

# Parkinson's Disease: Health-Related Quality of Life, Economic Cost, and Implications of Early Treatment

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## Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder, marked by increasing movement-related disability, including tremor and bradykinesia, impaired balance and coordination, and cognitive changes. It affects up to 1 million people in the United States and up to 5 million worldwide.<sup>1</sup> The prevalence of PD increases with age, with approximately 1% of those aged 60 years or older affected, 4% or more of those aged 80 years or older,<sup>2</sup> and approximately 5.2% of those in nursing homes.<sup>3</sup> Given the growing elderly population in the United States, the number of individuals with PD is expected to double by 2030.<sup>4</sup>

Such an increase will place a significant burden on healthcare systems and caregivers given the progressive nature of PD, associated disability, and significant caregiving required in the later stages of the disease. With the expected increase in PD prevalence, it can be anticipated that the disease will continue to exact a significant direct and indirect economic cost. Thoughtful consideration into treatment decisions can result in more optimal healthcare utilization without sacrificing health-related quality of life (HRQOL) and economic costs.

## Economic Costs of PD and Impact on Health-Related Quality of Life

Overall, the annual economic impact of PD in the United States is estimated at \$10.8 billion, 58% of which is related to direct medical costs.<sup>5</sup> Annual direct medical costs per patient with PD are estimated to be between \$10,043 and \$12,491, more than double that of patients without the disease.<sup>5,6</sup> Prescription drugs account for approximately 14% to 22% of costs, with nursing home care the largest component at approximately 41%. Annual indirect costs, including lost workdays for patients and caregivers, are estimated at \$9135.<sup>5</sup>

As important as economic costs are to any discussion of PD-related resource utilization, it is also critical that payers and providers consider the significant impact the disease has on HRQOL. HRQOL assesses an individual's perceived effect of the illness on their physical, psychological, and social daily lives.<sup>7</sup> It is important in determining the effectiveness of therapies for PD at both the individual and population levels.<sup>8</sup> For managed care providers, it presents an important parameter to measure the effectiveness

## Abstract

Parkinson's disease (PD) is the second most common neurodegenerative disorder, marked by progressive increases in movement-related disability, impaired balance, and nonmotor symptoms. Its prevalence in the United States is expected to double within the next 20 years as the percentage of the elderly in the population grows. Patients with PD have twice the direct medical costs of those without PD, the majority of which occur later in the disease as disability and therapy-related complications increase. Greater awareness of a prodromal/premotor stage of the disease, efforts toward early and accurate diagnosis, and the continuous refinement of treatment paradigms provide an opportunity for discussion on the use of potential disease-modifying agents to slow or halt the progression of motor and nonmotor disability. Such compounds could not only significantly improve patient and caregiver quality of life, but substantially reduce direct and indirect costs. To date, numerous compounds have been evaluated in clinical trials, including coenzyme Q10, creatine, levodopa, pramipexole, rasagiline, ropinirole, and selegiline. None has demonstrated irrefutable and enduring disease-modifying qualities, although the best available clinical evidence appears most promising for rasagiline.

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of management strategies and quality of care.<sup>7</sup> HRQOL measures are also important in assessing the value of drug therapy, particularly for chronic conditions such as PD, and in determining the appropriate placement of medications on plan formularies.<sup>9,10</sup>

As would be expected for any chronic and progressively worsening disorder, PD has a significant impact on the HRQOL for both patients and their caregivers.<sup>11</sup> In a large Veterans Administration cohort, patients with PD exhibited lower scores on the physical and mental health dimensions of HRQOL compared with patients with 8 other neurologic or chronic conditions, including diabetes, congestive heart failure, angina/coronary heart disease, and stroke.<sup>12</sup> Of note, nonmotor disability, particularly depression, insomnia, and other mental health factors, appear to have a greater negative effect on HRQOL than motor deficits.<sup>8,13-15</sup>

### Etiology and Clinical Course of PD

Aging, in addition to multiple other factors, appears to contribute to the pathoetiology of PD. Approximately 5% to 10% of patients demonstrate a familial pattern of the disease, some of which are associated with linkages to a dozen different gene mutations.<sup>16</sup> Environmental factors likely interact with genetic factors to increase the risk of PD, including herbicide or pesticide exposure.<sup>17-20</sup> Interestingly, epidemiologic studies have consistently associated an inverse correlation between cigarette smoking and coffee consumption for the lifetime development of PD.<sup>21</sup>

The brains of individuals with PD are marked by degeneration and loss of dopaminergic neurons in the substantia nigra.<sup>1</sup> Nondopaminergic pathways are also involved, including cholinergic and norepinephrine neurons in the basal forebrain, serotonin neurons in the midbrain raphe, and other neurons in the brain stem, spinal cord, and peripheral autonomic nervous system. Pathology in many of these neuronal systems likely contributes to the nonmotor manifestations of the disease.<sup>16,22</sup>

More recently, it has been postulated that PD may be a prion disorder given the prion-like behavior of alpha-synuclein protein aggregates. These aggregates comprise a significant portion of the Lewy bodies that are a cellular hallmark of PD.<sup>23</sup>

The clinical course of PD often begins with nonmotor symptoms such as constipation, hyposmia (reduced sense of smell), and rapid eye movement (REM) sleep behavior disorder (RBD). Patients are usually not diagnosed, however, until they exhibit obvious motor symptoms, consisting of resting tremor, rigidity, and/or slowness of movement (bradykinesia).<sup>1,24,25</sup> About one third of patients do not develop

a resting tremor, and this has been reported to be prognostic of a more rapidly progressive disease course.<sup>26</sup> As the disease progresses, patients exhibit disability due to bradykinesia, rigidity, gait and balance difficulty, and falls.<sup>24</sup> Additionally, dopaminergic-related side effects from medications become more problematic. In more advanced stages of the disease, disabling cognitive symptoms, such as dementia, are more common.<sup>24</sup>

Several assessment and rating scales provide clinically important information on changes in PD severity and disability. These include the Unified Parkinson's Disease Rating Scale (UPDRS), which is undergoing revision to better account for nonmotor symptoms, Webster's Columbia University Rating Scale (CURS), Northwestern University Disability Scale (NUDS), and the Hoehn and Yahr scale.<sup>27</sup> A recent analysis correlated disability with the UPDRS and identified specific motor and total scores to assist clinicians in determining clinically meaningful changes in PD progression and response to therapy.<sup>28</sup>

### Implications of Prodromal/Premotor Stage

PD is comprised of motor and nonmotor signs and symptoms. It is recognized that extranigral neuropathologic changes precede the degeneration of nigrostriatal dopaminergic neurons; thus, nonmotor features antedate the onset of motor features. However, diagnostic criteria for PD are validated based on motor features. Premotor clinical features include autonomic dysfunction (impaired olfaction, cardiac sympathetic denervation, urinary disturbances), gastrointestinal disturbances (constipation), neuropsychiatric disorders (depression, mild cognitive impairment, RBD), and sensory disorders (pain, restless legs syndrome). Such symptoms may occur up to 10 years prior to motor symptoms and diagnosis.<sup>29-32</sup> The **Table** describes nonmotor symptoms that may be present in the premotor stage of PD.

There are several stages related to neuronal changes, with earlier stages occurring in areas other than the substantia nigra. As Braak and his coauthors noted: "Were it to become possible to diagnose PD in the presymptomatic stages 1 or 2, and were a causal therapy to become available, the subsequent neuronal loss in the substantia nigra could be entirely prevented."<sup>32,33</sup> By the time patients are diagnosed, however, substantial neuronal damage has already occurred in the substantia nigra, with dopamine levels at least 30% to 40% lower than normal.<sup>16,34</sup>

Greater awareness and recognition of the presence of premotor symptoms of PD have raised the possibility of very early diagnosis (before appearance of motor features). Imaging studies utilizing dopamine transporter tracers and

**Table.** Symptoms in the Premotor Phase of Parkinson’s Disease (PD) and Their Neuropathologic Substrates

Nonmotor Symptoms in PD	Presumed Underlying Brain Structures	Nonmotor Symptoms Well Documented in the Premotor Phase	Corresponding Braak Stage
Olfaction: impairments in odor detection, identification, and discrimination	Olfactory bulb; anterior olfactory nucleus; amygdala; perirhinal cortex	Olfactory impairment	1 Olfactory bulb and anterior olfactory nucleus
Dysautonomia Gastrointestinal disturbances: gastroparesis, constipation Urinary dysfunction: urinary frequency and urgency, nocturia Sexual dysfunction: Men—impaired erection and ejaculation dysfunction; Women—impaired vaginal lubrication, problems in reaching orgasm Orthostatic hypotension	Amygdala; dorsal nucleus of the vagus; intermediolateral column of the spinal cord; sympathetic ganglia; enteric and abdominopelvic autonomic plexuses	Constipation; genitourinary dysfunction Cardiac postganglionic sympathetic denervation	1 Dorsal nucleus of the vagus (sympathetic ganglia; enteric and abdominopelvic autonomic plexi?)
Mood disorders (behavioral/emotional dysfunction): depression, anxiety	Locus coeruleus; raphe nuclei; amygdala; mesolimbic, mesocortical cortex	Depression; anxiety	2-3 Locus coeruleus; raphe nuclei
Sleep disturbances: REM behavior disorder, restless legs syndrome	Dorsal midbrain; nucleus subcoeruleus; pedunculopontine nucleus; pons	REM behavior disorder; restless legs syndrome	2 Nucleus subcoeruleus; pedunculopontine nucleus; dorsal midbrain; pons
Other nonmotor symptoms: pain, apathy, fatigue	Unclear	Unknown	Unclear
Cognitive dysfunction	Frontal and ventral temporal lobe/neocortex; hippocampus; amygdala; nucleus basalis of Meynert; locus coeruleus	? <sup>a</sup>	5-6

REM indicates rapid eye movement.

<sup>a</sup>Cognitive impairment can be considered as a possible premotor manifestation of PD. When severe cognitive impairment (dementia) occurs before motor symptoms, it is regarded, arbitrarily, as the early manifestation of dementia with Lewy bodies and not as a premotor manifestation of PD. Adapted with permission from Tolosa E, et al. *Neurology*. 2009;72(7 suppl):S12-S20.

nigral ultrasound methods demonstrate the potential for use in earlier diagnosis.<sup>34</sup> Given increased knowledge of the premotor phenotype of PD, a battery of tests including assessment of nonmotor features, olfactory testing, cardiac scintigraphy, and neuroimaging may one day provide a means of reliably diagnosing PD at an early stage of the disease. Ideally, then, disease-modifying (neuroprotective) therapies designed to slow or halt disease progression would be initiated. Although disease-modifying therapies may provide a benefit in moderate-to-advanced PD, initiation of therapy in early disease would provide greater benefit.

Such approaches could result in significant direct and indirect cost savings as well as improve patient and caregiver quality-of-life indicators. As noted earlier, the bulk of

direct medical costs occur in the later stages of the disease. Part of that is related to the levodopa-induced dyskinesia that patients develop after several years on the drug. A recent review of studies found that approximately 25% of all patients develop levodopa-related dyskinesia between 2.5 and 3.5 years, and up to 39% between 4 and 6 years.<sup>35</sup> Semiannual direct medical costs were more than double in patients with PD experiencing severe dyskinesia compared with those without motor complications.<sup>36</sup> Levodopa-induced dyskinesia also has a significant negative impact on patient quality-of-life scores and depression severity.<sup>36</sup> In addition, approximately 15% to 20% of patients on dopamine agonists exhibit impulse control disorder behavior (eg, gambling, hypersexuality), imposing a significant economic and quality-of-life burden on patients and their caregivers.<sup>37</sup>

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Numerous pharmacologic medications are available to treat early PD, including amantadine, anticholinergic agents, dopamine agonists, levodopa, and monoamine oxidase type B (MAO-B) inhibitors. Additional detail on early pharmacologic treatment is located in the article by Hauser<sup>38</sup> in this supplement. However, none are routinely used or recommended for treatment in patients with asymptomatic motor PD.<sup>39,40</sup> Instead, treatment is traditionally delayed until patients exhibit functional impairment. This limits exposure to the adverse effects of antiparkinson medications as well as delays the long-term negative effects of levodopa-induced motor complications described earlier.<sup>41</sup>

Given the significant economic burden of PD and knowledge of the premotor phase, there is significant interest in identifying disease-modifying compounds that can be initiated very early in the disease, possibly before any functional motor impairment or disability appears. Not to be dismissed, in patients with moderate-to-advanced stages of PD, therapies that delay the onset of gait and balance impairment and cognitive impairment will also allow patients to function independently for a longer period of time, thus reducing costs and preserving HRQOL.<sup>36</sup> Evidence already shows that initial therapy with nonlevodopa agents is cost-effective, prolongs time to levodopa initiation, and delays the onset of dyskinesia.<sup>42,43</sup>

Numerous targets for neuroprotection have been identified, including oxidative stress, neuroinflammation, protein aggregation and misfolding, excitotoxicity, apoptosis, and loss of trophic factors.<sup>44</sup> Clinical trials to test disease modification, however, have been particularly difficult to design and conduct. Among the challenges are the need to identify and recruit large numbers of untreated patients with early PD; heterogeneity of criteria used to evaluate disease progression; lack of a specific biomarker of disease progression; lack of agreement on the magnitude of effect that should be expected of a disease-modifying agent; and difficulty differentiating between symptomatic and disease-modifying effects of the intervention.<sup>45,46</sup> To overcome this last barrier, researchers have utilized a delayed-start design in which patients are randomized to begin treatment with the study drug or placebo for a certain amount of time, after which the placebo group is switched to the study drug and followed, along with the intervention group, for the remainder of the study. A sustained difference (improvement) in the early-start group after the second phase of the trial suggests that early treatment confers a benefit that would not appear if the drug were introduced later in the disease (delayed start).<sup>47</sup>

### Clinical Trials With Disease-Modifying Agents

To date, at least 23 trials with potential disease-modifying agents have been conducted or are ongoing.<sup>46</sup>

The ADAGIO (Attenuation of Disease Progression with Azilect Given Once-Daily) trial is the largest such study. It was a prospective, multicenter, placebo-controlled, double-blind clinical trial with a delayed-start design developed to assess the efficacy of rasagiline as a disease-modifying compound in 1176 patients with early, nondisabling PD. The ADAGIO trial was initiated based on results from a preliminary trial which suggested that rasagiline given early in the disease might have disease-modifying benefits.<sup>48</sup>

Patients in the ADAGIO trial (mean duration of disease from the time of diagnosis, 4.5 months; baseline mean total UPDRS score, 20.4) who received rasagiline 1 mg/day for 72 weeks (the early-start group) exhibited greater improvement (ie, a smaller mean increase) in the UPDRS score between weeks 12 and 36 than the placebo group (thus reconfirming efficacy relative to placebo), and less worsening overall between baseline and week 72 than the delayed-start, active-treatment group (thus confirming that earlier initiation of rasagiline is associated with better outcomes compared with later initiation).<sup>49</sup>

Not all of the end points were met with a 2-mg/day dose of rasagiline.<sup>49</sup> However, a post hoc subgroup analysis showed that patients with the highest quartile baseline UPDRS scores (>25.5) who received rasagiline 2 mg/day did meet all primary end points. Among patients given rasagiline 1 and 2 mg/day, those in the early-start (active treatment) groups had significantly less worsening of UPDRS scores between baseline and week 72 (−3.40 points and −3.63 points, respectively) compared with the delayed-start (active treatment) groups ( $P = .04$  for both). Patients with the highest quartile baseline UPDRS scores given rasagiline 1 mg/day and 2 mg/day also demonstrated significantly greater improvement of scores from baseline to week 36 (−6.43 points and −7.13 points, respectively;  $P < .001$  vs placebo); these were clinically important differences.<sup>28</sup> Of note, in clinical practice, the majority of patients with early PD who seek medical attention for their symptoms would fall into this upper quartile subgroup. Additionally, the UPDRS score in this subgroup is representative of that in other clinical trials involving early PD patients. There were no significant differences in adverse events between the 2 groups. Additional detail and discussion of the ADAGIO trial appear in the article by Hauser<sup>38</sup> in this supplement.

A later analysis of the trial data demonstrated that rasagiline also reduced the progression of nonmotor symptoms (eg, altered mood, apathy, cognitive impairment, sleepiness, pain, fatigue, urinary problems) as assessed with the Movement Disorder Society (MDS)-UPDRS.<sup>50</sup> The efficacy and safety results of ADAGIO have spurred a growing number of clinical

cians to consider beginning rasagiline treatment in functionally unimpaired patients (ie, not yet requiring levodopa or dopamine agonists).

The outcomes associated with rasagiline should not be considered a class effect of MAO-B inhibitors. Specifically, the results of ADAGIO cannot necessarily be extrapolated to selegiline, another available MAO-B inhibitor. Selegiline is metabolized to the amphetamine derivatives L-methamphetamine and L-amphetamine,<sup>51</sup> which are present in sufficient concentrations to produce side effects in patients with PD. Additionally, chronic exposure to these compounds has been shown to induce neurotoxicity in animal and laboratory studies,<sup>52,53</sup> and studies demonstrate that L-methamphetamine inhibits the potential neuroprotective activities of selegiline.<sup>54</sup> Rasagiline, on the other hand, is devoid of amphetamine-derived or neurotoxic metabolites. Thus, the pharmacologic differences between rasagiline and selegiline preclude any meaningful comparisons of clinical efficacy or safety.

Selegiline was evaluated as a possible disease-modifying agent in DATATOP (Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism), a large trial designed to assess the ability of early intervention with selegiline or tocopherol to postpone levodopa initiation in 800 patients. While tocopherol showed no benefit, patients receiving selegiline as monotherapy were able to significantly delay the need for levodopa therapy compared with the group receiving placebo and demonstrated a significant reduction in disease progression as measured by the UPDRS ( $P < .001$  vs placebo).<sup>55</sup> However, upon completion of the study, a subset of patients given placebo were initiated on open-label selegiline (ie, received delayed-start selegiline), and UPDRS outcome scores in this group were no different than in the original selegiline monotherapy group. Thus, the benefits appear to be largely related to the symptomatic effects of the drug rather than to disease-modifying effects.<sup>56</sup>

A trial from the Swedish Parkinson Study Group also demonstrated a delay of levodopa initiation with selegiline.<sup>57</sup> In the second phase of this study ( $n = 140$ ), patients who received long-term selegiline therapy in combination with levodopa for 5 years had significantly better UPDRS outcomes compared with patients who received only levodopa.<sup>43</sup> Additional detail and discussion of the clinical trials with selegiline appear in the article by Hauser<sup>38</sup> in this supplement.

Other compounds that have undergone clinical testing for disease modification in PD or are still being evaluated include levodopa and the dopamine agonists pramipexole and ropinirole. In the ELLDOPA (Earlier versus Later Levodopa

Therapy in Parkinson Disease) trial, levodopa (150, 300, and 600 mg/day) was significantly better than placebo in reducing the worsening of Parkinson's symptoms at week 42 ( $P < .001$ ).<sup>58</sup> However, patients in the levodopa group had significantly more adverse events (including dyskinesias) than those in the placebo group. Results from the ELLDOPA trial are described in detail in the article by Hauser<sup>38</sup> in this supplement.

The REAL-PET (Requip as Early Therapy versus L-dopa-PET) trial used F-dopa positron emission tomography (PET) as a biomarker of neuronal degeneration to evaluate the effects of ropinirole versus carbidopa/levodopa on disease progression.<sup>59</sup> After 2 years, the ropinirole group demonstrated significantly greater preservation in biomarker uptake in the putamen and substantia nigra than the levodopa group ( $P = .022$ ). However, in contrast with the biomarker results, the clinical benefit in the levodopa group was significantly better as assessed by the UPDRS.

Pramipexole was evaluated in the PROUD (Pramipexole on Underlying Disease) trial, a placebo-controlled, delayed-start study designed to evaluate the potential disease-modifying effect of pramipexole 1.5 mg/day. Preliminary results reported as an abstract reported no significant difference in UPDRS scores at final study visit (after 15 months) between the early- and delayed-start pramipexole groups ( $P = .65$ ) and no difference in loss of striatal dopaminergic neurons ( $P = .84$ ).<sup>60</sup>

Several compounds have been tested in futility trials and warrant additional investigation, including coenzyme Q10 and creatine.<sup>61,62</sup> Coenzyme Q10 is currently being evaluated as a potential disease-modifying agent in an ongoing 16-month clinical study known as QE3.<sup>63</sup> Creatine is also currently being evaluated as a potential disease-modifying agent in a large ongoing 5-year clinical trial (known as LS-1) sponsored by the National Institute of Neurological Disorders and Stroke as part of the NET-PD (NIH Exploratory Trials in Parkinson's Disease) initiative.<sup>64,65</sup>

## Conclusion

The progressive, debilitating nature of PD results in significant direct and indirect medical costs for providers, patients and their families, and society as a whole. Such costs will only grow more extensive as the population ages and the prevalence of the disease increases. An increasing awareness of the presence of a premotor phase of the disease, in which early signs of PD may be present as much as a decade before the classic tremor and other movement-related symptoms, gives new urgency toward the identification of prospective agents that may be disease modifying. Several agents have been tested or are being tested as disease-modifying agents in

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PD, including coenzyme Q10, creatine, levodopa, pramipexole, rasagiline, ropinirole, and selegiline. None of these drugs have demonstrated long-lasting disease-modifying effects; however, the best available evidence suggests that rasagiline holds promise in the treatment of early PD.

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## REFERENCES

1. Olanow CW, Stern MB, Sethi K. The scientific and clinical basis for the treatment of Parkinson disease. *Neurology*. 2009;72(21 suppl 4):S1-S136.
2. de Lau LM, Breteler MM. Epidemiology of Parkinson's disease. *Lancet Neurol*. 2006;5(6):525-535.
3. Lapane KL, Fernandez HH, Friedman JH. Prevalence, clinical characteristics, and pharmacologic treatment of Parkinson's disease in residents in long-term care facilities. SAGE Study Group. *Pharmacotherapy*. 1999;19(11):1321-1327.
4. Dorsey ER, Constantinescu R, Thompson JP, et al. Projected number of people with Parkinson disease in the most populous nations, 2005 through 2030. *Neurology*. 2007;68(5):384-386.
5. O'Brien JA, Ward A, Michels SL, Tziveleakis S, Brandt NJ. Economic burden associated with Parkinson disease. *Drug Benefit Trends*. 2009;21(6):179-190.
6. Huse DM, Schulman K, Orsini L, Castelli-Haley J, Kennedy S, Lenhart G. Burden of illness in Parkinson's disease. *Mov Disord*. 2005;20(11):1449-1454.
7. Centers for Disease Control and Prevention. *Measuring Healthy Days: Population Assessment of Health-Related Quality of Life*. Atlanta, GA: CDC; November 2000.
8. Karlsen KH, Tandberg E, Arsland D, Larsen JP. Health related quality of life in Parkinson's disease: a prospective longitudinal study. *J Neurol Neurosurg Psychiatry*. 2000;69(5):584-589.
9. Badia X, Herdman M. The importance of health-related quality-of-life data in determining the value of drug therapy. *Clin Ther*. 2001;23(1):168-175.
10. Wu WK, Sause RB, Zacker C. Use of health-related quality of life information in managed care formulary decision-making. *Res Social Admin Pharm*. 2005;1:579-598.
11. Martinez-Martin P, Arroyo S, Rojo-Abuin JM, Rodriguez-Blazquez C, Frades B, de Pedro Cuesta J; Longitudinal Parkinson's Disease Patient Study Group. Burden, perceived health status, and mood among caregivers of Parkinson's disease patients. *Mov Disord*. 2008;23(12):1673-1680.
12. Gage H, Hendricks A, Zhang S, Kazis L. The relative health related quality of life of veterans with Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 2003;74(2):163-169.
13. Chrischilles EA, Rubenstein LM, Voelker MD, Wallace RB, Rodnitzky RL. The health burdens of Parkinson's disease. *Mov Disord*. 1998;13(3):406-413.
14. Global Parkinson's Disease Survey Steering Committee. Factors impacting on quality of life in Parkinson's disease: results from an international survey. *Mov Disord*. 2002;17(1):60-67.
15. Ravina B, Camicioli R, Como PG, et al. The impact of depressive symptoms in early Parkinson disease. *Neurology*. 2007;69(4):342-347.
16. Schapira AH. Etiology and pathogenesis of Parkinson disease. *Neurol Clin*. 2009;27(3):583-603, v.
17. Semchuk KM, Love EJ, Lee RG. Parkinson's disease and exposure to agricultural work and pesticide chemicals. *Neurology*. 1992;42(7):1328-1335.
18. Barbeau A, Roy M, Bernier G, Campanella G, Paris S. Ecogenetics of Parkinson's disease: prevalence and environmental aspects in rural areas. *Can J Neurol Sci*. 1987;14(1):36-41.
19. Di Monte DA. The environment and Parkinson's disease: is the nigrostriatal system preferentially targeted by neurotoxins? *Lancet Neurol*. 2003;2:531-538.
20. Logroscino G. The role of early life environmental risk factors in Parkinson disease: what is the evidence? *Environ Health Perspect*. 2005;113(9):1234-1238.
21. Hernan MA, Takkouche B, Caamano-Isorno F, Gestal-Otero JJ. A meta-analysis of coffee drinking, cigarette smoking, and the risk of Parkinson's disease. *Ann Neurol*. 2002;52(3):276-284.
22. Forno LS. Neuropathology of Parkinson's disease. *J Neuropathol Exp Neurol*. 1996; 55(3):259-272.
23. Olanow CW, Prusiner SB. Is Parkinson's disease a prion disorder? *Proc Natl Acad Sci U S A*. 2009;106(31):12571-12572.
24. Fauci AS, Braunwald E, Kasper DL, et al. Parkinson's Disease and Other Extrapyrmidal Movement Disorders. In: *Harrison's Principles of Internal Medicine*. 17th ed. New York, NY: McGraw-Hill; 2008.
25. Gelb DJ, Oliver E, Gilman S. Diagnostic criteria for Parkinson disease. *Arch Neurol*. 1999;56:33-39.
26. Jankovic J. Parkinson's disease: clinical features and diagnosis. *J Neurol Neurosurg Psychiatry*. 2008;79(4):368-376.
27. Ramaker C, Marinus J, Stiggelbout AM, Van Hilten BJ. Systematic evaluation of rating scales for impairment and disability in Parkinson's disease. *Mov Disord*. 2002;17(5):867-876.
28. Shulman LM, Gruber-Baldini AL, Anderson KE, Fishman PS, Reich SG, Weiner WJ. The clinically important difference on the unified Parkinson's disease rating scale. *Arch Neurol*. 2010;67(1):64-70.
29. Tolosa E, Gaig C, Santamaria J, Compta Y. Diagnosis and the premotor phase of Parkinson disease. *Neurology*. 2009;72(7 suppl):S12-S20.
30. Fearnley JM, Lees AJ. Aging and Parkinson's disease: substantia nigra regional selectivity. *Brain*. 1991;114(5):2283-2301.
31. Morrish PK, Rakshi JS, Bailey DL, Sawle DV, Brooks DJ. Measuring the rate of progression and estimating the preclinical period of Parkinson's disease with [18F]dopa PET. *J Neurol Neurosurg Psychiatry*. 1998;64(3):314-319.
32. Braak HK, Del Tredici K, Rub U, de Vos RA, Jansen Steur EN, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol Aging*. 2003;24(2):197-211.
33. Braak H, Ghebremedhin E, Rüb U, Bratzke H, Del Tredici K. Stages in the development of Parkinson's disease-related pathology. *Cell Tissue Res*. 2004;318(1):121-134.
34. Marek K, Jennings D. Can we image premotor Parkinson disease? *Neurology*. 2009;72(7 suppl):S21-S26.
35. Ahlskog JE, Muenter MD. Frequency of levodopa-related dyskinesias and motor fluctuations as estimated from the cumulative literature. *Mov Disord*. 2001;16(3):448-458.
36. Pechevis M, Clarke CE, Vieregge P, et al. Effects of dyskinesias in Parkinson's disease on quality of life and health-related costs: a prospective European study. *Eur J Neurol*. 2005;12(12):956-963.
37. Bostwick JM, Hecksel KA, Stevens SR, Bower JH, Ahlskog JE. Frequency of new-onset pathologic compulsive gambling or

- hypersexuality after drug treatment of idiopathic Parkinson disease. *Mayo Clin Proc.* 2009;84(4):310-316.
38. **Hauser RA.** Early pharmacologic treatment in Parkinson's disease. *Am J Manag Care.* 2010;16(suppl):S100-S107.
39. **Eggert KM, Reese JP, Oertel WH, Dodel R.** Cost effectiveness of pharmacotherapies in early Parkinson's disease. *CNS Drugs.* 2008;22(10):841-860.
40. **Miyasaki JM, Martin W, Suchowersky O, Weiner WJ, Lang AE.** Practice parameter: initiation of treatment for Parkinson's disease: An evidence-based review: report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology.* 2002;58(1):11-17.
41. **Horstink M, Tolosa E, Bonucelli U, et al.** Review of the therapeutic management of Parkinson's disease. Report of a joint task force of the European Federation of Neurological Societies and the Movement Disorder Society; European Section. Part I: early (uncomplicated) Parkinson's disease. *Eur J Neurol.* 2006;13(11):1170-1185.
42. **Haycox A, Armand C, Murteira S, Cochran J, Francois C.** Cost effectiveness of rasagiline and pramipexole as treatment strategies in early Parkinson's disease in the UK setting: an economic Markov model evaluation. *Drugs Aging.* 2009;26(9):791-801.
43. **Pålhagen S, Heinonen E, Hagglund J, Kaugesaar T, Maki-Ikola O, Palm R; Swedish Parkinson Study Group.** Selegiline slows the progression of the symptoms of Parkinson disease. *Neurology.* 2006;66(8):1200-1206.
44. **Yacoubian TA, Standaert DG.** Targets for neuroprotection in Parkinson's disease. *Biochim Biophys Acta.* 2009;1792(7):676-687.
45. **Clarke CE.** A "cure" for Parkinson's disease: can neuroprotection be proven with current trial designs? *Mov Disord.* 2004;19(5):491-498.
46. **Hart RG, Pearce LA, Ravina BM, Yalthro TC, Marler JR.** Neuroprotection trials in Parkinson's disease: systematic review. *Mov Disord.* 2009;24(5):647-654.
47. **Olanow CW, Hauser RA, Jankovic J, et al.** A randomized, double-blind, placebo-controlled, delayed start study to assess rasagiline as a disease modifying therapy in Parkinson's disease (the ADAGIO study): rationale, design, and baseline characteristics. *Mov Disord.* 2008;23(15):2194-2201.
48. **Parkinson Study Group.** A controlled, randomized, delayed-start study of rasagiline in early Parkinson disease. *Arch Neurol.* 2004;61(4):561-566.
49. **Olanow CW, Rascol O, Hauser R, et al; ADAGIO Study Investigators.** A double-blind, delayed-start trial of rasagiline in Parkinson's disease. *N Engl J Med.* 2009;361(13):1268-1278.
50. **Poewe W, Hauser R.** Rasagiline 1 mg/day provides benefits in the progression of non-motor symptoms in patients with early Parkinson's disease. Presented at: American Academy of Neurology 61st Annual Meeting; April 25-May 2, 2009; Seattle, WA.
51. **Mahmood I.** Clinical pharmacokinetics and pharmacodynamics of selegiline: an update. *Clin Pharmacokinet.* 1997;33(2):91-102.
52. **Yasar S, Goldberg JP, Goldberg SR.** Are metabolites of l-deprenyl (selegiline) useful or harmful? Indications from preclinical research. *J Neural Transm Suppl.* 1996;48:61-73.
53. **Abu-Raya S, Tabakman R, Blaugrund E, Trembovler V, Lazarovici P.** Neuroprotective and neurotoxic effects of monoamine oxidase-B inhibitors and derived metabolites under ischemia in PC12 cells. *Eur J Pharmacol.* 2002;434(3):109-116.
54. **Bar Am O, Amit T, Youdim MB.** Contrasting neuroprotective and neurotoxic actions of respective metabolites of anti-Parkinson drugs rasagiline and selegiline. *Neurosci Lett.* 2004;355(3):169-172.
55. **Parkinson Study Group.** Effects of tocopherol and deprenyl on the progression of disability in early Parkinson's disease. The Parkinson Study Group. *N Engl J Med.* 1993;328(3):176-183.
56. **Parkinson Study Group.** Impact of deprenyl and tocopherol treatment on Parkinson's disease in DATATOP subjects not requiring levodopa. Parkinson Study Group. *Ann Neurol.* 1996;39(1):29-36.
57. **Pålhagen S, Heinonen EH, Hagglund J.** Selegiline delays the onset of disability in de novo parkinsonian patients. Swedish Parkinson Study Group. *Neurology.* 1998;51(2):520-525.
58. **Fahn S, Oakes D, Shoulson I, et al; Parkinson Study Group.** Levodopa and the progression of Parkinson's disease. *N Engl J Med.* 2004;351(24):2498-2508.
59. **Whone AL, Watts RL, Stoessl AJ, et al; REAL-PET Study Group.** Slower progression of Parkinson's disease with ropinirole versus levodopa: the REAL-PET study. *Ann Neurol.* 2003;54(1):93-101.
60. **Schapira A, Albrecht S, Barone P, et al; on behalf of the PROUD Study Group.** Immediate vs. delayed-start pramipexole in early Parkinson's disease: the PROUD study. *Parkinsonism Relat Disord.* 2009;15(suppl 2):S81.
61. **NINDS NET-PD Investigators.** A randomized, double-blind, futility clinical trial of creatine and minocycline in early Parkinson disease. *Neurology.* 2006;66(5):664-671.
62. **NINDS NET-PD Investigators.** A randomized clinical trial of coenzyme Q10 and GPI-1485 in early Parkinson disease. *Neurology.* 2007;68(1):20-28.
63. **Clinicaltrials.gov.** Effects of coenzyme Q10 (CoQ) in Parkinson disease (QE3). <http://clinicaltrials.gov/ct2/show/NCT00740714?term=qe3&rank=1>. Accessed March 10, 2010.
64. **National Institute of Neurological Disorders and Stroke.** Parkinson's study. <http://parkinsontrial.ninds.nih.gov/>. Accessed February 23, 2010.
65. **Clinicaltrials.gov.** NET-PD LS-1 Creatine in Parkinson's disease. <http://clinicaltrials.gov/ct2/show/NCT00449865?term=creatine+parkinson+disease&rank=1>. Accessed March 10, 2010.