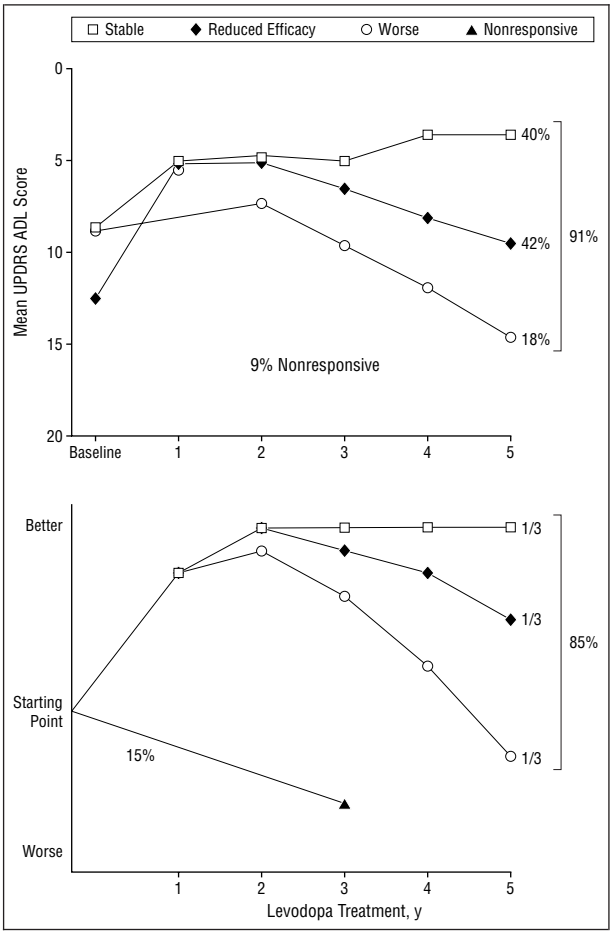
Levodopa-Treated Parkinson Disease Has Better Long-term Outcome Than Previously Predicted

The recent article by Dr Stanley Fahn[1] well describes the importance of a controlled clinical trial to determine the effect of levodopa on Parkinson disease (PD). The frequency of adverse motor events ("wearing-off," "on-off," and dyskinesias) is not well established. Fahn states that after 5 years of levodopa treatment, 75% of patients no longer have a smooth, stable, and effective response.[1] However, his estimate is based on a sample that included many patients who had used levodopa for more than 5 years (10-15 years, 37% of patients; >15 years, 8% of patients).[2]

Perhaps the best known and most often quoted description of long-term response to levodopa was published by Marsden and Parkes[3] in 1977. They reported that 85% of their patients initially responded to levodopa. They estimated that only a third retained the initial benefit after 5 years, a third had lost some benefit but were still better than they were before starting levodopa therapy, and a third were worse than when they began therapy. It is commonly held that about half of patients with PD develop motor fluctuations within 5 years of beginning levodopa therapy.

We participated in a placebo-controlled trial[4,5] comparing immediate-release (Sinemet 25/100; DuPont Merck Pharmaceutical Co, Wilmington, Del) and controlled-release (Sinemet CR 50/200; DuPont Merck Pharmaceutical Co) carbidopa-levodopa therapy over 5 years in 618 levodopa-naive patients (CR FIRST [Controlled-Release Five-Year International Response Fluctuation Study]). The Unified Parkinson's Disease Rating Scale (UPDRS) was administered during the trial to assess efficacy. To characterize the long-term outcome of levodopa therapy, we reexamined the UPDRS activities of daily living (ADL) scores recorded at the end of 5 years of treatment. To compare the outcome of levodopa therapy with that reported by Marsden and Parkes,[3] we operationally defined *stable* as an improvement in ADL of 4 points or more from baseline, *worse* as worsening of 4 points or more, and *reduced efficacy* as a difference of 3 points or less. Fewer of our subjects (18% in the controlled-release group and 20% in the immediate-release group) were worse after 5 years (Marsden and Parkes, one third) (**Figure**). The initial levodopa benefit was maintained (stable) throughout the 5-year study period in 33% of our patients in the immediate-release group and 40% in the controlled-released group. Some of the initial benefit was lost (reduced efficacy) in 47% of patients in the immediate-release group and 42% in the controlled-release group. Based on an initial improvement in ADL scores, a somewhat higher proportion of our patients were responsive to levodopa (87% of patients in the immediate-release group and 91% in the controlled-release group as compared with 85% reported by Marsden and Parkes).

Onset of motor fluctuations was determined by patient diary of motor function and questionnaire; these results were reported previously.[4,5] As defined by the patient diary, the *time to onset of motor fluctuations* was the time until the earlier of 2 consecutive clinic visits when more than 20% of the day was "off" or more than 10% of the day was "on with dyskinesias." At the end of 5 years of treatment, by patient diary, 20.6% of patients in the



Outcomes after 5 years of treatment with levodopa in 2 studies. Top, CR FIRST (Controlled-Release Five-Year International Response Fluctuation Study).[4,5] Controlled-release carbidopa-levodopa (Sinemet CR 50/200) was used. Mean Unified Parkinson's Disease Rating Scale (UPDRS) activities of daily living (ADL) scores are shown throughout 5 years of therapy. Nine percent of patients did not show an initial response to therapy and are not included. Of those patients who did respond, 40% maintained the initial benefit (stable), 42% lost some of the initial benefit (reduced efficacy), and 18% were worse than before starting treatment (worse). Bottom, Marsden and Parkes.[3] Of the patients in the study, 85% showed an initial response to therapy, while 15% were nonresponsive and underwent deterioration or died. Of those who did respond, one third held their initial improvement (stable), one third lost some of the benefit (reduced efficacy), and one third were worse than before starting therapy (worse) (adapted from Marsden and Parkes[3]).

immediate-release group and 21.8% in the controlled-release group had motor fluctuations. Only 16% in each group had fluctuations according to the questionnaire. There were no significant differences in motor fluctuations between the 2 treatment groups by either diary or questionnaire.

In contrast to the retrospective accounting of Marsden and Parkes[3] and of Fahn,[1,2] our prospective data are more encouraging. These results show that most patients can be well treated with levodopa therapy, without adjunctive dopamine agonists, throughout a 5-year period. More than 80% of patients had ADL scores at or above baseline after 5 years of treatment, and only about 20% experienced motor fluctuations. These results show a substantially better outcome than previously reported by Fahn or by Marsden and Parkes and demonstrate a long-term, effective response to levodopa. Reasonable clinicians may disagree as to whether the definitions of *off* and *on with dyskinesia* used in the CR FIRST study are too strict or too lenient. Regardless, the findings we report based on patient diaries and examiner confirmation in a prospective fashion are believed to describe the outcome of long-term levodopa treatment more accurately than retrospective observations based solely on patient reporting.

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Chronic Cryptogenic Sensory Polyneuropathy

We read with great interest the article by Wolfe and colleagues[1] on chronic cryptogenic sensory polyneuropathy (CSPN) and their conclusion on the clinical and laboratory characteristics of the disease. The authors provided an extensive overview on their large series of patients with CSPN. However, we have some questions about the criteria recommended to define the diagnosis. Sensory symptoms were mandatory, and minimal weakness or atrophy in muscle supplying toes and fingers was allowable, while patients with symptoms of weakness were excluded. Tendon hyporeflexia was not mandatory. Nerve conduction studies should show the predominant impairment of sensory fibers, but motor involvement was also allowed. The authors identified 93 patients who had positive and/or negative sensory disturbances and met the diagnostic criteria for CSPN. Consistent with the proposed criteria, no one complained of motor symptoms, although 41% showed distal weakness and 15% had muscle atrophy of lower or even upper extremities. Results of electrodiagnostic studies revealed decreased compound muscle action potential (CMAP) amplitude and motor conduction velocity in the lower extremities in more than 50% of patients and in the upper extremities in about 8% of patients. Surprisingly, increased ulnar motor distal latency and decreased conduction velocity were found in 20.8% and 8.3% of cases, respectively. Similarly, the median motor distal latency was abnormal in 17.6% of patients and conduction velocity was impaired in 20.3% of cases. Results of electromyography were abnormal in 70% of patients.

Although we agree with the authors that CSPN needs to be ascertained by means of both clinical and neurophysiological, and in some instances neuropathological, examinations, we believe that the diagnosis should be defined according to the results of all these investigations. Patients with chronic peripheral neuropathy frequently complain only of sensory disturbances, while motor involvement is usually observed by the physician. Therefore, striking discrepancies between symptoms, clinical findings, and results of neurophysiological tests can occur, even in chronic inflammatory demyelinating polyneuropathy.

Predominantly sensory axonal neuropathies, either idiopathic or secondary, represent an intriguing subgroup of peripheral neuropathies that can be classified not only by the involvement of different fiber classes (large or small diameter) but also by the site where the disease primarily occurs (axonopathies or ganglionopathies). We believe that clear-cut clinical and neurophysiological findings are needed to define the diagnosis. Unfortunately, a consensus on the criteria is not yet available. Although in sensory axonal neuropathies and, occasionally, even in ganglionopathies,[2] subclinical motor involvement can be found, these abnormalities are usually restricted to mild decrease of CMAP amplitude in individual nerves of the lower extremities and minimal denervation revealed on electromyography in distal muscles. Conversely, when motor conduction velocities also are decreased, we believe that the diagnosis should be of sensorimotor polyneuropathy, despite the absence of symptoms of weakness. Furthermore, if motor distal latencies are increased, particularly in the upper extremities, and there is no evidence of entrapment mononeuropathies, an F-wave study should be performed to definitely rule out a demyelinating neuropathy. In a recent study, Notermans et al[3] reported that 21 of 75 patients with idiopathic axonal neuropathy had predominant sensory involvement on both clinical and neurophysiological grounds. All of them had normal strength according to the Medical Research Council gradient score, while subclinical motor

electrophysiological abnormalities, which were found in most cases, were limited to decreased CMAP amplitude and presence of fibrillations on electromyography. However, in only 62% of the patients, neuropathy remained sensory at a 5-year follow-up. A similar trend was observed by Wolfe and coworkers.

Wolfe and colleagues focused on an important topic and also provided interesting data on the therapeutic approach to painful neuropathies. Although sensory cryptogenic axonal neuropathies are somewhat less common than sensorimotor neuropathies, they should be fully characterized to help provide clues to localize the likely site of disease. Indeed, obtaining skin biopsy specimens is a useful tool for the diagnosis and the follow-up of small-fiber sensory neuropathies[4]; frequently, nerve conduction studies do not show abnormalities and tendon reflexes are retained. In addition, T2-weighted magnetic resonance imaging can detect signal abnormalities in the posterior columns of the spinal cord consistent with the impairment of the central sensory projections in ganglionopathies.[2] Therefore, we believe that narrow clinical and neurophysiological criteria should be recommended, particularly in follow-up studies, to address the diagnosis of CSPN.

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In reply

We read with interest the comments of Lauria et al about our article describing the clinical features of chronic cryptogenic sensory polyneuropathy (CSPN).[1] In our experience and from the accounts of colleagues, cryptogenic sensory-predominant polyneuropathy is a common clinical problem found in neuropathy centers, typically presenting in the sixth to seventh decade of the patient's life.[2] These unclassified neuropathies have received limited attention in the literature, and we welcome the opportunity to discuss them further.

Classifying neuropathies, whether from a diagnostic or semantic standpoint, is often difficult, and developing a consensus on the terminology and classification of cryptogenic or idiopathic neuropathies is particularly challenging. While Lauria et al present valid points that highlight certain shortcomings in our term CSPN, *we have chosen this term because it focuses attention on the principal clinical features of these patients. Sensory symptoms and signs predominate and are the main causes of disability in CSPN, whether from refractory neuropathic pain or gait instability. In our experience, these patients rarely have significant motor weakness, and we based our criteria for motor involvement on these observations. Although patients were excluded if they presented with motor symptoms, we allowed for mild distal weakness on examination in foot or hand intrinsic muscles. One reason for this approach is that the decision whether mild distal weakness or atrophy is present, especially in toe extensors and flexors, is often equivocal and will vary between examiners.*

From an electrophysiological standpoint, we have found motor nerve involvement in a majority of patients, including those who exhibit pure sensory neuropathy on examination. These findings are in agreement with the limited data from other studies showing that results of electromyography or motor nerve conduction studies are abnormal in 50% or more of patients with idiopathic sensory neuropathy who have no or minimal weakness.[3,4] As in our study, Notermans et al[5] defined neuropathies *as sensory or sensorimotor based on clinical grounds. In their follow-up study,[6] 7 (25%) of 28 patients with sensory neuropathy on entry developed sensorimotor neuropathy within 5 years. Of the remaining 21 who had pure sensory neuropathy on examination, 13 (62%) had subclinical motor electrophysiological abnormalities. In addition,[3,6] these studies have not found mild degrees of motor involvement to reflect fundamental clinical differences or portend a significantly worse prognosis, providing further reason not to separate these patients from those who exhibit pure sensory neuropathy. Finally, we would like to reiterate that distal latencies, conduction velocities, and F waves did not satisfy demyelinating criteria in our population with CSPN.*

We have found the term CSPN *to be a simple, convenient moniker emphasizing the sensory impairment that predominates in this large group of patients. In an attempt to be inclusive and simplify the identification of these patients, our diagnostic criteria do not exclude patients with mild or subclinical motor involvement, whether on neurologic examination or electrophysiologic testing.*

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