Annals of African Medicine Vol. 9, No. 2; 2010:55-61
DOI: 10.4103/1596-3519.64743

Review Article

Current management of Parkinson's disease

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Abstract

Although Parkinson's disease (PD) is still incurable, a large number of different treatments have become available to improve the quality of life and physical and psychological morbidity, and its early treatment is of prime importance. This article reviews the current situation of PD. This review was based on a search of Medline, the Cochrane Database of Systemic Reviews, and citation lists of relevant publications. The subject headings and keywords used were Parkinson's disease and therapeutic advances. Only articles written in English were included.The management of PD has evolved rapidly over the last 10 years with the advent of new drugs and new classes of drugs, but the currently available treatment methods are all symptomatic ones. However, some of these may have marginal disease-modifying effects. Progress in manufacture of newer drugs has markedly improved the treatment of early PD; however, the management of advanced Parkinson's symptoms remains a challenge. Currently no treatment has been proven to slow the progression of PD. Although symptomatic therapy can provide benefit for many years, PD will eventually result in significant morbidity.

Keywords: Anti-Parkinson agents, management, movement disorder, neuroprotection, new drugs, Parkinson's disease, symptom progression, treatment

Résumé

Maladie de Parkinson bien (PD) est encore incurable, un grand nombre de traitements différents est devenus disponible pour améliorer la qualité de vie et de la morbidité physique et psychologique, et son traitement précoce est de première importance. Cet article passe en revue la situation actuelle de PD. Cette révision était fondée sur une recherche de Medline, la base de données de Cochrane d'avis systémique, et citation des listes de publications pertinentes. Les descripteurs et les mots-clés utilisés étaient la maladie de Parkinson et les progrès thérapeutiques. Seulement les articles rédigés en anglais ont été incluses. Gestion du PD a évolué rapidement les 10 dernières années avec l'arrivée de nouveaux médicaments et de nouvelles classes de médicaments, mais les méthodes de traitement actuellement disponibles sont tous symptomatiques. Cependant, certains d'entre eux peuvent avoir maladie marginal, modifier les effets. Progrès dans la fabrication de nouveaux médicaments a nettement amélioré le traitement précoce PD; toutefois, la gestion des symptômes de la maladie de Parkinson avancée reste un défi. Actuellement, aucun traitement n'a été prouvé à ralentir la progression du PD. Bien que le traitement symptomatique peut fournir des prestations pendant de nombreuses années, PD aboutira finalement à morbidité significative.

Mots clés: la maladie de Parkinson, de gestion, de nouveaux médicaments, de progression symptôme

Introduction

Parkinson's disease (PD) is a neurodegenerative disorder associated with loss of dopamine-producing neurons in the substantia nigra pars compacta.[1] James Parkinson first described the disease in 1817,[2] and his description remains remarkably accurate. It is characterized clinically by rest tremor, cogwheel rigidity (stiffness), bradykinesia (slowness) and postural instability (impaired balance); and pathologically by neuronal loss and Lewy body formation in the substantia

nigra. Furthermore, similar changes are seen in the peripheral postganglionic sympathetic nerve fibers, olfactory bulb, the dorsal motor nucleus of the vagal nerve, raphe nucleus, locus coeruleus, pedunculopontine nucleus, nucleus basalis of Meynert, amygdaloid nucleus and cortical neurons.[3] Neurodegeneration of these nuclei is responsible for nonmotor symptoms and an L-dopa–resistant symptom of PD.[3] PD occurs worldwide, but little is known about the epidemiol ogy and genetic studies of the disease in Africa.[4] The prevalence of PD in Africa suggests some intracontinental geographical variation, and overall the prevalence figures and incidence rates of PD in Africa appear lower than those reported for European and North American populations.[4]

Early treatment for PD was disappointing and consisted of anticholinergic medications to reduce tremor.[5] The 20th century witnessed unheralded advancements in medical and surgical treatments for PD, foremost of which was the discovery that the dopamine precursor, levodopa, substantially improves motor symptoms.[6] Today there are many options for the treatment of PD. This article will focus on drug therapy in PD.

When to Commence Therapy

The initial question in the management of idiopathic PD is whether any pharmacotherapy is indicated. To decide upon the timing when to start drug treatment in PD, particularly in the very early stages of the illness, when there may be little functional deficit, can be difficult. There is no conclusive evidence that treatment is helpful before symptoms start to affect the patient's life, although some neurologists believe that deprenyl, also known as selegiline, could be helpful.[7] Usually drug therapy is started when the disability of the patient reaches a certain level because the currently available anti-Parkinson drugs are considered to have only symptom-alleviating effects on Parkinsonism. Once functional deficits begin to interfere with the patient's work or social activities, treating symptoms becomes appropriate. Initiating treatment in a patient with PD requires consideration of age, degree of disease activity and consequences of long-term treatment.

Therapeutic options

There are multiple possible initial pharmacologic choices for the initial treatment of PD, including monoamine oxidase type B inhibitors, dopamine agonists and levodopa/ carbidopa.[8] However, no treatment has yet been proven to affect disease progression, and the development of medications that can slow the disease process and thereby forestall disability remains a critical research goal. The pharmacologic options for patients with early disease include several agents known or presumed to improve the striatum's surviving dopaminergic activity.

One of these is selegiline. This drug inhibits monoamine oxidase B (MAO-B), a brain enzyme that would otherwise metabolize dopamine. Inhibition of MAO-B reduces formation of hydrogen peroxide, presumably reducing intraneuronal oxidative stress. Based on this, a neuroprotective effect has been hypothesized.

Another option is amantadine, an antiviral medication that provides mild benefit in treating PD signs and symptoms.[9] While amantadine's mechanism of action is not completely understood, it is thought to cause release of dopamine, delay its neuronal uptake and antagonize another neurotransmitter, glutamine.[10] It should be used cautiously in elderly patients and in those with dementia, as it can cause or worsen hallucinations. Edema of the legs has been troublesome in some patients. However, it is effective in combination with L-dopa and may reduce the dyskinesias and motor fluctuations associated with advanced disease.[10]

Anticholinergic agents are in fact the oldest class of drugs used in PD and are still given occasionally, either in conjunction with L-dopa or to patients who cannot tolerate the latter drug. Several synthetic preparations are available, the most widely used being trihexyphenidyl (Artane) and benztropine mesylate (Cogentin).[5] As a group, they are effective in reducing tremor in some patients but have little effect on bradykinesia and rigidity. In order to obtain maximum benefit from the use of these drugs, they should be given in gradually increasing dosage to the point where toxic effects appear: dryness of the mouth (which can be beneficial when drooling of saliva is a problem), blurring of vision from pupillary mydriasis, constipation and sometimes urinary retention. These drugs must be used with caution in older adults and in patients with glaucoma.

Because of the marked dopamine depletion in the brains of individuals with PD symptomatic treatments have revolved largely around correcting this deficit. Three main approaches are effective to varying degrees in this regard: using the 1) dopamine precursor levodopa (L-dopa), 2) drugs that directly stimulate dopamine receptors bypassing the presynaptic dopamine neurons and 3) drugs

that block the metabolism of dopamine.[11] Of these, L-dopa continues to be the most efficacious and is considered the 'gold standard' treatment, which almost all patients with PD require at some point in the course of their disease and generally for life thereafter. L-dopa is routinely combined with a peripheral dopa decarboxylase inhibitor, such as benserazide or carbidopa, which minimizes the gastrointestinal and cardiovascular side effects of dopamine.[11] The co-administration of the dopa decarboxylase inhibitor modestly increases the plasma half-life of L-dopa and doubles its bioavailability, allowing more of the amino acid to access the brain and exert its intended therapeutic action.[12] Several dopamine agonists have been developed, including apomorphine, piribedil, bromocriptine, lisuride, pergolide, pramipexole, ropinirole and cabergoline. A common feature is that their efficacy is inferior to L-dopa, with the exception of apomorphine, which has its own limitations related to administration route and adverse effects.[13,14] The third approach of inhibiting dopamine metabolism is by blocking catechol-O-methyl transferase (COMT) with entacapone or tolcapone or by blocking monoamine oxidase B (MAO-B) with selegiline or rasagiline. These enzyme inhibitors enhance and prolong the effects of co-administered L-dopa. In addition, MAO-B inhibitors as monotherapy have some anti-parkinsonian efficacy.[15,16]

Do We have Neuroprotective Drugs for Parkinson's Disease?

Several drugs were tested for disease-modifying effects in PD, and many others are being tested in animal experiments and in clinical trials. How far have we gone? We will review the results on dopamine agonists, L-dopa, MAO-B inhibitors, coenzyme Q_{10} (CoQ_{10}), creatine and minocycline.

Dopamine agonists

Following a period of stable response to dopaminergic medication, PD patients gradually develop two progressive clinical phenomena requiring changes in the clinical management: motor fluctuations and dyskinesia.[17] Studies have shown that dyskinesias clearly have an adverse impact on the patient's quality of life.[18] The motor complications that occur with levodopa administration prompted the development of alternative medications, including the dopamine agonists (DAs). A change of handwriting with micrographia is often an early feature of PD as is reduced facial expression. A loss of arm swing on one side is also an early and useful diagnostic criterion.[19] A reduced sense of smell is however worth asking about since this may be one of the first symptoms in early PD.[20] DAs are effective as monotherapy in early PD to improve motor symptoms and as adjuncts to levodopa in patients with motor fluctuations to reduce off time. The off time also a common and troublesome effect of chronic use of L-dopa, refers to an unpredictable change in the patient, with periods of return of PD symptoms when medication effect wears off.[21] Multiple clinical trials have demonstrated that initial treatment with a DA to which levodopa can be added causes fewer motor fluctuations and dyskinesia than treatment with levodopa alone.[22,23] This benefit may be due primarily to delay in the need for levodopa.[22] Dopamine transporter single-photon–emission computerized tomography (SPECT) and fluorodopa photon emission tomography (PET), respectively, tested pramipexole (Mirapex), a nonergot D2/D3 synthetic aminobenzothiazide derivative; and ropinirole (Requip), a nonergot DA with strong affinity for D2 receptors. A study of 301 patients in early stages of PD, followed in a double-blind fashion for a mean of 2 years, after randomization to pramipexole or levodopa (CALM-PD), found marked reduction in the risk of motor complications in the pramipexole group.[24,25] Furthermore, striatal uptake shows that the rate of loss of dopamine transporters, as measured by sequential (^{123} I) beta-CIT (2-beta-carbomethoxy-3-beta-(4-iodophenyl) tropane) SPECT, declined by 16% in the pramipexole-treated patients compared with 25.5% in L-dopa–treated patients at 46 months from baseline ($P = 0.01$).[26]

The use of ropinirole controlled the symptoms of PD satisfactorily, and in addition reduced the incidence of dyskinesia, compared to treatment with levodopa. A 5-year study that randomized 268 patients with early PD to either ropinirole ($n = 179$) or levodopa ($n = 89$) to which levodopa could be added when necessary found only 20% of patients assigned to ropinirole developed dyskinesia, compared with 46% of those assigned to levodopa.[22] Putaminal fluorodopa uptake, measured by PET, declined by 13% in the ropinirole-treated patients, compared with 20% in the L-dopa–treated patients ($P = 0.022$). The authors concluded that ropinirole as initial therapy slowed nigral degeneration by 30% compared with L-dopa. Another study found that the addition of pramipexole to levodopa in patients with motor fluctuations reduced off time by 17% compared with placebo.[27]

These results can be interpreted as slowing neurodegeneration of nigral neurons in the dopamine agonist–treated patients.[28] However, other interpretations are also possible. First, higher dopamine content in the dopamine uptake sites in

L-dopa-treated patients compared with the agonist-treated groups might have had a pharmacodynamic effect in terms of decreasing the number of dopamine uptake sites. The second possibility is that neurons with decreased dopamine uptake sites are still living cells not reflecting neuronal death. Therefore, the evidence does not seem sufficient to conclude that dopamine agonists are neuroprotective.[28]

The usual maximum dose of pramipexole is 4.5 mg/d in three divided doses. It is started at a dosage of 0.125 mg tds for a week and then titrated to 0.5 mg tds. Recent reports indicate that pathological gambling may be associated with DAs, especially pramipexole, usually at higher doses. In one review, the incidence of pathological gambling was 1.5% in patients taking pramipexole (mean dosage, 4.3 mg/d; range, 2 to 8 mg/d), compared with an overall incidence of 0.05% in patients with PD regardless of therapy.[29] Excessive shopping and hypersexuality are other forms of impulse-control disorders that may occur with DA use. Patients should be warned about these behaviors when DAs are prescribed, and DA dosages need to be reduced if these problems emerge. The recommended initial dosage for ropinirole is 0.25 mg three times daily (total 0.75 mg/d). Pergolide (Permax), an ergot with strong affinity for D2 receptors, is effective in reducing motor symptoms in PD. Several studies have shown that the use of pergolide permits a significant reduction in levodopa dosage when it is used as adjunct therapy in patients with motor fluctuations compared with placebo.[30] Pergolide is usually initiated at a dose of 0.05 mg for the first two days and increased by 0.1 mg/d or 0.15 mg/d everyday over the next 12 days. Studies have identified an increased frequency of valvular heart disease in patients taking pergolide. This appears to be a potential side effect of all ergot agonists, and the mechanism is believed to be activation of 5-hydroxytrptamine 2B (5-HT_{2B}) receptors.[31]

Levodopa

Levodopa remains the most effective medication to improve motor features of PD with the fewest short-term side effects. It effectively ameliorates bradykinesia and rigidity but is variably effective for tremor.[32] By combining a decarboxylase inhibitor (carbidopa or benserazide), which is unable to penetrate the central nervous system, with levodopa, the decarboxylation of levodopa to dopamine is greatly diminished in peripheral tissue. This permits a greater proportion of levodopa to reach nigral neurons and at the same time, a reduction in the peripheral side effects of levodopa and dopamine (nausea, hypotension etc). The Parkinson Study Group[33] compared the effect of L-dopa versus placebo on disease progression. Early-stage PD patients were divided into 4 groups: those who received L-dopa/carbidopa 150, 300 or 600 mg/d and placebo groups. Patients were treated for 40 weeks and medication was discontinued for 2 weeks. Outcome measures were Unified Parkinson Disease Rating Scale (UPDRS) score and the beta-CIT SPECT.[32] The UPDRS has long been the major rating scale that is used to assess severity of symptoms of PD. The original version of the scale assessed daily activities, motor skills and mental capacity (including behavior and mood). The higher the UPDRS score, the greater is the disability due to PD. All of the L-dopa groups showed significant improvement of the UPDRS scores compared with the placebo group. After the 2-week drug washout period, UPDRS scores in all L-dopa groups returned to near-baseline levels; on the other hand, UPDRS scores were significantly worse than baseline levels in the placebo group. UPDRS score after drug washout was best in the L-dopa 600 mg group. These results suggest that L-dopa has a disease-modifying effect in PD; the disease-modifying effect may be due to neuroprotection of the substantia nigra or neuroplasticity effect on neuronal networks. Whatever the mechanism, early use of L-dopa appears to be good for PD patients, as evaluated by UPDRS. On the other hand, however, beta-CIT showed opposing results: a decline in the decrease of beta-CIT uptake was largest in the group treated with L-dopa 600 mg. Guttman *et al*.[24] reported reduced uptake of beta-CIT in early-stage PD patients treated with L-dopa. However, other studies showed no effect of L-dopa treatment on striatal beta-CIT uptake and fluorodopa PET scan.[26,34,35] Another possibility entertained was that low dopamine in the placebo group up-regulated dopamine transporter activity, resulting in a smaller decline in beta-CIT uptake. The answer to the question as to whether L-dopa has disease-modifying effects must await further studies.

Entacapone

The idea of using catechol-*O*-methyltransferase (COMT) inhibitor was proposed in the 1950s, but no effective and safe substances were available at that time.[36,37] The idea to use COMT inhibition re-emerged in the early 1980s. Double-blind, placebo-controlled trials have demonstrated that entacapone increases "on" time, decreases "off" time and improves motor scores for patients with PD who experience motor fluctuation.[38] Entacapone (Comtan) is a selective, reversible peripherally acting COMT inhibitor that is used in conjunction with carbidopa/ levodopa to extend the levodopa half-life and allow more levodopa to be delivered to the brain over a longer time. The addition of

entacapone reduced "off" time in patients with motor fluctuations on controlled release carbidopa/levodopa.[39] Stalevo is a combination of carbidopa, levodopa and entacapone and is available as Stalevo 50, 100 and 150.[40]

Monoamine Oxidase Type B Inhibitors

The deprenyl and tocopherol antioxidative therapy of Parkinsonism (DATATOP) study initially suggested disease-modifying effects of selegiline.[41,42] However, further analysis revealed that this was accounted for by the symptomatic effect of selegiline.[43,44] Palhagen *et al.*[45] looked at the question of the disease-modifying effects of long-term selegiline administration versus placebo therapy in early-stage *de novo* PD patients. Patients initially assigned to selegiline showed less progression as evaluated by total UPDRS score at 4 years and tended to delay wearing off compared with placebo (34% versus 20%), but there was no difference between the two groups in the time taken to develop dyskinesia. Thus, these researchers postulated that selegiline might have a delaying effect on the progression of PD. The study conducted by Olanow *et al.*[46] also suggested a disease-modifying effect of selegiline. Rasagiline (Azilect) is a new irreversible MAO-B inhibitor with anti-apoptotic and antioxidative properties. Its effect on disease progression in PD was tested in a unique way. The Parkinson Study Group[47] investigated rasagiline in early-stage drug-naïve PD patients in a delayed-start study design. Patients were allotted to three groups receiving rasagiline 1 or 2 mg/d or placebo, respectively. After 6 months, patients in the three groups were re-randomized to receive rasagiline at either 1 or 2 mg/d; thus after 6 months, all patients enrolled received rasagiline. It was hypothesized that if the effects of rasagiline were purely symptomatic, then the placebo group that received rasagiline afterwards would catch up with the initially assigned rasagiline groups. As a result, the UPDRS scores of the initial placebo and initial rasagiline groups became parallel. This was interpreted as indicative of the disease-modifying effect of rasagiline.

Coenzyme Q_{10}

Coenzyme Q_{10} is a cofactor for complex I, which acts as a bioenergetic and an antioxidant. It has been tested as a putative neuroprotective agent in PD based on laboratory studies showing that it protects dopamine neurons in PD models.[48] Shults *et al.*[49] studied the effects of high-dose CoQ_{10} on the development of disability in early PD patients. They randomized 80 patients who were not yet on L-dopa to receive placebo or one of the three doses of CoQ_{10}, viz., 300, 600 or 1200 mg/d, for a follow-up period of <16 months. The primary response variable was change in total UPDRS score. Subjects treated with CoQ_{10} had less disability as shown by a change in UPDRS from baseline (8 in controls and 6.4 in the 1,200-mg group) ($P = 09$). Although the results did not reach statistical significance, they did meet pre-specified criteria for positive trends. However, the authors concluded that their results need confirmation in large phase III studies and that until then it would be premature to recommend the use of CoQ_{10} for the treatment of PD.

Creatine

Creatine is widely used as a health food; as a component of creatine phosphate, it forms part of the most important energy reservoir for adenosine triphosphate (ATP). Studies have suggested that it can improve the function of mitochondria, which produce energy inside cells. It also may act as an antioxidant that prevents damage from compounds that are harmful to cells in the brain. The National Institute of Neurological Disorders and Stroke Neuroprotection Exploratory Trials in Parkinson Disease (NINDS NET-PD) investigators[50] treated a cohort of *de novo* PD patients with either placebo or creatine. Mean decline of total UPDRS score at the end of 12 months was 5.6 in the creatine group and 8.39 in the placebo group; the difference was small but statistically significant. The authors concluded that creatine warrants further study in randomized controlled trials (RCTs) to assess whether it has disease-modifying effects in PD.

Minocycline

Minocycline, a tetracycline derivative, is a caspase inhibitor, and it inhibits the inducible nitric oxide synthases, which are important for apoptotic cell death. Furthermore, minocycline has been shown to block microglial activation of 6-hydroxydopamine and 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine–lesioned Parkinsonism in animal models and protect against nigrostriatal dopaminergic neurodegeneration.[51] Because inflammatory processes might be involved in the progression of PD, anti-inflammatory agents could have neuroprotective effects. The NINDS NET-PD investigators[50] studied minocycline in the same way as they assessed creatine and noted that the average decline of UPDRS score at the end of 12 months was 7.09 in the minocycline group and 8.39 in those assigned to placebo. These studies were done as part of a futility study that was introduced to screen drugs that might have disease-modifying effects in PD.

In summary, our review of the literature on pramipexole, ropinirole, levodopa, selegiline, rasagiline, CoQ_{10}, creatine and minocycline suggests that these agents might elicit small disease-modifying effects in PD. It is not known whether this is due to slowing down of the neurodegenerative processes, effect on the plasticity of the brain, a combination of both or due to some other mechanism. So far, none of the tested drugs for PD has explicitly been shown to have neuroprotective effects.

Conclusion: Where Do We Stand in the Treatment of PD?

PD is age-related neurodegenerative disorder with an average age of onset of about 60 years, and it occurs worldwide but appears to be less common in Africa than elsewhere in the world. With the ageing of the population, the frequency of PD is expected to increase, perhaps slowly in the developing countries, because of the high prevalence of chronic diseases such as malaria and HIV/ AIDS. A goal of vital importance in neuroscience today is to elucidate the etiology of neurodegenerative disorders — a prerequisite for the development of curative therapy. Although our insight into the great complexity of pathophysiological mechanisms in PD has rapidly increased, introduction of effective neuroprotective or curative clinical treatment in this disease is not expected in the near future. On the other hand, regarding symptomatic therapy the situation is quite different. Today we have many options for the treatment of PD. Symptomatic treatment should be considered for patients with functional impairments caused by PD. The therapeutic goal is to reverse functional disability, completely if possible, without leading to short- or long-term side effects and toxicity. Although L-dopa is still the gold standard of treatment, relying solely on levodopa may cause various problems in the long term.

References

1. Bernheimer H, Birkmayer W, Hornykiewicz O, Jellinger K, Seitelberger F. Brain dopamine and the syndromes of Parkinson and Huntington: Clinical, morphological and neurochemical correlations. J Neurol Sci 1973;20:415-55.
2. Parkinson J. Essay on the shaking palsy. Sherwood London: Neely and Jones; 1817.
3. Braak H, 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;24:197-211.
4. Okubadejo NU, Bower JH, Rocca WA, Maraganore DM. Parkinson's disease in Africa: A systematic review of epidemiologic and genetic studies. Mov Disord 2006;21:2150-6.
5. Hermanowicz N. Management of Parkinson's disease: Strategies, pitfalls, and future directions. Postgrad Med 2001;110:15-8, 21-3, 28.
6. Cotzias GC, Papavasiliou PS, Gellene R. Experimental treatment of Parkinsonism with L-dopa. Neurology 1968;18:276-7.
7. Calne DB. Initiating treatment for idiopathic parkinsonism. Neurology 1994;44:S19-22.
8. Weiner WJ. Early diagnosis of Parkinson's disease and initiation of treatment. Rev Neurol Dis 2008;5:46-53.
9. Thomas A, Iacono D, Luciano AL, Armellino K, Di Iorio A, Onofrj M. Duration of amantadine benefit on dyskinesia of severe Parkinson's disease. J Neurol Neurosurg Psychiatry 2004;75:141-3.
10. Verhagen Metman L, Del Dotto P, van den Munckhof P, Fang J, Mouradian MM, Chase TN. Amantadine as treatment for dyskinesias and motor fluctuation in Parkinson's disease. Neurology 1998;50:1323-6.
11. Mouradian MM. The continuous dopaminergic stimulation concept and evidence to date. Managing advanced Parkinson's disease: The role of continuous dopaminergic stimulation. In: Aquilonius SM, Lees AJ, editors. Tonbridge, London. Scope Medical Ltd; 2007.
12. Nutt JG, Woodward WR, Anderson JL. The effect of carbidopa on the pharmacokinetics of intravenously administered levodopa: The mechanism of action in the treatment of Parkinsonism. Ann Neurol 1985;18:537-43.
13. Manson AJ, Turner K, Lees AJ. Apomorphine monotherapy in the treatment of refractory motor complications of Parkinson's disease: Long time follow-up study of 64 patients. Mov Disord 2002;17:1235-41.
14. Kolls BJ, Stacy M. Apomorphine: A rapid rescue agent for the management of motor fluctuations in advanced Parkinson's disease. Clin Neuropharmacol 2006;29:292-301.
15. Allain H, Pollak P, Neukirch HC. Symptomatic effect of selegiline in *de novo* Parkinsonian patients: The French Selegiline Multicentre Trial. Mov Disord 1993;8:S36-40.
16. Stern MB, Marek KL, Friedman J, Hauser RA, LeWitt PA, Tarsy D, *et al*. Double-blind, randomized, controlled trial of rasagiline as monotherapy in early Parkinson's disease patients. Mov Disord 2004;19:916-23.
17. Jankovic J. Motor fluctuations and dyskinesias in Parkinson's disease: Clinical manifestations. Mov Disord 2005;20:S11-6.
18. Chapuis S, Ouchchane L, Metz O, Gerbaud L, Durif F. Impact of the motor complications of Parkinson's disease on the quality of life. Mov Disord 2005;20:224-30.
19. Davie CA. A review of Parkinson's disease. Br Med Bull 2008;86:109-27.
20. Hawkes CM. Diagnosis and treatment of Parkinson's disease: Anosmia is a common finding. BMJ 1995;310:1668.
21. Chase TN, Fabbrini G, Juncos JL, Mouradian MM. Motor response complications with chronic levodopa therapy. Adv Neurol 1990;53:377-81.
22. Rascol O, Brooks DJ, Korczyn AD, De Deyn PP, Clarke CE, Lang AE. A five-year study of the incidence of dyskinesia in patients with early Parkinson's disease who were treated with ropinirole or levodopa. 056 Study Group. New Engl J Med 2000;342:1484-91.
23. Holloway RG, Shoulson I, Fahn S, Kieburtz K, Lang A, Marek K, *et al*. Pramipexole vs. levodopa as initial treatment for Parkinson disease: A 4-year randomised controlled trial. Arch Neurol 2004;61:1044-53.
24. Guttman M, Stewart D, Hussey D, Wilson A, Houle S, Kish S. Influence of L-dopa and pramipexole on striatal dopamine transporter in early PD. Neurology 2001;56:1559-64.
25. Parkinson Study Group. Pramipexole vs. L-dopa as initial treatment on Parkinson's disease: A randomized controlled trial. JAMA 2000;284:1931-8.
26. Parkinson Study Group. Dopamine transporter brain imaging to assess the effects of pramipexole vs. L-dopa on

Parkinson disease progression. JAMA 2002;287:1653-61.
27. Lieberman A, Ranhosky A, Korts D. Clinical evaluation of pramipexole in advanced Parkinson's disease: Results of a double blind, placebo-controlled, parallel-group study. Neurology 1997;49:162-8.
28. Mizuno Y. Where do we stand in the treatment of Parkinson's disease? J Neurol 2007;254:13-8.
29. Driver-Dunckley E, Samanta J, Stacy M. Pathological gambling associated with dopamine agonist therapy in Parkinson's disease. Neurology 2003;61:422-3.
30. Olanow CW, Fahn S, Muenter M, Klauwans H, Hurtig H, Stern M *et al*. A multicentre double-blind placebo controlled trial of pergolide as an adjunct to sinemet in Parkinson's disease. Mov Disord 1994; 9:40-7.
31. Antonini A, Poewe W. Fibrotic heart valve reaction to dopamine agonist treatment in Parkinson's disease. Lancet Neurol 2007;6:826-9.
32. Lev N, Djaldetti R, Melamed E. Initiation of symptomatic therapy in Parkinson's disease: Dopamine agonists versus levodopa. J Neurol 2007;254:19-26.
33. Fahn S, Oakes D, Shoulson I, Kieburtz K, Rudolph A, Lang A, *et al*. L-dopa and the progression of Parkinson's disease. N Engl J Med 2004;351:2498-508.
34. Innis RB, Marek KL, Sheff K, Zoghbi S, Castronuovo J, Feigin A, *et al*. Effect of treatment with L-dopa/carbidopa or L-selegiline on striatal dopamine transporter SPECT imaging with [^{123}I] beta-CIT. Mov Disord 1999;14:436-42.
35. Nurmi E, Bergman J, Eskola O, Solin O, Hinkka SM, Sonninen P, *et al*. Reproducibility and effect of L-dopa on dopamine transporter function measurements: A [F-18] CFT PET study. J Cereb Blood Flow Metab 2000;20:1604-9.
36. Mannisto PT, Kaakkola S. New selective COMT inhibitors: Useful adjuncts for Parkinson's disease? Trends Pharmacol Sci 1989;10:54-6.
37. Mannisto PT, Kaakkola S. Rationale for selective COMT inhibitors as adjuncts in the drug treatment of Parkinson's disease. Pharmacol Toxicol 1990;66:317-23.
38. Schrag A. Entacapone in the treatment of Parkinson's disease. Lancet Neurol 2005;4:366-70.
39. Poewe WH, Deuschl G, Gordin A, Kultalahti ER, Leinonen M; Celomen Study Group. Efficacy and safety of entacapone in Parkinson's disease patients with suboptimal levodopa response: A 6-month randomized placebo-controlled double blind study in Germany and Austria (Celomen study). Acta Neurol Scand 2002;105:245-55.
40. Hauser RA. Levodopa/carbidopa/entacapone (Stalevo). Neurology 2004;62:S64-71.
41. The Parkinson Study Group. Effect of deprenyl on the progression of disability in early Parkinson's disease. N Engl J Med 1989;321:1364-71.
42. The Parkinson Study Group. Effect of tocopherol and deprenyl on the progression of disability in early Parkinson's disease. N Engl J Med 1993;328:176-83.
43. Parkinson Study Group. Impact of deprenyl and tocopherol treatment on Parkinson's disease in DATATOP subjects not requiring L-dopa. Ann Neurol 1996;39:29-36.
44. Parkinson Study Group. Impact of deprenyl and tocopherol treatment on Parkinson's disease in DATATOP patients requiring L-dopa. Ann Neurol 1996;39:37-45.
45. Pålhagen S, Heinonen E, Hägglund J, Kaugesaar T, Mäki-Ikola O, Palm R, *et al*. Selegiline slows the progression of the symptoms of Parkinson's disease. Neurology 2006;66:1200-6.
46. Olanow CW, Hauser RA, Gauger L, Malapira T, Koller W, Hubble J, *et al*. The effect of deprenyl and L-dopa on the progression of Parkinson's disease. Ann Neurol 1995;38:771-7.
47. Parkinson Study Group. A controlled, randomized, delayed-start study of rasagiline in early Parkinson's disease. Arch Neurol 2004;61:561-6.
48. Beal MF. Bioenergetic approaches for neuroprotection in Parkinson's disease. Ann Neurol 2003;53:S39-47; discussion S47-8.
49. Shults CW, Oakes D, Kieburtz K, Beal MF, Haas R, Plumb S, *et al*. Effect of coenzyme Q_{10} in early Parkinson disease: Evidence of slowing of the functional decline. Arch Neurol 2002;59:1541-50.
50. NINDS NET-PD Investigators. A randomized, double blind, futility clinical trial of creatine and minocycline in early Parkinson disease. Neurology 2006;66:664-71.
51. Thomas M, Le WD. Minocycline: Neuroprotective mechanisms in Parkinson's disease. Curr Pharm Des 2004;10:679-86.

Source of Support: Nil, **Conflict of Interest:** None declared.