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Nicotine may relieve symptoms of Parkinson's disease

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Abstract. Two elderly patients with Parkinson's disease were treated with nicotine gum and patch. Reliable changes in symptomatology were noted, using a single-subject, placebo-control reversal design. Improvement was associated with active nicotine dosing and involved diminished tremor and disorganized thinking in one patient and diminished bradykinesia and increased energy in the other.

Key words: Parkinson's disease – Treatment – Nicotine patch – Nicotine gum

A negative relationship between Parkinson's disease (PD) and tobacco smoking has frequently been noted (Baron 1986). Of particular relevance to the neuropathology of PD is that through its effects on cholinergic pathways, nicotine – the psychoactive constituent in tobacco – modulates dopamine (DA) activity by exerting an excitatory action at the level of DA nerve cells in the substantia nigra (Lichtensteiger et al. 1982). Several investigators have noted that repeated administration of nicotine leads to potentiation of mesolimbic DA secretion as well as to enhanced locomotor responsivity in animals (Kita et al. 1992), and chronic nicotine dosing has been shown to protect against degeneration of central DA neurons induced by mechanical lesions (Fuxe et al. 1991). Despite encouraging results in a 1926 case study by Moll (1926), in which post-encephalitic parkinsonism patients were treated with nicotine, we are not aware of other reports on the use of nicotine in the management of PD. Below, we describe the clinical response to nicotine in two PD patients.

Case 1

The first patient, a never-smoker, was a 69-year-old woman exhibiting predominantly dystonic PD symptoms. During the 15-month therapeutic period, the patient received Disipal (orphenadine, 50 mg 5 times/day). (L-Dopa had been administered shortly after the initial diagnosis but with little effect, suggesting atypical PD.)

The patient was treated in an open trial with nicotine polacrilex (Nicorette gum) for 7 months. As she had evinced considerable benefit from nicotine starting from the second month of nicotine use, she was asked to serve as a research subject. To elucidate more precisely the role of nicotine, a double-blind (patient, rater, and dispenser blind to conditions), placebo-controlled dose-reversal study was initiated.

Phase A. Eight pieces of 4 mg polacrilex gum/day (each piece yielded about 1.5 mg nicotine) for 5 days.

Phase B. Nicotine 15 mg per day via 16-h transdermal patch over the next 7 days.

Phase C. Placebo patch treatment (nicotine washout) for 7 days.

Phase D. Nicotine 15 mg patch treatment for a final 7 days.

The patient and an observer (patient's son) rated tremor, rigidity, sleep, and disorganized thinking over the 26-day trial; the ratings shown in Fig. 1 are means of assessments of symptoms.

Clinical benefits included decreased tremor, less muscular rigidity, and a reduction in disorganized thinking; sleep was much improved due to a reduction in dystonic movements. As can be seen, introduction of placebo was associated with deterioration on all symptom measures (Student's-test; $P<0.01$), and return to active patch was associated with restoration of benefits (Student's-test; $P>0.01$). After completion of the experimental manipulations, the patient was maintained on a regimen of 15 mg patch plus four pieces of 4 mg gum per day, resulting in a plasma level of cotinine (a nicotine metabolite with a half-life of app. 20 h) of 525 ng/ml, a level comparable

Commercial development of this approach is under consideration

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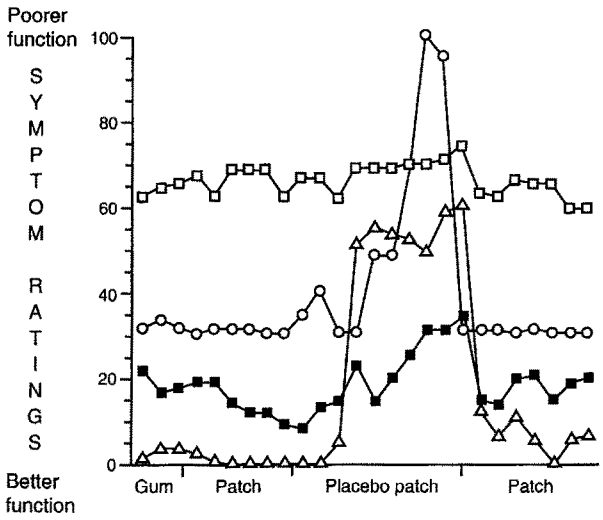

Fig. 1. Daily symptom ratings during exposure to different nicotine-dosing vehicles. □, rigidity; ○, sleep; ■, tremor; △, disorganised thinking

to that of a heavy cigarette smoker. Fifteen months after the experimental manipulations (23 months from the beginning of nicotine therapy), the patient and her son both indicate that the improvements have been sustained.

Case 2

The second patient, a former smoker, was a 64-year-old man exhibiting characteristic features of PD, including muscular rigidity, masked facies, blurred speech, and illegible handwriting; while no resting tremor was evident at the time he was first seen, motor activity was slowed (bradykinesia) and rocking movements were evident several times a minute when the patient was sitting (dystonia was attributed to PD therapy). During the 8-month treatment period, the patient took Sinemet (carbidopa[levodopa] 25/100 t.i.d.) and Eldepryl (MAO-B inhibitor[selegiline] 5 mg b.i.d.).

At the time of the first visit, the patient's self-rated level of global function (pre-morbid level defined as 100%) had declined to 20%, down precipitously from a high of nearly 100% when he first started taking Eldepryl (5 years before) and Sinemet (6 years before). The patient reported that in order to avoid bradykinesia later in the day, he now required a nap of 4–5 h each afternoon (added to his usual 5–6 h of regular sleep).

Nicotine treatment was initiated using 16-h nicotine patches, and dosing was supplemented by the addition of nicotine polacrilex a month later. With the exception of a transient problem with more frequent awakenings at night (which was managed by taking off one of the patches a few hours before bedtime), there were no notable adverse events. To evaluate the therapeutic effects of nicotine, a double-blind (patient and raters blind to the conditions), placebo-controlled reversal design was used:

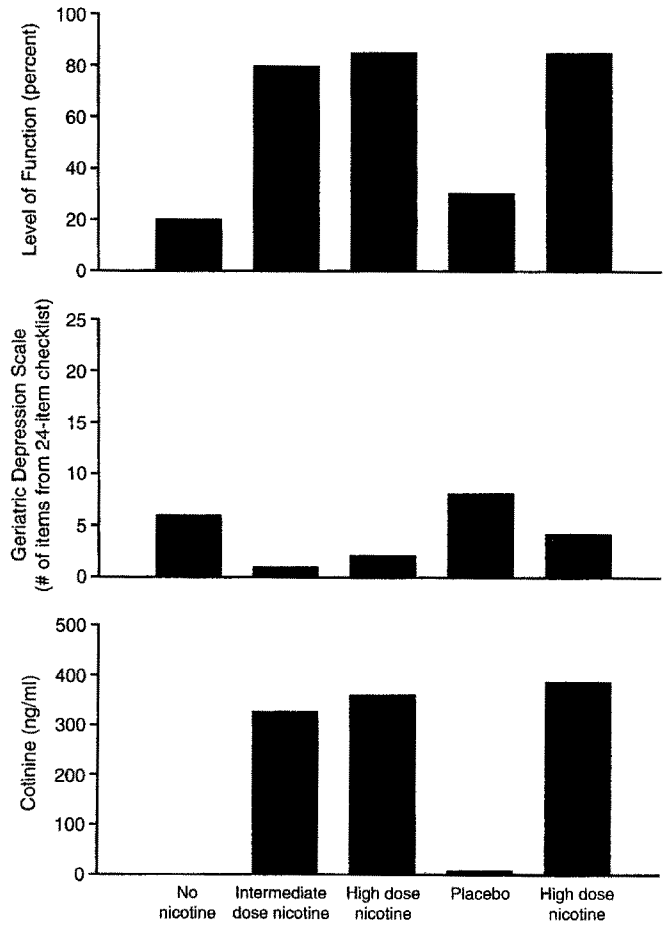

Fig. 2. Level of function, depressive mood, and cotinine level after exposure to different nicotine dosages

Condition A. No nicotine (baseline prior to nicotine dosing).

Condition B. Maximum of 20 mg patch plus six pieces of 4 mg gum (distributed throughout the day) over 11 weeks.

Condition C. 20 mg patch plus up to 11 pieces of 4 mg gum (distributed throughout the day) over 4 weeks.

Condition D. Placebo patch and placebo gum (nicotine washout) over 2 weeks.

Condition E. Maximum of 35 mg patch plus up to four pieces of 4 mg gum (used only as needed) over 10 weeks.

Compared with condition A (no nicotine) by condition C (exposure to the higher nicotine dose), the patient reported more efficient sleep (feeling well rested in the morning), more energy (his afternoon nap went down to 1–2 h and was often skipped), being able to carry out various tasks with renewed satisfaction, restoration of the ability to drive an automobile, and greatly improved mood and outlook; as corroborated both by the referring neurologist (who conducted independent examinations toward the end of each condition) and the patient's wife,

speech was clearer, handwriting was improved, facial expression of emotion was restored, and dystonic movements were nearly absent. Return to nicotine dosing in condition E (second exposure to high nicotine), restored function lost in condition D (nicotine wash out), through it took nearly 2 months to get back fully to the levels observed in condition C.

As can be seen in Fig. 2, the patient's self-rating of overall function was directly related to cotinine levels which, in turn, were proportional to the nicotine dosage administered. Scores on the Geriatric Depression Scale (range 0–24; cutoff-score for depression, ≥ 12) suggest that improvement shown in the two high nicotine-dose conditions involved changes in both mood and conduct of daily activities. The therapeutic response to nicotine treatment in the second patient, a former smoker, was entirely consistent with that observed in the first patient, a never-smoker.

Comment

We hope these observations will stimulate others to investigate the use of nicotine in the management of neurodegenerative disorders. In his report on the treatment of PD, Moll stated that "treatment by nicotine failed to give any permanent cures, although the immediate results were indisputable", and concluded that "treatment should therefore be repeated at frequent intervals". In Moll's study, nicotine was administered by hypodermic injection; today, nicotine can be administered with much greater convenience and safety by patch and polacrilex gum.

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