyond the scope of this review to comprehensively discuss the various hypotheses proposed to explain the neurodegeneration underlying

Table 1. Treatment of nonmotor symptoms

Nonmotor symptoms	Possible treatments
Cognitive impairment, dementia	Rivastigmine, donepezil, galantamine, memantine
Psychosis	Quetiapine, clozapine
Depression	SSRIs, SNRIs, tricyclics
Apathy, anhedonia, fatigue	Armodafinil, modafinil, CNS stimulants
Orthostatic hypotension	Fludrocortisone, midodrine, etilefrine, droxidopa
Constipation	Polyethylene glycol, lubiprostone, macrogol, prucalopride, neostigmine
Urinary dysfunction (overactive bladder)	Oxybutinin, tolterodine, trospium chloride, BoNT, sacral nerve stimulation
Sexual dysfunction	Solifenacin, darifenacin, sildenafil
Hyperhidrosis	Anticholinergcs, intracutaneous BoNT injections
Seborrhea	Topical steroids, intracutaneous BoNT injections
Weight loss	Nutritional management
Daytime drowsiness	Armodafinil, modafinil, CNS stimulants
RBD, vivid dreams	Clonazepam, melatonin, quetiapine
Insomnia, sleep fragmentation	Nighttime levodopa, dopamine agonists, trazodone,tricyclics (doxepin), zolpidem, eszopiclon, melatonin
Pain (e.g. shoulder), paresthesias	Levodopa, gabapentin, pregabalin, duloxetine

BoNT, botulinum toxin; CNS, central nervous system; RBD, rapid eye movement (REM) and behavioral disorder; SNRI, serotonin and norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

Parkinson's disease and how they relate to potential therapeutic strategies; the reader is referred to other recent reviews on this topic [13▪▪]. In addition to increased oxidative stress and mitochondrial dysfunction, many environmental and genetic mechanisms have been proposed to play a role in the cell death of motor and nonmotor neurons. There is now a growing body of evidence that degeneration of axons, not cell bodies, is the primary determinant of progression of disease [14,15]. Another emerging hypothesis is that the progression of neurodegenerative disease is mediated via seeding of misfolded proteins, including alpha-synuclein [16]. In support of this hypothesis are the findings that preformed fibrils generated from full-length and truncated recombinant α-synuclein enter neurons, probably by endocytosis, and act as 'seeds' that induce recruitment of soluble endogenous α-synuclein into insoluble Lewy body-like inclusions [17]. Disrupting this spread of pathology along axons and eventual neuron-to-neuron transmission would have far reaching therapeutic implications.

Monoamine oxidase type B inhibitors and antiapoptotic drugs

Selegiline (also known as deprenyl), the L-isomer of *N*-propynyl-methamphetamine and an irreversible inhibitor of monoamine oxidase (MAO) type B, was one of the first agents studied as a potential neuroprotective drug in the 'Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism' (DATATOP) trial, first published in 1989 [18]. The results showed that the projected median length of time to reach the end point of clinical need for levodopa was about 9 months longer in the selegiline treated group as compared to the group treated with placebo or tocopherol. The waning of the effects of selegiline on delaying endpoint after the first year, coupled with slight, but significant improvement in motor performance after initiation of selegiline, a reduction of mean of 1.9 points on the Unified Parkinson's Disease Rating Scale (UPDRS) scale after 4 weeks, has been used in part as an argument in favor of a predominantly symptomatic rather than neuroprotective effect of selegiline. In a follow-up study, levodopa-treated Parkinson's disease patients who have been taking selegiline for 7 years compared with those who were changed to placebo after 5 years showed significantly slower decline, less wearing off, on–off motor fluctuations, and less freezing, but more dyskinesias [19]. Similar findings were also observed in a Scandinavian study of 157 patients with Parkinson's disease in which selegiline treatment delayed the need for levodopa and was associated with better long-term outcome [20].

Rasagiline (TVP-1012), another selective, irreversible MAO-B inhibitor, is five times more potent than selegiline in preventing MPTP-induced parkinsonism. In contrast to selegiline, 1-(R)-aminoindan, the major metabolite of rasagiline, is devoid of amphetamine-like properties. Rasagiline affects numerous mechanisms besides inhibiting MAO-B,

such as preventing the opening of the mitochondrial transition pores and thus decreasing the release of cytochrome C, altering pro-antiapoptotic genes and proteins, inhibiting the nuclear translocation of glyceraldehyde-3-phosphate dehydrogenase, and increasing neurotrophic factors [21].

In clinical studies, rasagiline provides a modest symptomatic benefit as monotherapy and as an adjunctive therapy in Parkinson's disease patients experiencing levodopa-related motor fluctuations. In a trial called TVP-1012 in Early Monotherapy for Parkinson's Disease Outpatients (TEMPO), rasagiline monotherapy (1–2 mg per day) significantly reduced total UPDRS score compared with placebo without important adverse effects [22]. In this 26-week, multicenter, parallel-group, randomized, double-blind, placebo-controlled study, the total UPDRS score decreased by 4.2 units with 1 mg rasagiline compared with placebo and by 3.6 units with 2 mg of rasagiline. Significant differences between rasagiline and placebo were also found with respect to QoL and activities of daily living (ADL). In a second part of this study ($n = 371$), using 'randomized, delayed-start' design in an attempt to distinguish between symptomatic and disease-modifying effects of the medication, patients randomized to 1 or 2 mg per day for the first 6 months of the trial were continued on their assigned study drug for a second 6-month period whereas patients randomized to placebo for the first 6 months were switched to rasagiline, 2 mg per day [23]. This design allowed for testing of differences in UPDRS scores at study end between early and delayed starters which – if present – could not be explained by the drug's symptomatic effects. At the end of 1 year, patients treated with rasagiline, 1 or 2 mg per day, had a 2.3-unit smaller increase in mean-adjusted total UPDRS score compared with those treated with placebo for 6 months followed by rasagiline, 2 mg per day, for 6 months ($P = 0.01$). Thus, treatment with rasagiline for 1 year was associated with less functional decline than if the treatment was delayed for 6 months.

The 'delayed start design' was subsequently used in a much larger trial called Attenuation of Disease Progression with Azilect Given Once-Daily (ADAGIO). In this trial, 1176 patients with early untreated Parkinson's disease (mean time from diagnosis 4.5 months) were randomized into four treatment groups: 1or 2 mg of rasagiline from study start until end of study at 18 months (1 mg and 2 mg early start groups) and the other two groups of patients were receiving placebo for the first 9 months and then switched to 1 or 2 mg of rasagiline for the second period (1 and 2 mg delayed start groups) [24]. The primary analyses of the trial were based on a hierarchical three-step endpoint: first, superiority of the slopes of UPDRS decline in the rasagiline vs. placebo groups in the placebo-controlled phase; second, difference between early and delayed start groups in change from baseline to week 72 of UPDRS scores; and lastly, noninferiority of UPDRS slopes between early-start and delayed-start slopes during the active phase. Although the 1 mg dose group met all three endpoints, the second endpoint was not met with the 2 mg dose. Secondary analyses of the ADAGIO study confirmed rasagiline's symptomatic efficacy with a delay in the need for symptomatic antiparkinsonian drugs and improved UPDRS ADL scores in the placebo-controlled phase [25▪▪].

The ADAGIO study has been a subject of some controversy [26,27]. For example, some have questioned whether the relatively small, although statistically significant, effect of 1.7 point difference (which actually represents a 38% reduction in the degree of change from baseline) in motor UPDRS score at the end of 72 weeks between the early-start and delayed-start groups is clinically meaningful. Proposed explanations for the observed lack of effect of the 2 mg dose include the possibility that early symptomatic treatment masked the protective benefit due to floor effects of the UPDRS. In support of this possibility, a post-hoc sub-group analysis of patients in the upper quartile range of UPDRS baseline scores showed that also the 2 mg dose did meet all three primary endpoints [25▪▪]. Despite some signals for a possible disease-modifying effect from the TEMPO and ADAGIO studies, the US Food and Drug Administration (FDA) Advisory Committee concluded in October 2011 that the evidence was not compelling enough to support the proposed expanded indication for rasagiline in slowing of clinical progression of Parkinson's disease.

Mitochondrial enhancers and other potential disease-modifying strategies

Many patients access information about treatment of Parkinson's disease from the internet, and based on their interpretation, often from unreliable sources, they take a variety of vitamins, nutritional supplements, anti-inflammatory drugs and other over-the-counter agents or drugs, such as glutathione [28,29], in an unfounded belief that they can slow the progression of their disease [30]. There is little or no evidence that any of these supplements are effective as symptomatic or disease-modifying therapies. Coenzyme Q10 (CoQ10), an essential cofactor in the mitochondrial electron transport chain, has been tested in the QE3 Phase III study, designed to study the disease-modifying effects of 1200 mg or 2400 mg of CoQ10 vs. placebo.

Sponsored in part by the National Institute of Neurological Disorders and Stroke (NINDS) and administered by the Parkinson Study Group, the study enrolled 600 patients with early Parkinson's disease at 67 sites throughout North America. In May 2011, the NINDS stopped the trial based on an interim analysis, which showed that longer patient follow-up was not likely to demonstrate a statistically significant difference between active treatment and placebo. There were no safety concerns related to CoQ10 for up to 16 months of treatment.

The NET-PD LS-1 is an ongoing multicenter, double-blind, parallel group, placebo-controlled long-term study of creatine in 1720 patients with early treated Parkinson's disease, supported by the NINDS (http://clinicaltrials.gov/ct2/show/NCT00449865). With the estimated completion in 2015, the trial is designed to test if creatine, a nutritional supplement [31], slows clinical decline as assessed by the Global Statistical Test that comprises the following primary outcome measures: the Schwab and England ADL, PDQ-39, ambulatory capacity (sum of five UPDRS questions: falling, freezing, walking, gait, postural stability), Symbol Digit Modalities, and the Modified Rankin value in the creatine group vs. the placebo group against a background of dopaminergic therapy and best Parkinson's disease care over a 5 to 7-year period. Until the NET-PD LS-1 study is completed, we cannot recommend creatine for the treatment of Parkinson's disease.

Physical exercise

Any discussion of the management of Parkinson's disease would not be complete without emphasizing the importance of physical activity and exercise, although it is not yet known whether these measures actually favorably modify progression of the disease. Based on studies in animal models and in patients with Parkinson's disease, exercise has been shown to not only improve motor performance, but also improve learning, memory, and depression, facilitate synaptogenesis, induce neurotrophic factors, enhance neuroplasticity, and reverse some neurochemical deficits (e.g., increases D2 receptors) [32–34]. In a randomized controlled trial, 195 patients with Parkinson's disease (Hoehn-Yahr stage 1–4) were randomized to one of three groups: tai chi, resistance training, or stretching [35]. All patients participated in two 1-h exercise sessions per week for 24 weeks. The tai chi group performed better than the other groups in range of movement, balance, stride length and functional reach, and had a lower frequency of falls. Although intuitively exercise should be recommended when the diagnosis of Parkinson's disease is first made, there is no evidence that this strategy actually slows the progression of the disease.

TREATMENT OF EARLY PARKINSON'S DISEASE

Although anticholinergic drugs or amantadine may be considered as initial treatment options in individual patients with early Parkinson's disease, symptomatic therapy with MAO-B inhibitors and dopaminergic drugs becomes necessary once Parkinson's disease-related symptoms become troublesome for the patient and begin to interfere with ADL or other activities at home or at work (Fig. 1).

Monoamine oxidase type B inhibitors

The TEMPO and ADAGIO studies, discussed above, provided evidence for early use of rasagiline as a potentially disease-modifying agent and also for the symptomatic treatment of Parkinson's disease. Since its introduction, various new formulations of selegiline have been developed. For example, Zydis (Zelapar), formulated in a freeze-dried tablet, which contains 1.25 mg of a fast dissolving selegiline, results in T_{max} of only 15 min, four times shorter than conventional selegiline [36]. This is particularly useful for patients who have difficulties swallowing. A transdermal patch formulation of selegiline, called EMSAM, was approved in 2006 for the treatment of depression, but has not been tested in Parkinson's disease.

Dopamine agonists

Dopamine agonists are considered by many, but not all, parkinsonologists as the first-line option for initial monotherapy of patients with early Parkinson's disease. A recent review of all randomized controlled trials targeting the motor symptoms of Parkinson's disease has concluded that 'piribedil, pramipexole, pramipexole extended release, ropinirole, rotigotine, cabergoline, and pergolide were all efficacious as symptomatic monotherapy' [37]. The ergoline dopamine agonists, bromocriptine, cabergoline and pergolide, are now almost never used because of well-documented risk of complications such as peptic ulcer disease, vasoconstrictive effects, erythromelalgia, and, especially, cardiovalvular, retroperitoneal, and pulmonary fibrosis [38].

Although monotherapy with dopamine agonists usually sufficiently controls motor symptoms in early stages of the disease, the addition of levodopa is required in the majority of patients after

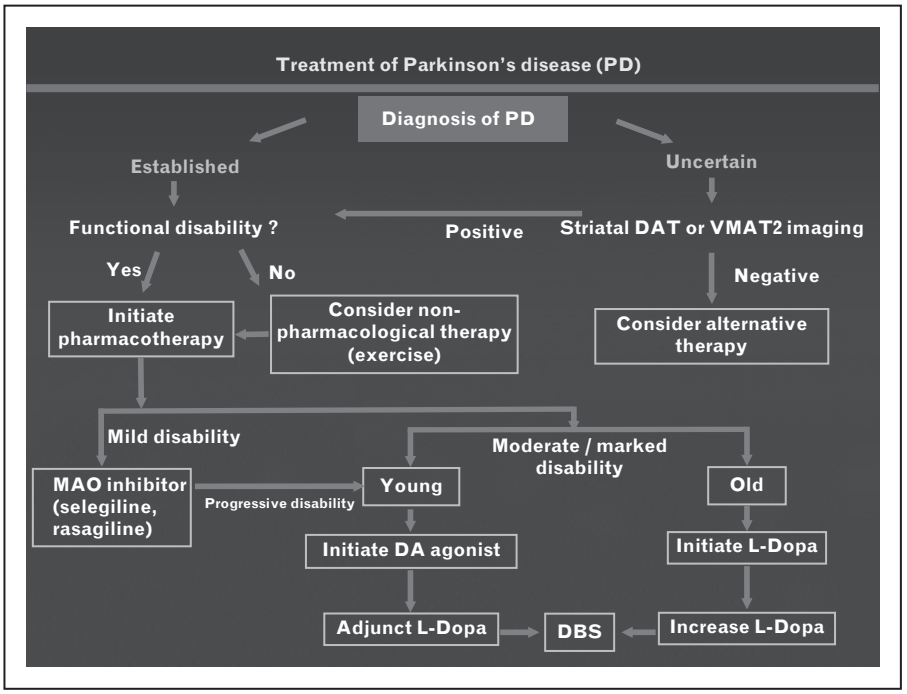

FIGURE 1. Suggested guideline for the treatment of Parkinson's disease from early to advanced staged. DA, dopamine; DAT, dopamine transporter; DBS, deep brain stimulation; MAO, monoamine oxidase; VMAT2, vesicular monoamine transporter type 2.

2–5 years [39]. The role of dopamine agonists as the first choice of initial dopaminergic therapy, however, has been increasingly challenged. For example, in an open-label, pragmatic, multicenter trial involving 782 patients randomized to levodopa, levodopa–selegiline, or bromocriptine, after a median duration of follow-up of 14 years at final assessment of 166 (21%) patients, the investigators concluded that there was no evidence of a long-term benefit or clinically relevant disease-modifying effect with initial dopamine agonist treatment [40]. A systematic review and metanalysis of 15 clinical trials involving 4380 patients concluded that the combination of dopamine agonists and levodopa is superior to levodopa alone in reducing Parkinson's disease symptoms in patients not controlled with monotherapy [41].

Dopamine agonists are less efficacious than levodopa in treating motor symptoms of Parkinson's disease and are associated with higher frequency of somnolence, edema, and psychiatric side effects, particularly hallucinations and impulse control disorder (ICD) [39,42]. Although the various ICD symptoms, such as pathological gambling, hypersexuality, and compulsive shopping and eating, have been attributed chiefly to the use of dopamine agonists, ICD can also complicate the use of levodopa and there does not appear to be a direct relationship between these symptoms and the dosage of the offending drug [43▪▪,44–46]. Many studies have identified levodopa use, younger age, cigarette smoking, and a family history of gambling problems as major risk factors for ICD. These symptoms are best treated by discontinuation of the offending drug, but dopamine agonist withdrawal syndrome manifested by anxiety, agoraphobia, depression, pain, orthostatic hypotension, drug cravings and other behavioral symptoms occurred in 5/26 (19%) of patients undergoing dopamine agonist taper [47]. Not all agonist-related adverse effects, however, require reduction or discontinuation of dosage of the offending drug. For example, the central nervous system (CNS) stimulants modafinil or armodafinil can effectively reverse the excessive daytime drowsiness [48,49].

Levodopa

Whether levodopa should be used in early stages of Parkinson's disease or delayed until Parkinson's symptoms become more troublesome and begin to interfere with ADL, QoL, or occupation, has been debated for a long time. To address the question whether levodopa is neurotoxic, a correlation between levodopa exposure and density of pigmented neurons in substantia nigra was explored [50]. The investigators examined unilateral substantia nigra in 96 cases with Parkinson's disease, 40 of which had young-onset Parkinson's disease, with clinical records relating to antiparkinsonian drug

treatment and followed for more than 15 years. Based on this retrospective clinical–pathological study, they concluded that 'Chronic use of L-dopa in Parkinson's disease does not enhance progression of Parkinson's disease pathology as far as can be determined by our observations with substantia nigra neuronal counts and Lewy body densities.' This conclusion is consistent with findings from some [51▪,52], but not other [53▪], studies. Despite the paucity of evidence for clinically relevant levodopa toxicity, many newly diagnosed patients express 'levodopa phobia', partly fueled by publicity in the lay media about potential risks associated with levodopa therapy. This intense fear of levodopa-related adverse effects has often led to unintended denial of this most effective therapy to many patients who are clearly troubled or disabled by their Parkinson's disease symptoms and would benefit from levodopa therapy. The traditional practice of delaying levodopa therapy in newly diagnosed patients has been increasingly challenged for the following reasons:

(1) Starting levodopa at the time of diagnosis is associated with better QoL than when levodopa therapy is delayed [54].
(2) Early levodopa therapy may normalize basal ganglia physiology by restoring normal dopaminergic tone and reversing the compensatory mechanisms, such as subthalamic nucleus overactivity [55].
(3) The concern about possible levodopa toxicity, demonstrated by numerous in-vitro studies, has been largely diminished by lack of evidence for levodopa toxicity from in-vivo and postmortem studies [50,51▪,52].

Although there is little or no evidence of in-vivo levodopa neurotoxicity, it is well recognized that early introduction of levodopa is associated with early appearance of levodopa-related motor complications. As younger patients have a higher risk of levodopa-related motor complications, particularly dyskinesias, delaying levodopa therapy seems to be a prudent practice at least in this population of Parkinson's disease patients who will require levodopa therapy longer than the late-onset group. On the other hand, levodopa may be appropriately used early as a first-line symptomatic therapy in patients whose job security is in jeopardy because of Parkinson's disease-related symptoms or in mildly cognitively impaired or elderly patients who are more susceptible to psychiatric side effects of dopamine agonists. Thus, although published guidelines are helpful, particularly to the novices in the field, the decision when and whether to begin levodopa must be tailored to a patient's individual needs, age, and other characteristics [37,56] (Fig. 1).

TREATMENT OF ADVANCED PARKINSON'S DISEASE

Despite therapeutic advances over the past few decades, Parkinson's disease continues to be a relentlessly progressive disorder and advanced Parkinson's disease presents one of the most complex treatment challenges in clinical neurology, largely because of its combination of motor and nonmotor complications. Managing Parkinson's disease patients in an outpatient setting often requires numerous phone calls, most frequently related to symptoms such as anxiety, sleep disorders, dyskinesias and adverse effects due to dopamine-agonist use [57]. In one study, a total of 633 calls were generated by 397 patients; the average time per call was 6.6 ± 4.7 min [58]. Although most patients with Parkinson's disease can be managed effectively on outpatient basis, some require hospitalization. The most frequent reasons for hospitalization are worsening motor disturbances, but other reasons include reduced mobility, lack of compliance, inappropriate use of neuroleptics, falls, fractures, pneumonia, and other medical problems [59]. Educational programs, training and guidelines for the in-patient management of Parkinson's disease patients are being developed [60].

Medical management of motor fluctuations and dyskinesias

One of the most challenging problems in the management of patients in this stage of illness is the treatment of levodopa-related motor complications, particularly motor fluctuations and dyskinesias, experienced by at least a third of the patients within 2 years after starting levodopa therapy [61,62]. Sprouting of dopamine terminals and decreased dopamine uptake transporter function initially compensate for the presynaptic dopamine loss and prevent the appearance of parkinsonian symptoms until about 60% loss of nigral neurons, but these compensatory mechanisms may also contribute to dysregulated striatal dopamine release and to the emergence of dyskinesias and 'wearing-off' [63]. It has been hypothesized that the initial compensatory downregulation in dopamine transporter, associated with increased synaptic dopamine levels, may lead to increased risk of motor complications as the disease progresses. Based on studies in 36 patients with Parkinson's disease, 27 of whom had motor fluctuations and dyskinesia, using functional PET and [11C]-d-threo-methylphenidate

and 11C-dihydrotetrabenazine as ligands, the authors postulated that the downregulation of dopamine transporter early in the disease compensates for the presynaptic terminal loss and dopamine depletion by increasing synaptic availability of dopamine [64]. As the disease progresses, however, this increased intrasynaptic dopamine can be detrimental as it diffuses extrasynaptically and is metabolized by MAO and catechol-O-methyl transferase (COMT) leading to an increased dopamine turnover.

The main approaches used to control motor fluctuations in levodopa-treated patients with advanced Parkinson's disease include modifications of levodopa pharmacokinetics and delivery via COMT-inhibition, extended-release formulations or duodenal infusions, the adjunct use of long-acting dopamine agonists or MAO-B inhibitors, subcutaneous injections or infusions of apomorphine, and deep brain stimulation (DBS) [37] (Fig. 2).

Over the past few years, as dopamine agonists have become generic, there has been an emergence of new formulations of dopamine agonists that can be administered once a day [65,66▪,67▪]. In a double-blind, placebo-controlled, 24-week study (Efficacy and Safety Evaluation in Parkinson's disease Adjunct or EASE-PD Adjunct) of 393 patients with Parkinson's disease, ropinirole 24-h ($n = 202$) and placebo ($n = 191$) were compared [68]. At 6 months, the mean dose of ropinirole 24-h was 18.8 mg per day and this was associated with a mean reduction in daily levodopa of 278 mg and a mean reduction in daily 'off' time of 2.1 h (compared to 0.3 h with placebo). A variety of secondary outcome measures also improved. Likewise, a double-blind, randomized, placebo and active comparator controlled trial in early, as well as advanced Parkinson's disease, established the superiority of pramipexole extended release over placebo with a similar adverse event profile to the immediate release pramipexole [69]. These long-acting formulations of dopamine agonists offer several advantages, including more continuous dopaminergic stimulation, the possibility of lowering levodopa daily dosage, and improved compliance.

Rotigotine constant delivery system (CDS), a highly selective, lipid-soluble, nonergoline D3 >

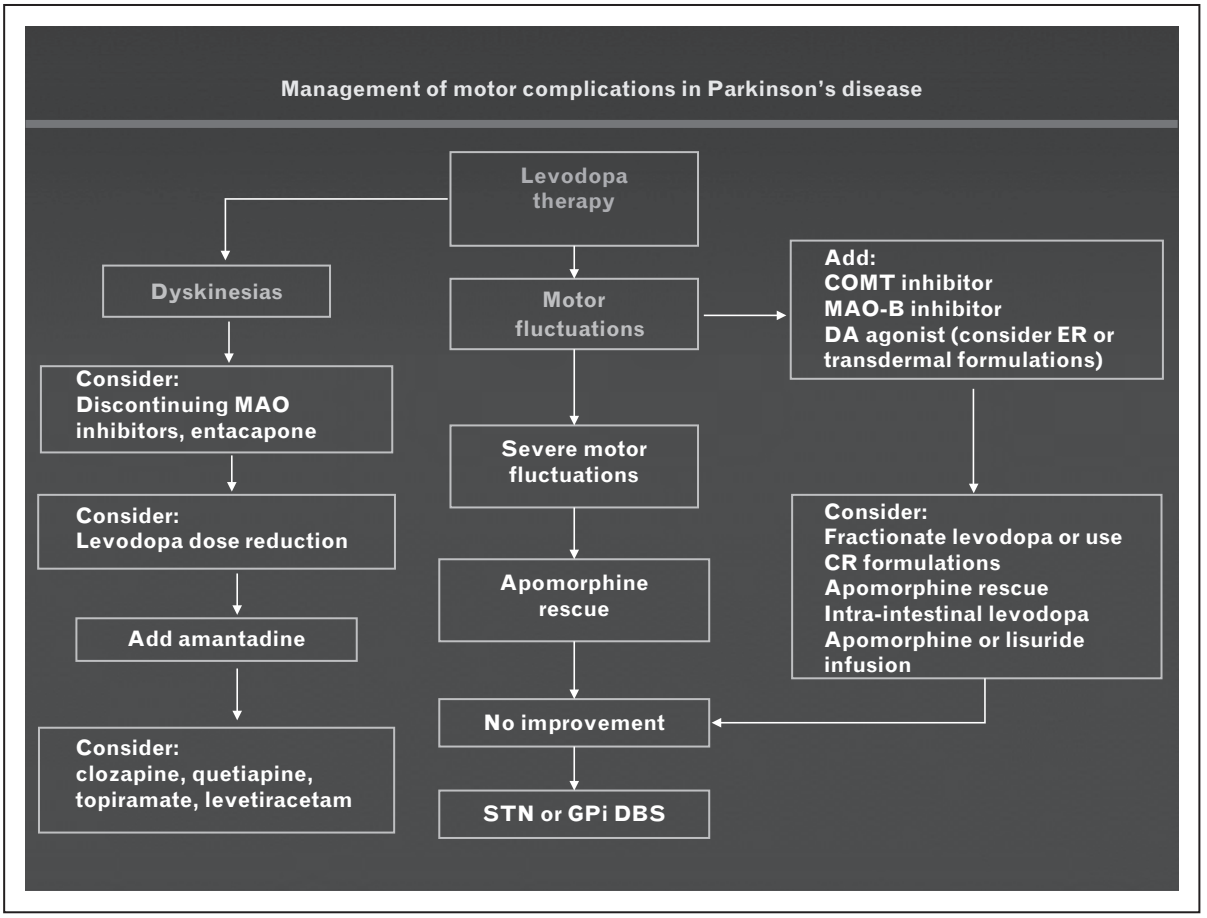

FIGURE 2. Suggested guideline for the treatment of levodopa-related motor fluctuations and dyskinesias. COMT, catechol-O-methyl transferase; CR, controlled release; DA, dopamine; ER, extended release; GPi, globus pallidus interna; MAO, monoamine oxidase; STN, subthalamic nucleus.

D2 > D1 and 5HT1A agonist and α2b antagonist, was approved by the FDA in the spring of 2007 for the treatment of early Parkinson's disease [70,71,72▪]. In the pivotal study, 96 patients with early Parkinson's disease were randomized to receive placebo and 181 to receive rotigotine (up to 6 mg per 24 h); there was a mean 3.5 point reduction in the UPDRS part III scores in the rotigotine group compared with the placebo group ($P < 0.0001$) [70]. The most commonly reported adverse events were application site reactions, nausea, somnolence, and dizziness [71]. In addition to its benefits in patients with early Parkinson's disease, the PREFER study, involving 131 patients, found rotigotine transdermal patch to be also effective in patients with advanced Parkinson's disease [73]. In this study 56.6% of patients treated with the 8 mg/24 h dose had at least 30% reduction in daily 'off' time, compared to 34.5% of patients in the placebo group. Furthermore, 'on' time without dyskinesias more than doubled in the rotigotine groups compared with the placebo group. In an active comparator study vs. placebo and pramipexole in advanced Parkinson's disease patients with motor fluctuations (CLEOPATRA-PD), the responder rates were 67% (134 of 200 patients) for pramipexole, 60% (120 of 201 patients) for rotigotine, and 35% (35 of 100 patients) for placebo, indicating that rotigotine was noninferior to pramipexole [74]. In a separate study involving 561 patients with Parkinson's disease, the responder rate was 52% in the rotigotine group compared to 30% in the placebo group [75]. In a double-blind, placebo-controlled trial involving 287 patients with Parkinson's disease and 'unsatisfactory early-morning motor symptom control' the mean Parkinson's Disease Sleep Scale total score decreased more than three-fold with rotigotine compared with placebo, indicating significant improvements in early-morning motor dysfunction and nocturnal sleep disturbances with once-day, morning administration of rotigotine patch [76]. In March 2008, Schwarz Pharma, a German pharmaceutical company who developed rotigotine, now marketed by UCB Pharma, withdrew the drug from the US market because of formation of crystals in the patches, but the drug has been re-approved for clinical use in 2012.

Although the use of dopamine agonists may be helpful in delaying and treating motor fluctuations, the treatment of levodopa-induced dyskinesias (LID) is more challenging [62] (Fig. 2). The best available medication for the treatment of LID is amantadine. Although in some cases the beneficial effects of amantadine wane, this *N*-methyl-D-aspartate (NMDA) antagonist appears to have relatively long-term antidyskinetic effects as evidenced by recurrence of dyskinesia when amantadine is discontinued after years of treatment [77]. Although currently the best anti-LID drug, amantadine's benefits in the treatment of LID are quite modest, hence there is a need for more effective anti-LID drugs [78,79].

Surgical treatment of Parkinson's disease

DBS has essentially replaced ablative procedures in the treatment of Parkinson's disease patients who respond well to levodopa but experience disabling motor fluctuations, dyskinesias, or both [80]. In one major study, a total of 255 patients were enrolled in a randomized, controlled trial, designed to compare the effects of DBS targeting either subthalamic nucleus (STN) or globus pallidus interna (GPi) and and best medical therapy after 6 months, at seven Veterans Affairs and six university hospitals [81]. Patients treated with DBS gained a mean of 4.6 h per day of on time without troubling dyskinesia compared with 0 h per day for patients who received best medical therapy ($P < 0.001$). Furthermore, motor function improved by at least 5 points on the motor UPDRS in 71% of DBS and in only 32% of medical therapy patients. This was accompanied by improvements in the majority of Parkinson's disease-related health-related QoL measures and only minimal decrement in neurocognitive testing. The overall risk of experiencing a serious adverse event, however, was 3.8 times higher in the DBS vs. the medical therapy group (40 vs. 11%). In a follow-up analysis of the Veterans Affairs Cooperative Studies Program, outcomes of STN versus GPi DBS were analyzed after 24 months in 299 patients [82▪]. There were no differences in mean changes in the motor (Part III) UPDRS between the two targets, but patients undergoing STN DBS required a lower dose of dopaminergic agents than those undergoing GPi stimulation ($P = 0.02$); also, visuomotor processing speed declined more after STN than after GPi stimulation ($P = 0.03$). On the other hand, there was worsening of depression after STN DBS, but mood improved after GPi DBS ($P = 0.02$). Slightly more than half of the patients experienced serious adverse events but there was no difference in the frequency of these events between the two groups. Based on these and other studies there is emerging evidence that GPi DBS may be particularly suitable for patients who may have troublesome dyskinesias as well as mild cognitive or behavioral impairment, whereas bilateral STN DBS may be the surgical choice for patients who are cognitively intact but in whom reduction in levodopa dosage is the primary goal. In the Parkinson's disease SURG trial, an ongoing randomized, open-label trial at 13 neurosurgical centers in the United Kingdom, 366

patients were randomly assigned to receive immediate surgery (DBS) and best medical therapy ($n=183$) or best medical therapy alone ($n=183$) [83▪]. At 1 year, the mean improvement in PDQ-39 summary index score compared with baseline was 5.0 points in the surgery group and 0.3 points in the medical therapy group ($P=0.001$), but there were significantly more adverse events in the surgical group than in the medical group. In a prospective, randomized, controlled multicenter study of a constant current DBS device (St. Jude Medical Neuromodulation, St. Paul, MN) 136 patients underwent DBS STN implantation and were randomly assigned to receive immediate stimulation ($n=101$) or control group ($n=35$) [84▪▪]. More 'good quality on time' was achieved in the stimulation group (4.27 vs. 1.77 h, $P=0.003$). UPDRS III motor scores off medication/on stimulation improved 40% as compared to baseline.

Several studies have addressed DBS-related hardware complications [85]. The reported rate of complications varied between 3.8 and 29% per electrode-year and included electrode misplacement or migration, lead fractures, infections, skin erosion, device malfunction and other complications [86]. Furthermore, 23.2% of patients required at least one visit to the emergency department for DBS-related complications. Although benefits associated with DBS extend beyond what can be achieved with medical therapy alone, selection of the appropriate patients and target as well as skills and experience of the DBS team are critical for excellent outcome. Selection of patients for DBS surgery is on the basis of the following criteria:

(1) Parkinson's disease more than 5 years (to allow for atypical features to emerge and to assess response to dopaminergic therapy);
(2) levodopa responsiveness (more than 33% reduction in motor UPDRS);
(3) troublesome motor fluctuations or dyskinesias despite optimal medical therapy;
(4) disabling medication resistant tremor;
(5) levodopa/dopamine agonist intolerance (rare);
(6) normal MRI;
(7) exclude atypical and secondary parkinsonism;
(8) exclude dementia and depression;
(9) good medical health;
(10) realistic expectations.

TREATMENT OF NONMOTOR ASPECTS OF PARKINSON'S DISEASE

Although generally referred to as a classic motor disorder, manifested typically by rest tremor, bradykinesia, rigidity and a variety of other motor symptoms, the clinical spectrum of Parkinson's disease includes a broad range of nonmotor symptoms [87]. After 20 years of disease duration over 80% of patients will have developed dementia, often accompanied by hallucinations and a variety of other psychiatric, autonomic, and other nonmotor problems [88]. Nonmotor problems are among the top five of the most troublesome symptoms of Parkinson's disease from a patient perspective [89]. The practice parameters on treatment of depression, psychosis and dementia in patients with Parkinson's disease have been summarized in the 2006 report by the American Academy of Neurology (AAN) Quality Standards Subcommittee [90]. Despite the enormous clinical impact of nonmotor symptoms, particularly in advanced Parkinson's disease, very few randomized controlled trials are available for interventions targeting these problems, and the management is often based on best clinical judgment and evidence from other disease areas (Table 1).

Dementia and psychosis

Several randomized controlled trials have assessed efficacy and safety of different acetylcholinesterase inhibitors as well as of memantine, an NMDA-antagonist, in Parkinson's disease dementia. To date the cholinesterase inhibitor rivastigmine remains the only anti-dementia agent for which efficacy has been proven in a large scale placebo-controlled study [91]. In this 24-week randomized, multicenter, double-blind clinical trial, involving 541 patients enrolled with Parkinson's disease and a relatively mild dementia (MMSE 10–24), the mean ADAS-cog score, the primary efficacy variable, improved by 2.1 points in the rivastigmine group and by 0.7 in the placebo group ($P<0.001$), and the MMSE improved by 0.8 in the rivastigmine group and worsened by 0.2 in the placebo group ($P=0.03$). The adverse effects that were significantly more frequent in the rivastigmine group were nausea, vomiting, dizziness, and tremor. In contrast, there is still insufficient evidence to unequivocally establish the efficacy of the two other cholinesterase inhibitors, donepezil and galantamine, although some studies did show signals for possible efficacy [92]. Likewise, three randomized controlled trials testing the efficacy of memantine [93–95] have failed to provide unequivocal and consistent evidence for efficacy of this NMDA receptor antagonist to treat Parkinson's disease dementia. The largest of these studies [95] examined a dose of up to 20 mg per day of memantine in a population consisting of 121 Parkinson's disease dementia patients and 78 patients with dementia with Lewy bodies (DLB). Treatment outcomes were inconsistent between

the total population and the two subgroups of patients. At week 24 there was no difference between memantine and placebo for the total population or for the patients with Parkinson's disease dementia on the primary outcome of Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change scores, whereas there was improvement in the DLB subgroup.

Psychosis is present in up to 70% of patients with advanced Parkinson's disease and the presence of hallucinations is the strongest predictor of nursing home placement and death [96]. To date, clozapine remains the only antipsychotic agent with unequivocal evidence for clinical efficacy from randomized placebo-controlled studies in patients with Parkinson's disease psychosis [92]. Quetiapine is a useful alternative to clozapine because of its more favorable safety profile without need for blood count monitoring. Similarly, based on a posthoc analysis of data from the large trial of rivastigmine in Parkinson's disease dementia [91], cholinesterase inhibitors may also have beneficial effects on hallucinosis in demented patients with Parkinson's disease [97].

Depression

Selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants remain the most commonly used drugs to treat depression in Parkinson's disease. Although SSRIs are the more commonly used type of agent, recent randomized comparative small scale studies suggest that efficacy may be greater with tricyclic antidepressants like desipramine [98] or nortriptyline [99]. The noradrenergic reuptake inhibitor atomoxetine has also been tested in randomized short-term placebo-controlled studies in 55 depressed Parkinson's disease patients, but after 8 weeks and partly because of the small sample size, atomoxetine (80 mg per day) was not significantly superior to placebo as measured by the Inventory of Depressive Symptomatology-Clinician (IDS-C) scores or CGI-I scores [100]. The largest randomized controlled clinical trial targeting Parkinson's disease depression to date tested the dopamine agonist pramipexole [101] in 296 patients with sufficient motor control and depressive symptoms. Pramipexole at a mean dose of 2.18 mg per day led to significantly greater improvement in the total score of the Beck Depression Inventory after 12 weeks as compared to placebo. One randomized study, the Study of Antidepressants in Parkinson's Disease, designed to evaluate the efficacy and safety of an SSRI, paroxetine, and a serotonin and norepinephrine reuptake inhibitor, venlafaxine extended release, showed that both drugs are effective in treating depression in patients with Parkinson's disease [102▪▪].

Autonomic dysfunction

Up to 60% of patients with advanced Parkinson's disease have clinically relevant signs and symptoms of autonomic dysfunction, but recent reviews have failed to identify any prospective randomized controlled trial meeting class I criteria as defined by the AAN [103▪] targeting autonomic outcomes. L-Threo-3,4,-dihydroxyphenylserine (also known as Droxidopa), a prodrug of norepinephrine that is converted mostly peripherally, but also centrally, into norepinephrine as it passes through the blood–brain barrier, has been studied recently in several placebo-controlled clinical trials in the United States (http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM294077.pdf). In one, phase 3, multicenter, multinational, double-blind, randomized, placebo-controlled, parallel-group, induction-design study (total of 4 weeks), patients with Parkinson's disease, pure autonomic failure, multiple system atrophy, or other dysautonomic disorders were randomized to droxidopa ($n = 82$; up to 1800 mg per day in three divided doses) or placebo ($n = 80$). The Orthostatic Hypotension Questionnaire Composite Score, the primary endpoint, decreased by 0.9 points in the droxidopa group compared with placebo ($P = 0.003$), and there was also a significant reduction in most of the secondary endpoints, including a significant increase in standing systolic blood pressure. Based on these studies, the FDA is currently considering the recommendation to approve the drug for the treatment of neurogenic orthostatic hypotension associated with Parkinson's disease, multiple system atrophy and pure autonomic failure. Although many symptomatic treatments for dysautonomia associated with Parkinson's disease are available [104] (Table 1), there is a need for well designed, controlled clinical trials of therapeutic interventions targeting these common nonmotor problems of Parkinson's disease.

Disorders of sleep and wakefulness

Disorders of sleep and wakefulness rank among the most common nonmotor problems in Parkinson's disease [105]. Based on a study of 457 unselected sleep-disturbed patients with Parkinson's disease who underwent video-supported polysomnography, the overall frequency of rapid eye movement (REM) sleep behavior disorder (RBD) was found to be 46% [106]. In some cases, RBD has been recorded up to 50 years before the onset of the initial symptoms of a neurodegenerative disorder, such as Parkinson's

disease, Parkinson's disease dementia, DLB, or multiple system atrophy [107]. RBD seems to be predictive of Parkinson's disease-associated dysautonomia and dementia [108▪,109]. In addition to these intrinsic problems of sleep-regulation/wake-regulation in Parkinson's disease, numerous comorbid and medication-related factors also impact sleep quality in this illness, including, nocturnal mobility, tremor, painful cramping, nocturia, nighttime confusion and hallucinosis, restless legs syndrome, and sleep disordered breathing [110].

Only a few interventions have been tested for their effects to improve sleep in Parkinson's disease. Although there was clear efficacy of the dopamine agonist rotigotine on sleep quality as assessed by the Parkinson's Disease Sleep Scale (PDSS) in a recent randomized, placebo-controlled trial [76], this was likely mediated through the drug's motor effect. Once-daily prolonged release ropinirole also has been found to improve nocturnal symptoms in patients with Parkinson's disease [111]. Smaller studies testing eszopiclon [112] or melatonin [113] were less clear with increases in total sleep time failing significance from placebo in the eszopiclon trial and inconsistent effects on different outcome measures and between doses in the melatonin trials. A pragmatic approach to improve sleep quality in Parkinson's disease should, therefore, be based on a careful clinical analysis of the principal problems contributing to poor sleep. This may include multiple measures, such as nighttime doses of dopaminergic agents to enhance nocturnal motor control and counteract off-periods, treatments with anticholinergic drugs reducing detrusor overactivity to reduce nocturia or nighttime doses of atypical antipsychotics (quetiapine) to reduce nocturnal confusion, clonazepam to treat symptoms of RBD, trazodone or tricyclics, including doxepin (Silenon), a histamine H(1) receptor antagonist, approved by the FDA for the treatment of insomnia (3 mg tablets, 1–2 tablets at bedtime) [114].

Excessive daytime sleepiness and sleep attacks have received major attention as a relatively common side effect of treatment with dopamine agonists. Several randomized controlled trials have tested the usefulness of a wake-promoting agent, modafinil, in patients with Parkinson's disease and excessive daytime sleepiness [48]. Overall, results between trials have been inconsistent. Recent evidence-based reviews have agreed on a level A recommendation for modafinil in improving patient perception of excessive daytime somnolence [103▪], but found the published data insufficient to conclude on the drug's efficacy in more severe manifestations of daytime sleepiness [92]. Excessive daytime drowsiness often overlaps with other nonmotor symptoms associated with Parkinson's disease such as fatigability, and various CNS stimulants have been used to control these symptoms (Table 1).

Pain and other sensory symptoms

One of the most troublesome nonmotor Parkinson's disease-related symptoms is a variety of sensory deficits such as anosmia and ageusia and sensory complaints, such as pain, particularly involving the shoulder, paresthesias, akathisia, and oral and genital discomfort [115]. Tricyclic antidepressants, carbamazepine, pregabalin, and gabapentin have been found effective in some patients with these complaints [116].

CONCLUSION

Despite disappointing results from recent clinical trials, better understanding of the genetic and other causes of Parkinson's disease may eventually translate into more effective disease-modifying and perhaps even pathogenesis-targeted therapies. Until then, it is critical that clinicians use the published evidence-based data as a guide and tailor the selected therapy to the needs of individual patients in order to optimize their functioning. True innovative ideas, coupled with advances in understanding the mechanisms of cell death, better animal models and presymptomatic biomarkers, as well as more reliable and sensitive clinical rating scales and quantitative instruments designed to measure progression, severity, and impact of the disease on QoL, should translate into more innovative and efficacious therapies in the future.

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This double-blind, parallel study of patients with early Parkinson's disease not receiving levodopa or dopamine agonists, randomly assigned to pramipexole immediate release ($n = 207$), pramipexole extended release (ER) ($n = 213$), or placebo ($n = 103$), showed that pramipexole ER monotherapy was noninferior to pramipexole immediate release and significantly more effective than placebo. Tolerability and safety did not differ between the formulations.

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In the PREPARED study, designed to evaluate the efficacy of adjunctive ropinirole prolonged release vs. immediate release, patients with advanced Parkinson's disease received once-daily prolonged release (2–24 mg per day; $n = 177$) or three-times-daily immediate release ropinirole (0.75–24 mg per day; $n = 173$) for 24 weeks. At week 24, prolonged release ropinirole significantly increased the proportion of patients maintaining at least 20% reduction in 'off' time vs. immediate release. Furthermore, the mean dose of levodopa was reduced by 162 mg in the prolonged release group and by only 113 mg in the immediate release group compared with baseline.

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In this prospective, open-label extension of a 6-month double-blind, placebo-controlled trial, patients with early-stage idiopathic Parkinson's disease received transdermal rotigotine for up to 6 years at optimal dose (up to 16 mg/24 h). Of the 217 patients entering the open-label study, only 74% initiated levodopa during the trial and 47% were still taking rotigotine at the end of the study; 24% discontinued the drug because of adverse events. The drug was generally well tolerated, but adverse events included somnolence (23% per patient-year), falls (17%), peripheral edema (14%), nausea (12%), and application site reactions (12%).

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In this study of 299 patients with Parkinson's disease conducted at seven Veterans Affairs and six university hospitals, similar improvement in motor function was achieved with either GPi or STN stimulation.

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The PD SURG trial is an ongoing open-label trial involving 366 patients with Parkinson's disease randomly assigned to receive immediate surgery (lesioning or deep brain stimulation at the discretion of the local clinician) and best medical therapy or best medical therapy alone. At 1 year, patients with surgery and best medical therapy improved had a better self-reported quality of life than those receiving only best medical therapy. Although these differences were thought to be clinically meaningful, 36 (19%) patients had serious surgery-related adverse events and one resulted in death.

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Although there was no comparison with voltage-driven devices, this study suggests that constant-current devices, such as the one used in this study, have theoretical advantages over voltage-driven devices in that the field of stimulation within brain tissue should be stable in size, whereas stimulation fields produced by voltage-driven devices are susceptible to changes in size caused by changing tissue impedance. This may, however, be a purely theoretical advantage that may or may not translate into a clinically meaningful benefit. Furthermore, new devices have the capability of using both constant-current or constant-voltage modes.

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A total of 115 patients with Parkinson's disease and depression were enrolled and randomized to receive either paroxetine or venlafaxine extended release (XR). All subjects scored >12 on the first 17 items of the Hamilton Rating Scale for Depression (HAM-D). After a follow-up of 12 weeks (6-week dosage adjustment, 6-week maintenance), compared to placebo the HAM-D score was reduced by 6.2 points [59% improvement compared to baseline; 97.5% confidence interval (CI) 2.2 to 10.3, $P=0.0007$] in the paroxetine group and by 4.2 points (52% improvement compared to baseline; 97.5% CI 0.1 to 8.4, $P=0.02$) in the venlafaxine XR group (32% for placebo compared to baseline). This study provides evidence that both antidepressants are effective in the treatment of depression associated with Parkinson's disease.

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