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*Neurological controversy*

# Drug treatment of Parkinson's disease: is "polypharmacy" best?

It is common for patients with Parkinson's disease to receive four or five antiparkinsonian drugs simultaneously, usually including carbidopa/levodopa (Sinemet, Madopar) sometimes in more than one form, a dopamine agonist (bromocriptine or pergolide), selegiline (deprenyl, Eldepryl), amantadine or an anticholinergic drug, and often vitamin E or C, or both. An Indian neurologist sitting next to me at the 1989 World Congress of Neurology remarked that in her country a week's supply of pills would cost an average worker a month's wages. It has been suggested that the best approach to drug treatment of parkinsonian patients is the "judicious concomitant use of several different classes of anti-parkinsonian drugs, including levodopa, dopamine agonists, monoamine oxidase inhibitors, anticholinergics, and amantadine HCl utilising the smallest effective dose for each drug".[1] I doubt that I am the only neurologist who remains unconvinced that such patients are much better off than they would be if they were taking carbidopa/levodopa alone or with only one additional agent. Is it possible that enthusiasm for new drugs has blinded us to the point that we are doing patients harm?

There are at least three ideas that influence the way in which we prescribe antiparkinsonian drugs: firstly, that levodopa taken for prolonged periods may harm the patient, perhaps by accelerating an auto-oxidation process in the substantia nigra; secondly, that dopamine agonists will allow lower doses of levodopa to be used and will reduce symptom fluctuations; and thirdly, that selegiline, with or without antioxidant vitamins, slows the progression of Parkinson's disease. Taking each of these postulates in turn, none has been convincingly shown to be correct.

## Levodopa treatment

*"Levodopa treatment may accelerate the degenerative process in the brains of patients with Parkinson's disease."*

This concern has been articulated by investigators who are proponents of the auto-oxidation theory of Parkinson's disease. Studies with animals or with systems in vitro can be used to support either side of this hypothesis. Perry *et al*[2] who were among the first to suggest that increased dopamine turnover may damage dopaminergic nerves, were unable to show changes in nigral cell counts or in contents of dopamine, dopamine metabolites, or in levels of tyrosine hydroxylase in rats fed maximally tolerated doses of levodopa and carbidopa for 120 days. Studies with mice given levodopa for 18 months also failed to demonstrate nigrostriatal toxicity.[3]

The possibility that levodopa therapy might damage nigral neurons that are already degenerating has been addressed by Blunt, Jenner, and Marsden,[4] who studied the effects of administration of for 27 weeks levodopa/carbidopa to rats that had received unilateral 6-hydroxydopamine lesions in the medial forebrain bundle six to seven weeks before. Although levodopa treatment produced no change on the intact side, on the lesioned side there was a levodopa-produced reduction in the number of remaining tyrosine hydroxylase positive cells in the ventral tegmental area.

Human postmortem studies have not resolved this issue. Yahr *et al*,[5] in the brains of parkinsonian patients treated with levodopa for one to 27 months, found pathological changes that were no different from changes in untreated patients. The case report of Quinn *et al*[6] demonstrated that four years of treatment with levodopa at a usual dose of 1·5 g daily did not damage substantia nigra or locus coeruleus neurons in a patient whose parkinsonian symptoms were attributed to striatal vascular disease.

Diamond *et al*[7] analysed the mortality data of 359 parkinsonian patients in regard to the duration of disease and the time of initiation of levodopa therapy. They concluded that patients started on levodopa within three years of onset of symptoms had a significantly better life expectancy than did patients for whom levodopa was not started for four or more years. Not only did early-treated patients have less mortality, but their increasing disability with age paralleled the rate of disability increase in late-treated groups.[8] Thus there seems to be a beneficial effect of levodopa both in early as well as late years. Diamond *et al* conclude that the main benefit of early levodopa treatment is to keep the patient active, which helps prolong the patient's life. Certainly their data and those of Blin, Bonnet, and Agid[9] do not suggest that early levodopa therapy accelerates the progression of Parkinson's disease.

*"Dopamine agonists should be used with levodopa to reduce subsequent side effects."*

The study of Rinne[10 11] is widely quoted as showing that early treatment with bromocriptine prevents clinical fluctuations attributed to levodopa. This study was, however, designed in an unusual way, making it difficult to know whether comparisons among groups are justified. Seventy-six patients who had not been previously treated were placed on bromocriptine. Forty-two of them did not have an adequate clinical response, so levodopa was added. During the five-year period, of these 76 patients, 71 withdrew from bromocriptine, usually because of lack of benefit or because of side effects. Only five patients remained on bromocriptine alone. The 25 patients on early levodopa plus bromocriptine were compared, presumably retrospectively, with 196 other patients who had been on levodopa alone and followed for five years. The study was neither randomised nor blinded. There were undoubtedly patient differences among the groups, with a higher proportion of severely affected patients in the levodopa-alone group. It is therefore difficult to accept the claim that the much higher incidence of dyskinesias (63% compared with 24%) in the levodopa group was due solely to the lack of treatment with bromocriptine.

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Most clinical trials with dopamine agonists have been of short duration and have shown only modest benefit of adding the agonist to levodopa. A large trial with dopamine agonist therapy was recently completed.[12-16] This five-year multicentre Japanese study was randomised but not blinded. There were 182 collaborating departments. Investigators followed 702 patients on bromocriptine alone (group 1), on bromocriptine plus levodopa (group 2A), or on levodopa alone (group 2B). Group 1 patients (n = 286) had not been treated previously with levodopa or had not taken levodopa for at least one year. Group 2 patients (n = 416) had been taking levodopa for up to five years and most were having problems such as dyskinesias, wearing-off, or on-off episodes. Although the group 2 patients were randomly allocated to the A or B subgroup, the study was not blinded. Moreover there were differences between these groups in the proportions of patients with various problems. The most recent report of this study suggests that there was little difference in levodopa efficacy between groups 2A and 2B. There were fewer side effects in the combined group, although one patient died of pulmonary fibrosis. Because of the absence of study blinding, the large number of collaborators, and the large number of study dropouts (46% in the combined group, 38% in the levodopa group), firm conclusions are difficult to draw. Of the patients begun on bromocriptine alone, only 78 of the 286 enrolled patients (45% of those continuing on the study) remained on bromocriptine alone, and this number was less than the number of patients for which levodopa was added.

Another large, randomised, controlled but unblinded study comparing levodopa (plus benzerazide) to levodopa plus bromocriptine (prado: *pra*videl + *do*pa) was terminated because of a higher mortality in the levodopa group.[17] There were 18 deaths in that group of 302 patients and eight deaths in the 285 patients taking bromocriptine plus levodopa. The deaths occurred after seven to 47 months of treatment. There were about the same number of myocardial infarctions or sudden cardiac deaths in each group, but the levodopa group had more cases of death due to cardiovascular failure and pulmonary embolism. Almost half the patients in this study dropped out, more often due to ineffectiveness of therapy in the levodopa group and to side effects in the combined group. The recommendation of this group to use combination therapy from the beginning are difficult to accept as differences in mortality were not reported in the Japanese study.

Recently, Weiner *et al*[18] conducted a small (22 patients), double-blind, randomised prospective study comparing patients on bromocriptine alone (group 1), carbidopa/levodopa (group 2) and combination therapy (group 3). Patients were followed up to 48 months. Group 1 patients had a mean illness duration of 34 months which was longer than that in the other two groups (group 2:11·6 months, group 3:13·9 months). The difference among groups was accounted for by inclusion of one patient who had had Parkinson's disease for 105 months. The study suggested that levodopa monotherapy is *more* effective than combination therapy and that early combination with bromocriptine does not prevent or delay the onset of motor fluctuations or dyskinesias in Parkinson's disease. If this study is correct, the rationale for early addition of a dopamine agonist to levodopa disappears. Of interest is the authors' comment that the study was part of a much larger multicentre trial. One hopes that the results of this study will be reported.

*"Selegiline with or without antioxidant vitamins, slows the progression of Parkinson's disease."*

Studies with selegiline in levodopa-naive patients have been interpreted by the investigators to show a slowing in the progression of Parkinson's disease. The DATATOP study[19 20] and the smaller study of Tetrud and Langston[21] did show that patients taking selegiline took longer to require levodopa than did placebo controls. Both studies were randomised and blinded. Questions about the possibility of the results being due to symptomatic improvement have not yet been agreed upon. Schulzer, Mak, and Calne[22] analysed the DATATOP results and estimated hazard functions from the published Kaplan-Meier curves. They concluded that the action of selegiline is transient and symptomatic and is not likely to be neuroprotective. There seems little doubt that Parkinson's disease continues to progress despite selegiline treatment. Elizan *et al*[23] treated 22 patients with selegiline alone. Seventeen of 22 patients (77%) were found to have worsening of their symptoms an average of 10·8 months from the start of selegiline therapy.

In another study,[24] the same investigators followed 200 patients who had been receiving levodopa therapy for eight years. Selegiline did improve parkinsonian symptoms during the first 6—24 months, but the improvement was not maintained. Baronti *et al*[25] also showed that selegiline improved the antiparkinsonian action of levodopa while also prolonging dyskinesias. There were no measurable alterations in available indices of free radical activity. A recent randomised, non-blinded multicentre United Kingdom study showed no difference in disability in early parkinsonian patients treated with levodopa alone or in combination with selegiline.[26]

*Vitamin therapy*

Although theoretically, vitamins C and E have antioxidant effects that might alter the prognosis of Parkinson's disease, the DATATOP study showed no difference in rates of symptom progression among patients on or off vitamin E.

## Conclusions

From the above considerations, there does not appear to be strong evidence to support the early use of multiple medications in patients with Parkinson's disease. Another reason to be cautious is the observation that such patients may develop a variety of side effects due to medications. The patient with visual hallucinations, confusion, or postural hypotension may be a difficult management problem. If the patient is taking amantadine, trihexyphenidyl, bromocriptine, selegiline, and levodopa/carbidopa, which drug should be reduced? A reasonable strategy is to reduce or stop the agents that are of least benefit to the patient. This implies that levodopa/carbidopa should be the last drug to be tapered.

Lieberman *et al*[27] stated that bromocriptine is "most useful in patients whose response to levodopa has diminished, and in whom attempts to increase or decrease the dose of levodopa were unsuccessful." This approach might also be applied to the other available antiparkinsonian medications. In epilepsy, many patients are treated with several anticonvulsant agents simultaneously. Studies in which the number of drugs has been reduced have usually shown that adequate amounts of one agent are as effective as multiple drugs.[28 29]

I suggest that the patient with Parkinson's disease might be managed more like the patient with a seizure disorder. If a patient is doing poorly with levodopa/carbidopa, consider the other agents as adjuncts. Rather than adding drug after drug to the regimen, consider sub-

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stituting one second line agent for another if the first loses its effectiveness. Drugs that are most easily managed such as amantadine or selegiline might be the first to be considered. Drugs that must be titrated upward would be reserved for those patients in whom treatment remains unsatisfactory.

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# NEUROLOGICAL STAMP

## Pierre Fidèle Bretonneau 1778–1862

Pierre Bretonneau established typhoid fever as a specific entity. He used the term "dothienenteritis", which was later replaced by the simple term typhoid. His more permanent place in history was assured by his observations on diphtheria which he began studying in 1818. The disease became epidemic and in 1821 he gave it its present name. The term was derived from the Greek *diphthera*, meaning a piece of hide or leather, as the condition was characterised by the formation of a membrane over the mucosa of the throat.

The paralysis associated with diphtheria had been observed by others some 70 years earlier. The classic account of the pathology of diphtheritic neuritis was written later by Meyer in 1881. The finding of conduction block in experimental diphtheritic neuropathy had to wait until Professor Ian McDonald's doctoral thesis in 1962, and subsequent publication in *Brain* in 1963.

Bretonneau performed the first successful tracheostomy in croup and laryngeal diphtheria in 1825. He proposed a germ theory for disease some 20 years before Pasteur.

In 1962 on the centenary of his death, his image appeared on a stamp issued by France (Stanley Gibbons 1561, Scott 1022).

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