Treatment of Early Parkinson’s Disease

Part 2

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However, the review did not include the management of early PD since there were no major changes since the last guidelines. Evidence-based treatment guidelines for early PD were published by the American Academy of Neurology in 2002 [4] and the Movement Disorder Society in 2005 [5], but since then new drugs and formulations have become available for the management of the disease. PD is a multifaceted disorder comprised of both motor and non-motor symptoms at all stages of the disease. This review seeks to integrate data from the newest treatment options with data from established therapies, so as to provide an up-to-date evidence-based reference for clinicians treating early PD. The article is presented in 2 parts: a review of the efficacy and safety of treatments for PD motor symptoms (part 1) and a review of key clinical trials examining potential neuroprotective therapies for PD and non-motor manifestations of PD (part 2). The following text is part 2.

Key Words
Parkinson’s disease • Dopamine agonists • Monoamine oxidase B inhibitors • Levodopa

Abstract
The management of early Parkinson’s disease (PD) involves the treatment of motor symptoms, and, increasingly, non-motor symptoms. Given the fast pace of clinical research in PD, clinicians are faced with the challenge of integrating the latest findings into the ongoing care of individual PD patients. Part 1 of this 2-part article reviews efficacy and safety data for the newest PD treatment options, as well as for established therapies. Part 2 of the article, presented here, reviews key data relevant to the assessment of potential neuroprotective therapies and the treatment of non-motor symptoms.

Introduction
The treatment options for Parkinson’s disease (PD) are rapidly expanding. The American Academy of Neurology published evidence-based practice parameters of selected topics in the management of PD in 2006 [1–3]; however, the review did not include the management of early PD since there were no major changes since the last guidelines. Evidence-based treatment guidelines for early PD were published by the American Academy of Neurology in 2002 [4] and the Movement Disorder Society in 2005 [5], but since then new drugs and formulations have become available for the management of the disease.

PD is a multifaceted disorder comprised of both motor and non-motor symptoms at all stages of the disease. This review seeks to integrate data from the newest treatment options with data from established therapies, so as to provide an up-to-date evidence-based reference for clinicians treating early PD. The article is presented in 2 parts: a review of the efficacy and safety of treatments for PD motor symptoms (part 1) and a review of key clinical trials examining potential neuroprotective therapies for PD and non-motor manifestations of PD (part 2). The following text is part 2.

Beyond Symptomatic Therapy: Neuroprotection Studies in PD
Neuroprotective therapies are interventions that produce enduring benefits by favorably influencing the underlying etiology or pathogenesis of neurodegenerative
disorders [6]. Although there is currently no definitive methodology to assess neuroprotection in PD patients [7], multiple attempts have been made to assess the effects of medications on disease progression.

**L-Dopa**

In the ELLDOPA trial, treatment outcome was assessed after a 2-week washout period following 40 weeks of treatment with L-dopa or placebo [8]. The change from baseline in UPDRS scores remained significantly lower (better) in each L-dopa group compared to the placebo group even after the washout, a result that is potentially consistent with neuroprotection, though also consistent with a long-duration symptomatic effect from L-dopa. In contrast, disease progression, as assessed by dopamine transporter (DAT) binding at baseline and 40 weeks using β-CIT single photon emission computed tomography (SPECT), was greater in the L-dopa groups than in the placebo group, a result that is consistent with a more rapid progression of the disease or a pharmacologic or pharmacodynamic effect of L-dopa on the DAT. Additional studies will be needed to reconcile the discrepancies between the clinical and neuroimaging data. At the current time, there is no clear evidence that L-dopa either hastens or slows disease progression.

**Dopamine Agonists**

The dopamine agonists (DAs) pramipexole and ropinirole exert neuroprotective effects in cell culture and animal models through antioxidative and anti-apoptotic mechanisms [9], and have been tested in clinical trials using SPECT or PET imaging techniques. The CALM-PD trial [10] compared pramipexole and L-dopa treatment over a period of 4 years, measuring estimated neuronal loss by DAT binding after 22, 34 and 46 months using β-CIT SPECT. Pramipexole treatment significantly reduced the loss of DAT binding at all 3 time points when compared to L-dopa (p = 0.004, 0.009 and 0.001 at 22, 34 and 36 months, respectively). The REAL-PET [11] study compared ropinirole and L-dopa treatment over 2 years and used 18F-dopa uptake detected by PET to assess neuronal loss. Ropinirole-treated patients had a smaller reduction in 18F-dopa uptake (13.4%) compared to those treated with L-dopa (20.3%, p = 0.022). Although these results are consistent with neuroprotection with a DA or neurotoxicity with L-dopa, other pharmacological effects may underlie the apparent neuronal preservation observed with ropinirole and pramipexole compared to L-dopa. Both DAs and L-dopa can, to varying degrees, alter aromatic acid decarboxylase levels and activity, and therefore the apparent amount of 18F-dopa uptake [12, 13]. Similarly, as SPECT analysis relies on the amount of DAT expressed, modulation of DAT levels by DAs or L-dopa may influence the estimation of neuronal preservation [12, 14].

These studies also are handicapped by the absence of placebo data and the lack of correlation between imaging and clinical measures of motor disability, making the interpretation of neuroprotection less than conclusive.

Rotigotine has exhibited neuroprotective properties in mouse and non-human primate models of PD [15–17], but neuroprotection has not been proven clinically. In a study of progressive MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) lesioning of macaques, treatment with rotigotine for 38 days followed by a two-week washout reduced motor disability and increased postmortem striatal DAT binding compared to treatment with vehicle [17]; however, in vivo measurement of DAT using SPECT failed to reveal differences between rotigotine and vehicle groups, suggesting that in vivo SPECT assessment is not as sensitive as postmortem DAT labeling. Studies in PD patients are required to determine if rotigotine can provide a neuroprotective effect in the clinical setting.

**MAO-B Inhibitors**

The irreversible MAO-B inhibitors selegiline and rasagiline confer mild symptomatic benefits for PD through MAO-B inhibition, but also may provide neuroprotection through independent mechanisms such as inhibition of GAPDH nuclear translocation and upregulation of Bcl-2 and other anti-apoptotic messengers [18]. The clinical assessment of neuroprotection by these agents is challenging because of their symptomatic benefits, which can confound the interpretation of clinical trials; nevertheless, several large-scale trials have been undertaken.

In the DATATOP trial, selegiline treatment delayed the requirement for L-dopa, but when treatment was halted, patients taking the MAO-B inhibitor worsened more than those given placebo, such that there were no differences between groups at the end of the washout period [19]. Subsequently, all patients were treated with open-label selegiline, creating a delayed-start trial paradigm [20]. No differences were found in UPDRS scores or other outcomes between patients continuously treated with selegiline and those who were later switched from placebo to selegiline, suggesting that selegiline failed to have any impact on the course of the disease. Another study examined treatment from untreated baseline to untreated endpoint following washout of symptomatic therapy with bromocriptine or L-dopa plus additional treatment with selegiline or placebo. Selegiline was discontinued 2
months before the final UPDRS assessment in an attempt to ensure complete washout of drug [21]. The authors found a significant difference in favor of selegiline-treated subjects, but it is not possible to determine if all of the symptomatic effects of selegiline were resolved by the washout. Even so, it is interesting to note that, despite a 2-month washout, selegiline still provided as much benefit as L-dopa, suggesting that neuroprotection may have been achieved.

Rasagiline has been investigated in 2 trials. The TEMPO study employed a delayed-start design [22]. At 12 months, patients taking rasagiline from the start of the trial had significantly lower UPDRS scores (less disability) than those who initiated rasagiline after 6 months of placebo treatment, suggesting that the earlier administration of rasagiline may have provided neuroprotection. This study has been extended for 6.5 years, and at several (but not all) time points, the delayed-start subjects showed significantly greater impairment on the UPDRS compared to subjects who initiated the trial with rasagiline [23]. A larger trial of rasagiline that was designed to confirm the results of the TEMPO study has been just completed: the ADAGIO study [24] also used a delayed-start design, but enrolled a larger cohort of subjects (n = 1,176), had a longer duration (72 weeks) and investigators remained blinded to the treatment assignment for the duration of the study. In the first phase of the study, subjects with early untreated PD were randomized to rasagiline 1 mg/day, 2 mg/day or matching placebo. After 36 weeks, the group initially treated with placebo was switched to 1 or 2 mg/day active treatment in a double-blind fashion. The study evaluated the change in UPDRS score from baseline to endpoint across each same-dose early and delayed-start group, and results from the complete report are awaited.

Other Treatments
The Neuroprotection Exploratory Trials in Parkinson's disease (NET-PD) initiative has been implemented by the NIH in order to 'fast track' evaluation of potential neuroprotective agents. Futility trials have been conducted to determine whether further studies of GPI-1485, minocycline, creatine and coenzyme Q10 (CoQ10) are warranted [25]. In these studies, progression of clinical disability was compared to progression of the placebo arm in the DATATOP study. Based on this predefined comparison to historical controls, none of these agents were found to be futile [26, 27]; however, an exploratory analysis adjusting the futility threshold using the placebo arm of PD progression, a concern that stems from the hypoth-
esis of a neurotoxic effect of L-dopa caused by the production of free oxygen radicals that could further potentiate the degenerative process in the substantia nigra [36]. However, several lines of evidence do not support the hypothesis of L-dopa toxicity [37]. While L-dopa has been shown to potentiate cell death in tissue culture, the concentration of L-dopa in those experiments far exceeded the concentrations achieved in humans. Animal data also do not demonstrate a neurotoxic effect of L-dopa at doses that approximate human use [38]. Most importantly, data from the ELLDOPA trial demonstrated clinically that early initiation of L-dopa was not deleterious, but rather resulted in a reduction of disability [8]. However, the imaging component of the trial was potentially consistent with a neurotoxic effect, and an increased risk of dyskinesia was observed. Thus, while L-dopa remains the most efficacious agent for the treatment of PD, the timing of initiation of L-dopa must be balanced against the risk of drug-induced motor complications.

An alternative strategy is the initiation of treatment with DAs or MAO-B inhibitors; however, the benefit of DAs has to be weighed against their relatively high rate of side effects, specifically drug-induced sedation and impulse control disorders. MAO-B inhibitors have few side effects, but are less efficacious than other dopaminergic agents. The current standard of practice is to initiate symptomatic therapy at the time of functional disability [4, 5]. The limitation of such an approach is that there is substantial variability in the interpretation of what constitutes functional disability. One of the major arguments against early initiation of treatment in PD has been the lack of a proven neuroprotective agent, and therefore a lack of ‘urgency’ to initiate treatment. While there remains no proven neuroprotective agent in PD, multiple clinical trials including the ELLDOPA (L-dopa) and TEMPO (rasagiline) studies suggest that early initiation of symptomatic therapy reduces the accumulation of disability. These data should serve as the rationale for physicians to offer symptomatic therapy early in PD, while carefully weighing the immediate and long-term benefits against potential side effects.

Treatment of Non-Motor Symptoms

Until recently, the majority of PD clinical trials were designed to assess the efficacy of novel therapeutic agents for motor disability; however, based on the results of a large survey of PD patients, depression and non-motor disability were found to be the major contributing factors to impairments in disease-related quality of life [39]. The scope of non-motor manifestations of PD is broad, and includes disturbances in mood, cognition, autonomic function, sleep, perceptual changes and impulse control. The pathogenesis of non-motor symptoms in PD is complex and not fully understood, but is believed to be related to the widespread nature of dopaminergic dysfunction involving structures beyond the substantia nigra, as well as the presence of PD-related pathology in non-dopaminergic nuclei, such as the locus coeruleus, nucleus basalis of Meynert and raphe nuclei [40]. In the past, non-motor symptoms were attributed to more advanced stages of PD; however, it is now known that many can manifest early in the course of the disease and can even precede the onset of motor symptoms (e.g. anosmia, depression, sleep dysfunction). The high prevalence, associated disability and often early occurrence of non-motor symptoms in PD not only warrant the development of therapeutic agents aimed specifically at their treatment, but also necessitate the reevaluation of existing PD agents for potential benefits in alleviating non-motor symptoms.

Depression

Depression remains the major factor contributing to quality of life impairments in PD. Depression can occur early in the course of the disease, and can even precede the onset of motor disability. Early recognition and treatment of depression is essential for effective disease management. The current estimated prevalence of depression in PD is 40%, though prevalence in early stages of the disease has not been well established [41]. Compared to depressive disorders in non-PD populations, depression in PD is often characterized by less guilt and lower suicide ideation, but higher rates of anxiety, pessimism and irrationality [42]. Similar to elderly patients in general, PD patients more commonly suffer from less severe forms of depression (i.e. minor depression and dysthymia rather than major depression). Other symptoms frequently seen in the spectrum of PD-related mood dysfunction include anhedonia (i.e. loss of pleasure), apathy (i.e. loss of interest or motivation) and anxiety.

Despite the high prevalence of depression in PD, there is a paucity of well-designed controlled clinical trials that systematically evaluate the efficacy of standard antidepressants or dopaminergic therapy for mood dysfunction, and no studies focusing on mood disorders in early PD have been performed. Recently published practice parameters on the treatment of depression in PD identified only 6 well-controlled studies, some of which were not sufficiently powered to detect efficacy of the tested agent
The conclusion of the practice parameter was that there is insufficient evidence to support or refute the efficacy of most antidepressants in the treatment of depression in PD; however, lack of literature demonstrating clear efficacy of antidepressants is not the same as absence of efficacy. A recent meta-analysis reviewed all English language studies published on the efficacy of antidepressants in PD from 1965 to December 2003 [44]. The data analysis concluded that there was a large effect size for both active treatment and placebo groups, but there was no significant difference between the two. Additional data are necessary and a number of studies are ongoing; however, in clinical practice, SSRIs (selective serotonin reuptake inhibitors) are the most commonly used antidepressants for the treatment of depression in PD [45].

Limited data on the role of dopaminergic therapy in the treatment of depression in PD are available [46, 47]. Pramipexole was shown to have comparable efficacy to sertraline for the treatment of depression in PD; however, the open-label trial design and low dose of sertraline used in that study limits the findings [48]. A randomized placebo-controlled study of pramipexole for depression in patients with early PD in Europe was recently completed, but the results have not been presented yet.

Cognitive Dysfunction

Compared to depression, which can be seen early in the course of PD, dementia is a manifestation of advanced disease; however, signs of cognitive dysfunction can be seen even in the early stages of PD. In a study of 115 consecutive newly diagnosed PD patients compared to 70 healthy controls, 24% of the newly diagnosed PD patients versus 4% of the controls had abnormal performance on at least 3 neuropsychological tests, with impairment predominantly in the domains of executive function and psychomotor speed [49]. The profile of cognitive impairment in PD is frequently labeled as ‘dysexecutive syndrome’ and characterized by impaired visuospatial abilities, attention, retrieval memory and executive function, with relative preservation of encoding memory, praxis and language compared with the mild cognitive impairment that precedes Alzheimer’s disease [50, 51]. The recommendations for the diagnostic evaluation of dementia in PD were recently published by the Movement Disorders Society task force [52].

Although no data on the treatment of mild cognitive impairment in early PD are available, a number of studies have investigated the role of cholinesterase inhibitors in the treatment of PD dementia. The largest study (n = 541) demonstrated a statistically significant but modest clinical benefit of rivastigmine (oral formulation) over placebo [53]. The most common side effects were gastrointestinal in nature, which is typical for this class of drug, and the worsening of PD tremor by patient report, though UPDRS scores did not reflect this. Based on this study and others, oral rivastigmine and more recently the transdermal patch, which is associated with less nausea and vomiting, have received FDA approval for the treatment of PD dementia. In smaller studies, other cholinesterase inhibitors also have been shown to be effective in the treatment of PD dementia [54]. While no data on the efficacy of the NMDA (N-methyl-D-aspartate) receptor antagonist memantine in the management of PD dementia have been published, studies are under way. Additional studies are necessary to evaluate the efficacy of all of these agents in patients with mild cognitive impairment in early PD.

Sleep Dysfunction

Disorders of sleep and wakefulness are ubiquitous in PD, with an estimated prevalence of 98% [55]. Sleep dysfunction can occur early in the course of PD, and PD-associated sleep dysfunction spans the spectrum of sleep pathology. The etiology is multifactorial and includes PD pathology affecting the reticular activating system, which, according to Braak et al. [40], is involved early in the course of the disease process. PD-related motor dysfunction directly impacting sleep quality and side effects of complex PD pharmacological therapy also play a role. Some of the specific problems that commonly contribute to sleep fragmentation and poor sleep efficiency in PD patients include parasomnias: specifically, rapid eye movement sleep behavior disorder (RBD), which is present in about 15–33% of patients [56], restless legs syndrome and obstructive sleep apnea [57]. RBD is of particular significance in early PD as it can precede the onset of motor disability by a number of years and is considered to be a potential premotor sign of PD [58]. Excessive daytime sleepiness (EDS) occurs in up to 50% of PD patients [59]. Interestingly, a prospective survey of 3,078 elderly men in the Honolulu-Asia Aging Study demonstrated that preexisting EDS was one of the risk factors for development of PD [60]. Risk factors for EDS in PD include advanced age, presence of cognitive dysfunction and cumulative dose of dopaminergic therapy [61]. Surprisingly, EDS does not correlate with the quality of nocturnal sleep. In addition to the more common sleep problems, a phenomenon of sudden onset sleep (SOS) – described as unintended episodes of sleep that occur without premon-
Modafinil has shown mixed results for PD-related EDS therapy, described as occurring with the use of any dopaminergic treatment. It was initially attributed to a specific DA, but later was de-escalation phase in the pramipexole- versus the L-dopa-treated group (17.3 vs. 5.6%) [75].

If psychotic symptoms in PD are significant enough to warrant intervention, the first step is to discontinue any non-essential non-PD medications that might contribute to mental impairment. Next, the risk:benefit ratio of each antiparkinsonian medication should be reviewed. In conjunction with the steps outlined above, antipsychotic treatment is initiated for persistent and problematic psychosis. Clozapine has been shown to be efficacious for PD psychosis in placebo-controlled studies at much lower dosages (mean dosages of 25–36 mg/day) than typically used in psychiatric populations [76, 77], but it is usually reserved for treatment-refractory patients. Clinically, quetiapine has become the most commonly used antipsychotic, a preference based upon clinical experience, the results of several positive open-label studies [78–81], and less adverse impact on parkinsonism than reported with typical antipsychotics and even other atypical antipsychotics [82].

Impulse Control Disorders
Over the last couple of years, there have been an increasing number of publications reporting impulse control disorders (ICDs) in PD patients [83]. ICDs are defined as failure to resist an impulse or temptation to perform an act that is harmful to the patient or others. The most common clinical manifestations of ICDs in PD are compulsive gambling, sexual behavior, buying and eating. A recently completed cross-sectional study of 3,090 treated PD patients reported an overall prevalence of ICD of 13.6% and a prevalence of ICD of 17.1% in patients treated with a DA [84]. The frequency of each ICD for the entire population was: compulsive buying (5.7%), problem or pathological gambling (5.0%), binge-eating disorder (4.3%) and compulsive sexual behavior (3.5%); over one third of patients with an ICD had more than one. ICDs were more common in DA-treated patients than in non-DA-treated ones (17.1 vs. 6.9%, respectively; odds ratio = 2.72, 95% CI: 2.08–3.54, p < 0.001). Among individual DAs, there was no difference in ICD frequency for pramipexole- and ropinirole-treated patients (17.7 vs. 15.5%, respectively; odds ratio = 1.22, 95% CI: 0.94–1.57, p = 0.14). Among individual DAs, there was no difference in ICD frequency for pramipexole- and ropinirole-treated patients.

Psychosis
Psychosis usually occurs later in the course of PD. Psychosis very early in the disease course suggests a diagnosis of dementia with Lewy bodies [72]. Exposure to dopaminergic therapy has been implicated as the major cause of psychosis in PD [73], and DAs are more prone to cause psychosis than L-dopa, even in early PD. In a placebo-controlled study of 3 L-dopa dosages, hallucinations were not reported as an adverse event in any of the treatment groups [8]. Comparing L-dopa to DA treatment, in a randomization comparison study of pramipexole and L-dopa in early PD, hallucinations were more common during the escalation phase in the pramipexole- versus the L-dopa-treated group (6.6 vs. 1.3%, respectively) [74]. Similarly, in a randomized comparison study of ropinirole and L-dopa in early PD, hallucinations were reported more frequently in the ropinirole- versus the L-dopa-treated group (17.3 vs. 5.6%) [75].

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Treatment of sleep dysfunction in PD should focus on an accurate diagnosis of the specific problem. PD medications should be reviewed and simplified if possible, and sleep studies should be ordered if other causes of sleep dysfunction are suspected. RBD can be effectively managed with clonazepam [56], though placebo-controlled studies are lacking, and nocturnal confusion can occur with bedtime benzodiazepine use in the geriatric population. Melatonin was reported to be effective in 1 small study at dose ranges of 3–12 mg and is generally well tolerated [64]. Donepezil, pramipexole and L-dopa have also been reported to be effective, though experience is limited to case reports [65, 66]. Restless legs syndrome is readily responsive to DAs [67, 68]. Use of hypnotics should be limited to cases that do not respond to behavioral modifications and other measures, as there are no efficacy data for specific hypnotic agents in PD. Physicians also should be vigilant about the treatment of depression and psychosis, as these are possible contributing factors to sleep dysfunction in PD patients. Treatment of EDS is challenging because the majority of dopaminergic agents can cause EDS; reducing or changing DAs should be attempted [69]. Modafinil has shown mixed results for PD-related EDS [69], with some studies showing mild improvement [70] and others showing no improvement [71].

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appears to be DA treatment, with additional risk factors being a history of related behaviors or substance abuse, younger age and male sex [83–86]. Additional data are necessary, but all patients who are to be treated with a DA should be counseled in advance about the potential risk for the development of 1 or more ICDs. Although there is no controlled treatment research, management options for patients with an ICD include discontinuation of the DA, using a lower DA dosage, switching to a different DA or adding a psychiatric medication (e.g. an SSRI) [87].

**Autonomic Dysfunction**

Autonomic dysfunction (ADS) is an intrinsic part of PD symptomatology. The spectrum of ADS in PD is broad and includes orthostatic hypotension, bladder and bowel dysfunction, erectile dysfunction and hyperhidrosis. Despite prior belief that ADS is a manifestation of advanced PD, ADS symptoms can be present early in the course of the disease and can have a major impact on quality of life [88, 89]. The etiology of ADS in PD is believed to be related to the spread of Lewy body pathology to the autonomic centers, augmented by the potential negative impact of dopaminergic medications on at least some of the symptoms (e.g. orthostatic hypotension and constipation). Studies have reported efficacy of domperidone, a peripheral dopamine receptor blocking agent, and pyridostigmine, a peripheral cholinesterase inhibitor, for the management of orthostatic hypotension in PD [90, 91]. While there is an increasing amount of data on the prevalence of ADS in PD, there is paucity of literature on disease-specific treatment options. Physicians should use a standard symptomatic treatment approach to manage ADS as in other disorders, but with an awareness of potential PD-specific side effects (e.g. confusion with the use of drugs for neurogenic bladder dysfunction).

**Anosmia and Other Sensory Manifestations of PD**

Loss of smell has long been reported to be an early sign of PD, present in 70–100% of PD patients [92]. As the loss of smell frequently can precede the onset of motor symptoms, recent research has focused on the role of smell-testing in the early identification of PD [92]. If proven to be sensitive and specific, a smell test would be an easy-to-administer inexpensive screening tool that would be useful for identifying populations at risk of PD and for enrollment in neuroprotection clinical trials. Anosmia does not improve with dopaminergic therapy, and thus cannot be used as a measure of efficacy for dopaminergic agents.

Pain is another common manifestation of PD [93]. The pattern and distribution of pain varies, but a subset of patients experiencing pain is responsive to dopaminergic therapy [93]. The nature of pain in PD is likely multifactorial, and more data on the mechanisms of pain and potential disease-specific treatment interventions are necessary.

**Conclusions**

Halting the progression of PD is currently a significant unmet need in the treatment of PD, despite a large number of clinical trials designed to investigate potential neuroprotective agents. The research effort to find effective neuroprotective agents is ongoing and will hopefully ultimately lead to the discovery of effective disease-modifying strategies. Clinicians will have to weigh newly evolving evidence as it becomes available to decide if potential neuroprotective benefits outweigh the cost and potential side effects for individual patients. Non-motor symptoms of PD can manifest even early in the disease and cause significant impact on patient quality of life. Recent data provide a better understanding of the scope of PD non-motor manifestations. Evaluation of new and existing therapeutic agents for these symptoms is an important focus of current research.

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