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Does levodopa slow or hasten the rate of progression of Parkinson's disease?

Abstract Levodopa therapy, as originally established by George Cotzias [2, 3], is the most powerful treatment for Parkinson's disease (PD). Levodopa's toxicity to neurons *in vitro* has raised concerns if it might hasten the progression of PD, although *in vivo* animal studies suggest it may be neuroprotective. *Objective* To discuss the results of the ELLDOPA trial that was carried out to determine if levodopa therapy influences the rate of progression of Parkinson's disease (PD). *Design* ELLDOPA was a multicenter, parallel-group, double-blind, dosage-ranging, randomized, controlled clinical trial. *Setting* Academic movement disorders clinics at 38 sites in the United States and Canada. *Patients* Three hundred and sixty-one patients with early PD of less than 2 years' duration who did not require symptomatic therapy. *Interventions* Subjects were randomly assigned to one of four treatment groups: carbidopa/levodopa 12.5/50 mg t. i. d. (N = 92), 25/100 mg t. i. d. (N = 88), 50/200 mg t. i. d. (N = 91), or matching placebo (N = 90). The dosage was gradually escalated over 9 weeks and then maintained until Week 40, at which time active treatment was withdrawn over 3 days. After 2 weeks without active treatment (Week 42), a final assessment of PD severity was obtained. *Outcome measures* The prespecified primary clinical outcome was the change in the total Unified Parkinson's Disease Rating Scale (UPDRS) between baseline and Week 42, comparing the four treatment groups. The primary neuroimaging component of the study in a subgroup of 142 subjects was the percent change in striatal ^{123}iodine 2-β-carboxymethoxy-3-β-(4-iodophenyl)tropane (β-CIT) uptake between baseline and Week 40 visits. The neuroimaging substudy utilized single photon emission computed tomography (SPECT) of the dopamine transporter. *Results* All dosages of levodopa exerted clinical benefit compared to placebo on the UPDRS scores throughout the study, including 2 weeks after discontinuing levodopa. The UPDRS scores at Week 42 failed to reach the level encountered in the placebo group (change of 7.8 ± 9.0, 1.9 ± 6.0, 1.9 ± 6.9, and –1.4 ± 7.8, for placebo, 150 mg/day, 300 mg/day, and 600 mg/day, respectively, $p < 0.0001$). Nausea ($p = 0.001$) and dyskinesias ($p = 0.0001$) were more common in the levodopa groups, especially with the higher dosages. Freezing appeared around the same time, but was more common in the placebo (14 %) and 150 mg/day group (10 %). The percent decline of β-CIT uptake in the striatum was significantly more pronounced in the levodopa groups than the placebo group (–7.2 %, –4 %, –6 %, and –1.4 % in 600 mg/day, 300 mg/day, 150 mg/day, and placebo, respectively; $p = 0.035$). *Conclusions* The clinical outcomes not only indicate that levodopa is effective in a dose-dependent manner in overcoming the signs and symptoms of PD, they also support the concept that the drug does not hasten the disease progression, but rather may slow down the rate of the disease. The clinical study failed to demonstrate any evidence of levodopa worsening early PD. However, the β-CIT SPECT substudy indicates the opposite effect, namely that levodopa causes a more rapid decline in the integrity of the dopamine transporter located in the nigrostriatal nerve terminals in the striatum. These contradictory findings warrant further investigation into the effect of levodopa on PD. *Other observations* The ELLDOPA study was the first levodopa dose-response study ever conducted. It showed that dose is a factor in the cause of producing

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motor complications of dyskinesias and wearing-off, and that these can develop as early as 5 to 6 months. On the other hand, freezing of gait could be delayed or its occurrence reduced by high dosage levodopa, compared to placebo or low-dose levodopa. Withdrawal of levodopa over a 3-day step-down can be safely carried out without inducing the neuroleptic-like syndrome. The UPDRS was shown to be a reliable linear marker for disease progression. The ELLDOPA study also called into question the interpretation of β-CIT SPECT in the presence of dopaminergic agents. Neuroimaging in ELLDOPA also showed that some people diagnosed with early PD do not have a dopaminergic deficit, calling into question how difficult the correct diagnosis may be in people with early symptoms of PD.

Key words Parkinson's disease · levodopa · natural history · toxicity · controlled clinical trial · dopamine transporter imaging

Introduction

Parkinson's disease (PD) is a progressively disabling neurodegenerative disorder manifested clinically by bradykinesia, tremor, rigidity, flexed posture, postural instability and the freezing phenomenon. It is characterized pathologically by loss of pigmented neurons in the brainstem, particularly dopaminergic neurons in the substantia nigra pars compacta and noradrenergic neurons in the locus ceruleus. The neuronal degeneration is accompanied by the presence of intracytoplasmic eosinophilic inclusions known as Lewy bodies and by gliosis [1]. The course of clinical decline parallels the progressive degeneration of remaining neurons [2]. Neurochemical and pharmacologic studies implicate striatal dopamine deficiency as the basis of most of the motor features of PD [3]. Dopamine replacement therapy with the precursor, levodopa, as originally established by George Cotzias [4, 5], is highly effective in ameliorating many signs and symptoms in the early stages of PD and in improving the quality of life and survival of treated patients. It provides superior benefit to all other currently available drugs [6]. Unfortunately, a host of disabling complications usually ensues within months to years, and sometimes within weeks after initiation of levodopa [7], greatly limiting the overall effectiveness of the drug. In fact, the motor complications of levodopa-induced dyskinesias and fluctuations (i. e., wearing-off) are the primary reasons for delaying the initiation of levodopa therapy [8].

Whether to introduce levodopa therapy early or later in the course of the disease has been a controversy that has engulfed the movement disorder community. Adding to this controversy were the findings that levodopa is neurotoxic to aminergic cells in vitro [see reviews 9, 10]. These findings have raised concerns that chronic levodopa exposure might hasten disease progression in PD patients by enhancing the degeneration of dopaminergic neurons. Accordingly, some physicians and patients have opted to defer the use of levodopa for as long as possible [8]. Others physicians support using levodopa as first-line therapy, arguing that it is inappropriate to withhold the most potent symptomatic treatment for PD in the absence of clinical evidence of toxicity [11–13].

Despite in vitro studies indicating that levodopa can be toxic to dopaminergic neurons, the results from in vivo studies in animals were mixed. Suggestive that levodopa could hasten the demise of dopamine neurons in patients with PD were two studies published in 2002, in which functional neuroimaging techniques had been used to compare patients initially treated with pramipexole vs. levodopa (CALM-PD) and ropinirole vs. levodopa (REAL-PET). The CALM-PD trial used single photon emission computerized tomography (SPECT) to look at striatal dopamine transporter (DAT) activity (β-CIT uptake) as a marker for intact nigrostriatal dopaminergic nerve terminals. This 4-year trial showed a more rapid rate of decline of β-CIT uptake in the group assigned to early levodopa compared with early pramipexole treatment [14]. On the other hand, the clinical results of this trial showed that levodopa was more effective than pramipexole in reducing the clinical signs of PD [15]. Similar imaging [16] and clinical [17] results were found in the REAL-PET trial, which used positron emission tomography (PET) to look at putaminal ^{18}F accumulation (due to ^{18}F-DOPA uptake and decarboxylation) as a marker for functional dopaminergic terminals. These studies showed a more rapid rate of reduction of ^{18}F accumulation in patients who were initially treated with levodopa vs. ropinirole, but a better clinical response with levodopa. Since there was no placebo group in either study, the findings of the two studies could be interpreted to show that dopamine agonists slow the progression of PD, levodopa hastens the progression of PD, or both. They also raise the question of whether levodopa or dopamine agonists have direct pharmacological effects on DAT or L-aromatic amino acid (dopa) decarboxylase that might confound the interpretation of these results. Thus, caution must be used in interpreting these and other studies that use imaging markers to document "neuroprotection" [18–20].

How might levodopa be toxic to aminergic neurons? The most common explanation is that levodopa augments oxidative stress via the production of quinones, hydrogen peroxide and oxyradicals. Because the

dopaminergic neurons in patients with PD are already under oxidative stress that contributes to neuronal death, adding further oxyradicals would enhance the demise of these neurons. The biochemical evidence of oxidative stress in the parkinsonian substantia nigra pars compacta is multiple. There is a reduction of reduced glutathione, increased levels of malondialdehyde and lipid hydroperoxides, oxidative DNA and protein damage, oxidative (nitrative) modification of α-synuclein, and reduced complex I activity; and both the MPTP and rotenone animal models of PD involve oxidative stress [21–23].

Because of ongoing controversy about whether levodopa is toxic to dopamine neurons in patients with PD, a large, multicenter, randomized controlled clinical trial comparing three different doses of levodopa with placebo treatment in patients with early PD (the ELLDOPA study) was designed and executed by the Parkinson Study Group to answer this question [24]. This article reviews the main results of the ELLDOPA study and discusses its contribution to the understanding of levodopa therapy in PD.

Analysis of the ELLDOPA study

This was a double-blind, placebo-controlled, parallel group, multicenter clinical trial of patients with early PD who had not been previously treated with symptomatic therapy. A total of 361 patients were enrolled, and were randomized to receive treatment with either low (150 mg/day), middle (300 mg/day), or high (600 mg/day) dosage levodopa, or placebo, with the medications divided into a dosing schedule of three times daily. The daily dose was built up gradually over a 9-week period. After 40 weeks of treatment, the patients underwent a 3-day taper of their medications, followed by a 2-week washout period during which they received no treatment for their PD. The primary outcome measure was the change in the total Unified Parkinson's Disease Rating Scale (UPDRS) score between baseline and after the washout period at Week 42. The goal of the study was to determine whether levodopa treatment affects the rate of progression of PD.

At the end of the 2-week washout period, the UPDRS scores of patients treated with all three doses of levodopa were lower (better) than those of the placebo-treated group, in a dose-response pattern (Fig. 1). These findings suggest that levodopa is not neurotoxic, and may even be neuroprotective, though the possibility that patients were experiencing a longer duration of symptomatic response to levodopa that had extended beyond the 2-week washout period could not be excluded. The highest dosage of levodopa was, however, associated with a higher incidence of motor complications, including dyskinesias and a trend to develop the "wearing-off" phenomenon (Table 1).

In addition to the clinical data, a subset of patients in the ELLDOPA trial was also evaluated with β-CIT SPECT imaging, which (as in the CALM-PD trial) was used as a marker for intact nigrostriatal dopaminergic neurons by labeling the dopamine transporter (DAT).

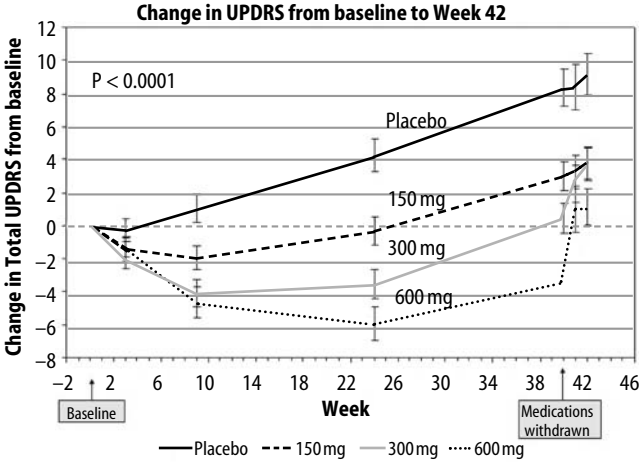

Fig. 1 Total UPDRS dose-response changes to levodopa and placebo therapy over 40 weeks of treatment and then 2 weeks of no medication. Ratings were obtained from the blinded Treating Investigators. The scores were obtained prior to the first daily dose of experimental medication. Figure reproduced from Ref. 24. Permission granted by Massachusetts Medical Society, which holds the copyright (2004)

Table 1 Dopaminergic adverse effects in the ELLDOPA study

Adverse event	Placebo	Levodopa 150 mg/day	Levodopa 300 mg/day	Levodopa 600 mg/day	P-value (Trend)
Subjects, N	90	92	88	91	
Dyskinesia	3 (3.3)	3 (3.3)	2 (2.3)	15 (16.5)	< 0.001
Dystonia	19 (21.1)	19 (20.1)	14 (15.9)	12 (13.2)	0.30
Freezing	13 (14.4)	9 (9.8)	6 (6.8)	5 (5.5)	0.15
On-Off	3 (3.3)	1 (1.1)	0 (0.0)	3 (3.3)	0.26
Wearing-Off	12 (13.3)	15 (16.3)	16 (18.2)	27 (29.7)	0.06

Data shown are the number of subjects (with percentages in parentheses) affected with each adverse effect. Data from Ref. 24. Permission granted

These neuroimaging studies showed that there was a larger decrease in striatal DAT binding in patients treated with levodopa, in a dose-response pattern (Fig. 2). Thus, in contrast with the clinical data, the imaging findings suggested that levodopa may hasten the progression of PD. As with other neuroimaging studies, however, it is possible that the observed changes in the levels of uptake of this marker reflected a pharmacological effect of levodopa on DAT activity, rather than evidence of injury to dopaminergic neurons.

Thus, intriguing as the results of the ELLDOPA study are, it remains unclear whether levodopa may (either positively or negatively) affect the natural history of PD. Given the evidence from the ELLDOPA study that the dosage of levodopa is important in the development of motor complications, it is reasonable to customize the dose of levodopa to fit the specific needs of each patient.

Other information learned from the ELLDOPA study

Dose-response

This is the first time that a dose-response curve with levodopa has been studied. The curves in Fig. 1 indicate the mean change of UPDRS from baseline at each visit. Error bars indicate ± SE. The scores were obtained from examinations carried out prior to the subjects receiving their first daily dose of medication. The highest dose of levodopa provided maximum improvement of UPDRS scores until Week 24 (mean benefit of 5 UPDRS units below the baseline level), at which time the symptoms started to revert towards baseline as seen at the Week 40 visit. Clinical benefit was seen even at the lowest dose tested, 12.5/50 mg t.i.d. The two lowest doses (150 mg/day and 300 mg/day) showed a reversal towards baseline beginning after Week 9; after Week 24, the worsening of Parkinson's disease was parallel to that encountered in the placebo group. The 150 mg/day group reached its baseline UPDRS scores around Week 27, and the 300 mg/day group around Week 40. The 600 mg/day group still showed improved UPDRS scores compared to baseline by the time levodopa was withdrawn at Week 40. The placebo and the two lowest levodopa groups showed a steady rate of worsening over the 2-week washout period, but almost all the worsening of UPDRS scores for the 600 mg/day group occurred during the first week of drug withdrawal, with little noticeable change afterwards. At Month 9 (Week 40), UPDRS scores improved after a dose of medication, and this short-duration benefit of the 300 and 600 mg/day dosages remained superior to the baseline score (data not shown). The group receiving 600 mg/day of levodopa maintained its degree of symptomatic benefit throughout even before the first dose of the day.

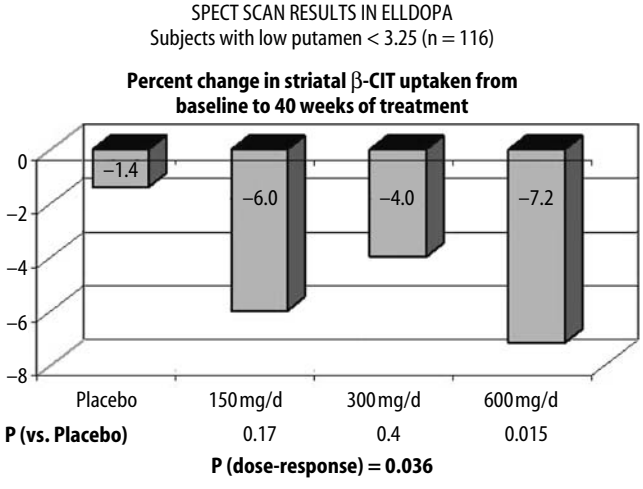

Fig. 2 Percent change of striatal β-CIT uptake from baseline to Week 40. Values are expressed mean changes. P-values refer to dose-response effect and to individual doses versus placebo. The 19 subjects eliminated had putaminal β-CIT uptake ≥ 3.25 (> 75 percent age expected uptake). Data from Ref. 24. Permission granted

Usefulness of UPDRS to measure progression of PD

Fig. 1 also shows that the total UPDRS scores in the control (placebo) group steadily (almost linearly) worsened over the 42 weeks of the study. The mean change from baseline varied from 7.8 units (results of the Primary Raters) to 9 units (results of the Treating Investigators) over the 42 weeks (9.5 months). This linear change indicates that total UPDRS is a valid scale in early PD. The consistency of the rate of change of total UPDRS among the several controlled clinical trials evaluating patients with early, mild PD is another indication that the UPDRS is a reliable scale to measure the progression of PD (Table 2).

Development of wearing-off and dyskinesias

The ELLDOPA study is the first time that dosage of levodopa was shown to be a factor in the development of dyskinesias ($P < 0.001$) and most likely also motor fluctuations ($P = 0.06$) (Table 1). Retrospective studies suggest that duration of levodopa therapy, severity of PD and duration of illness may be important factors [29–33]. The time of onset of the motor complications in ELLDOPA was 5–6 months after starting levodopa.

Table 2 Rate of worsening of PD in placebo arm of clinical trials in mild, untreated PD

Name of study	Drug being studied	tUPDRS/duration	tUPDRS/year	Reference
DATATOP	Deprenyl/tocopherol	12/year	12/year	25
ROADS	Lazabemide	8/year	8/year	26
QE2	Coenzyme Q10	12/16 months	9/year	27
TEMPO	Rasagiline	4.1/6 months	8.2/year	28
ELLDOPA	Levodopa	8.4/9.5 months	10.6/year	24

Freezing of gait

The ELLDOPA study also showed that levodopa, particularly high dosage, can delay the development of freezing of gait. Onset of freezing occurred mainly in the placebo group, with onset between 5 and 6 months. Whether the delay or prevention of freezing by levodopa is due to its symptomatic or to a neuroprotective effect is uncertain.

Withdrawal from levodopa

The withdrawal of levodopa was also studied in the ELLDOPA trial. Withdrawing levodopa over a 3-day step-down prior to its discontinuation did not produce the "neuroleptic malignant-like syndrome." Whether this step-down approach avoided this complication or whether it would not have occurred anyway, given the short duration of levodopa therapy and the mild state of PD, cannot be ascertained.

Without levodopa, the worsening of UPDRS scores occurred almost entirely in the first week off medication. Because the washout period was only 2 weeks, it is uncertain if the symptomatic benefit from levodopa would still be present beyond the 2-week washout period.

Neuroimaging

The placebo controlled imaging component in the ELLDOPA study was discordant from the clinical results. A dose-responsive reduced binding of β-CIT could reflect either enhanced progression of PD from levodopa or pharmacologic interference by levodopa of the activity of the dopamine transporter, which is labeled by β-CIT. Therefore, the ELLDOPA study calls into question the value of neuroimaging studies in the presence of dopaminergic agents. This applies to the interpretation of the CALM-PD and the REAL-PET studies described above.

SWEDDs

The ELLDOPA study confirmed that some patients diagnosed with early PD appear to have no striatal dopaminergic deficit, calling into question their diagnosis. These Scans Without Evidence of Dopaminergic Deficit (SWEDDs) have been seen in CALM-PD and REAL-PET, as well. What is the correct diagnosis for these patients? Is it possible that the diagnosis was incorrect, with patients possibly having some other illness, such as essential tremor or depression? Psychogenic parkinsonism, dopa-responsive dystonia and even a Parkinson-plus syndrome are possible alternative diagnoses. It is important to ascertain what the correct diagnosis is for such patients. Furthermore, a predetermined analysis plan needs to be formulated on how to handle these individuals when studying a population of early PD subjects for clinical trials.

One piece of evidence that those with SWEDDs do not have PD is their lack of any clinical response to levodopa therapy (Table 3). One would expect patients with PD to have symptomatic benefit when treated with 600 mg/day of levodopa, but those with SWEDDs failed to show improvement.

Interpretations of the ELLDOPA study

The clinical results suggest either a strong neuroprotective effect from levodopa, particularly a high dosage of at least 600 mg/day, or that there is a very long duration of clinical benefit not previously recognized. The discordance of the neuroimaging results indicate that if lev-

Table 3 Response of SWEDDs vs. non-SWEDDs in the 600 mg/day group

	Baseline		Week 40	
Category	N	UPDRS	N	ΔUPDRS (40-0)
SWEDDs	8	14.4±7.6	8	2.4±4.2
Non-SWEDDs	30	29.7±11.6	28	−4.9±10.4
P		0.004		0.002

UPDRS scores are Total UPDRS obtained by the Treating Investigators, mean ± S. D. P-value by Student's t-test. Their parkinsonian symptoms do not appear to be due to DA deficiency

odopa is neuroprotective, then the imaging results probably reflect interference of the binding of β-CIT due to levodopa. However, if the imaging result is a reflection of enhanced neuroprogression by levodopa, then the clinical results would reflect incomplete elimination of the symptomatic benefit with only a 2-week withdrawal of levodopa. Because of this uncertainty, one cannot recommend starting high dosage levodopa at the time of diagnosis. A follow-up study to resolve the uncertainty in interpretation is strongly recommended.

References

1. Fahn S, Przedborski S (2005) Parkinsonism. In: Rowland LP (ed) Merritt's Neurology, 11th edn, Lippincott Williams and Wilkins, Philadelphia, pp 828–846
2. Riederer P, Wuketich S (1976) Time course of nigrostriatal degeneration in Parkinson's disease. J Neural Transm 38:277–301
3. Hornykiewicz O (1982) Brain neurotransmitter changes in Parkinson's disease. In: Marsden CD, Fahn S (eds) Movement Disorders. Butterworth Scientific, London, pp 41–58
4. Cotzias GC, Van Woert MH, Schiffer LM (1967) Aromatic amino acids and modification of parkinsonism. N Engl J Med 276:374–379
5. Cotzias GC, Papavasiliou PS, Gellene R (1969) Modification of parkinsonism – chronic treatment with L-dopa. N Engl J Med 280:337–345
6. Miyasaki JM, Martin W, Suchowersky O, Weiner WJ, Lang AE (2002) Practice parameter: Initiation of treatment for Parkinson's disease: An evidence-based review. Neurology 58:11–17
7. Fahn S (1989) Adverse effects of levodopa in Parkinson's disease. In: Calne DB (ed) Drugs for the treatment of Parkinson's Disease. Handbook of Experimental Pharmacology 88. Springer, Berlin, pp 385–409
8. Fahn S (1999) Parkinson disease, the effect of levodopa, and the ELLDOPA trial. Arch Neurol 56:529–535
9. Fahn S (1996) Is levodopa toxic? Neurology 47:S184–S195
10. Fahn S (1997) Levodopa-induced neurotoxicity: Does it represent a problem for the treatment of Parkinson's disease? CNS Drugs 8:376–393
11. Agid Y (1998) Levodopa: is toxicity a myth? Neurology 50(4):858–863
12. Weiner WJ (1999) The initial treatment of Parkinson's disease should begin with levodopa. Mov Disord 14(5): 716–724
13. Factor SA (2000) The initial treatment of Parkinson's disease. Mov Disord 15(2):360–361
14. Parkinson Study Group (2002) Dopamine transporter brain imaging to assess the effects of pramipexole vs levodopa on Parkinson disease progression. JAMA 287(13):1653–1661
15. Parkinson Study Group (2004) Pramipexole vs levodopa as initial treatment for Parkinson disease – A 4-year randomized controlled trial. Arch Neurol 61(7):1044–1053
16. Whone AL, Watts RL, Stoessl AJ, et al. (2003) Slower progression of Parkinson's disease with ropinirole versus levodopa: The REAL-PET study. Ann Neurol 4(1):93–101
17. Rascol O, Brooks DJ, Korczyn AD, et al. (2000) 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. N Engl J Med 342(20):1484–1491
18. Morrish PK, Sawle GV, Brooks DJ (1996) An [F-18]dopa-PET and clinical study of the rate of progression in Parkinson's disease. Brain 119:585–591
19. Marek K, Jennings D, Seibyl J (2002) Do dopamine agonists or levodopa modify Parkinson's disease progression? Eur J Neurol 9(Suppl 3):15–22
20. Albin RL, Frey KA (2003) Initial agonist treatment of Parkinson disease: a critique. Neurology 60(3):390–394
21. Dauer W, Przedborski S (2003) Parkinson's Disease: Mechanisms and Models. Neuron 39:889–909
22. Vila M, Przedborski S (2003) Targeting programmed cell death in neurodegenerative diseases. Nat Rev Neurosci 4(5):365–375
23. Fahn S, Sulzer D (2004) Neurodegeneration and neuroprotection in Parkinson disease. NeuroRx 1:139–154
24. Parkinson Study Group (2004) Levodopa and the progression of Parkinson's disease. N Engl J Med 351(24):2498–2508
25. Parkinson Study Group (1993) Effects of tocopherol and deprenyl on the progression of disability in early parkinson's disease. N Engl J Med 328:176–183
26. Parkinson Study Group (1996) Effect of lazabemide on the progression of disability in early Parkinson's disease. Ann Neurol 40:99–107
27. Shults CW, Oakes D, Kieburtz K, Beal MF, Haas R, Plumb S, Juncos BL, Nutt J, Shoulson I, Carter J, Kompoliti K, Perlmutter JS, Reich S, Stern M, Watts RL, Kurlan R, Molho E, Harrison M, Lew M (2002) Effects of coenzyme Q(10) in early Parkinson disease – Evidence of slowing of the functional decline. Arch Neurol 59(10):1541–1550
28. Parkinson Study Group (2004) A controlled, randomized, delayed-start study of rasagiline in early Parkinson disease. Arch Neurol 61(4):561–566
29. de Jong GJ, Meerwaldt JD, Schmitz PIM (1987) Factors that influence the occurrence of response variations in Parkinson's disease. Ann Neurol 22:4–7
30. Quinn N, Critchley P, Marsden CD (1987) Young onset Parkinson's disease. Mov Disord 2:73–91
31. Blin J, Bonnet A-M, Agid Y (1988) Does levodopa aggravate Parkinson's disease? Neurology 38:1410–1416
32. Roos RAC, Vredevoogd CB, van der Velde EA (1990) Response fluctuations in Parkinson's disease. Neurology 40: 1344–1346
33. Cedarbaum JM, Gandy SE, McDowell FH (1991) Early initiation of levodopa treatment does not promote the development of motor response fluctuations, dyskinesias, or dementia in Parkinson's disease. Neurology 41: 622–629