Cannabinoids reduce levodopa-induced dyskinesia in Parkinson's disease: A pilot study

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Cannabinoids reduce levodopa-induced dyskinesia in Parkinson's disease: A pilot study

Article abstract—The lateral segment of the globus pallidus (GPl) is thought to be overactive in levodopa-induced dyskinesia in PD. Stimulation of cannabinoid receptors in the GPl reduces γ-aminobutyric acid (GABA) reuptake and enhances GABA transmission and may thus alleviate dyskinesia. In a randomized, double-blind, placebo-controlled, crossover trial (n = 7), the authors demonstrate that the cannabinoid receptor agonist nabilone significantly reduces levodopa-induced dyskinesia in PD.

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Therapeutic options for managing levodopa-induced dyskinesia in PD are limited. Nondopaminergic strategies have been proposed to reduce these dyskinetic side effects while maintaining the antiparkinsonian action of levodopa.[1] One such strategy may be the use of cannabinoids as adjuncts to levodopa.

In levodopa-induced dyskinesia, it has been suggested that the lateral globus pallidus (GPl) is overactive,[2,3] although this is not universally accepted.[4] Of interest, high levels of the cannabinoid CB_1 receptor are located, presynaptically on γ-aminobutyric acid (GABA) terminals of the striatopallidal pathway, in the globus pallidus.[5] Cannabinoid receptor stimulation enhances GABAergic transmission in the GPl by reducing GABA reuptake.[6] A potential means to reduce levodopa-induced dyskinesia might thus be to enhance GABAergic transmission in the GPl by stimulation of cannabinoid receptors.

This study aimed to assess whether the clinically available cannabinoid receptor agonist, nabilone, could reduce GABA reuptake in the GPl by activation of cannabinoid receptors and reduce levodopa-induced dyskinesia in patients with PD.

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Methods. *GABA reuptake assay.* Globus pallidus slices (400 μm) were obtained from Sprague-Dawley rats. GABA reuptake was assayed as previously described[6] by incubating slices in 0.1 μM [^{3}H]-GABA (70 Ci/mmol; New England Nuclear, Boston, MA) for 30 minutes at 20 °C. The effects on GABA reuptake of nabilone (1 to 100 μM) and the cannabinoid receptor antagonist N-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-3-pyrazolecarboxamide (SR141716A; 100 μM) were assessed.

Effect of nabilone on levodopa-induced dyskinesia in PD. Patients with a clinical diagnosis of idiopathic PD were recruited from a regional movement disorders clinic. All patients experienced stable levodopa-induced dyskinesia present for 25% to 50% of the day. Patient characteristics are shown in the table. The study was approved by the Central Manchester Ethics Committee and all patients gave informed written consent. The study was performed using a double-blind, randomized, placebo-controlled, crossover design, with two levodopa challenges performed 2 weeks apart. In one limb of the trial, the patient received nabilone and in the other, placebo.

All antiparkinsonian medication was omitted from 9 PM the night before the study. Nabilone, or placebo (0.03 mg/kg to nearest whole milligram, capsule of same color and taste) was administered in a double-blind fashion, in two split doses 12 hours and 1 hour before levodopa administration. (All assessments were made after the second dose of nabilone/placebo). Levodopa (200 mg as Madopar

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Table *Patient characteristics*

Patient age, y/sex	Duration of PD, y	Hoehn and Yahr score	Levodopa dose, mg/d	Other drugs, mg/d	Percentage reduction in total levodopa-induced dyskinesia with nabilone compared with placebo
59/M	8	3	500		Withdrawn
59/F	8	3	350	P, 2.25	62
49/F	12	4	950	P, 1.875 Apo, 25	15
60/F	8	3	375	P, 2.625	8.7
61/F	7	4	300		Withdrawn
56/M	7	3	425	P, 4.00	42
60/M	5	3	600		17.4
60/M	3	3	800	P, 3.75	6.3
69/F	10	3	575	P, 3.00	3.8

P = pergolide; Apo = apomorphine.

dispersible) was then administered in the "practically defined off state"[7] at 9 AM.

The primary outcome measure was total dyskinesia disability using the Rush Dyskinesia Disability Scale.[8] Patients were videotaped and assessment of dyskinesia performed by post-hoc video analysis, by an assessor blinded to the treatment. Dyskinesia was assessed in the practically defined off period and every 20 minutes after levodopa treatment during the on period. Total dyskinesia score was obtained by area under the curve summation. Secondary outcome measures were parkinsonian disability using the modified Webster Scale,[9] in the practically defined off state and at 20-minute intervals after levodopa. The "best-on" state was determined when the patient subjectively felt that he or she was experiencing maximal benefit from levodopa. Other measures attained included "latency," the time to reach best-on state from practically defined off state; the "duration of the on period," and percentage on-period dyskinesia. Lying and standing blood pressure was recorded and adverse effects noted.

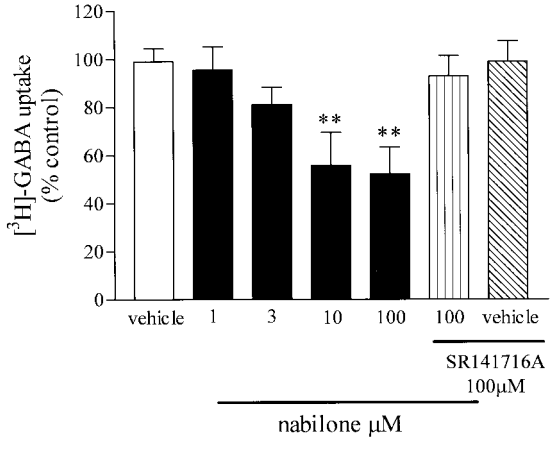

*Figure 1. Effect of nabilone on γ-aminobutyric acid (GABA) reuptake in rat globus pallidus slices. The effect of preincubation (for 40 minutes) with nabilone (1 to 100 μM) and nabilone (100 μM) with SR141716A (100 μM) on uptake of [3H]-GABA is shown in slices prepared from rat globus pallidus. Data are expressed as a mean percentage uptake ± SEM of vehicle-incubated slices. **p < 0.01 compared with vehicle, one-way analysis of variance followed by Dunnett's multiple comparisons test (n = 12 experiments, each with six to seven slices per condition from five to eight animals).*

Statistical analysis. GABA reuptake data were expressed as a percentage ± SEM of the GABA reuptake observed in the presence of the appropriate vehicle and compared using a one-way analysis of variance followed by Dunnett's multiple comparisons test. Dyskinesia disability and parkinsonian disability data were expressed as median values of total scores (and range) and compared using the Wilcoxon matched pairs test. The latency, duration, and percentage on-period dyskinesia and postural fall in systolic blood pressure data were expressed as mean ± SEM and compared using a paired *t*-test. All patients who completed the study were included in the analysis. Significance in all cases was assigned when $p < 0.05$.

Results. *GABA reuptake assay.* Nabilone caused a concentration-dependent decrease in the reuptake of [3H]-GABA (figure 1). This effect was significantly different to that in vehicle incubated slices for 10 and 100 μM (44% and 48% inhibition). The effect of 100 μM nabilone was blocked by coincubation with 100 μM SR141716A. SR141716A alone did not affect uptake compared with control.

Effect of nabilone on levodopa-induced dyskinesia in patients with PD. Nabilone significantly reduced total levodopa-induced dyskinesia compared with placebo. Thus, the median total dyskinesia score after treatment with levodopa and nabilone was 17 (range, 11 to 25), whereas after levodopa and placebo, the median total dyskinesia score was 22 (range, 16 to 26), as measured after the second dose of nabilone/placebo ($p < 0.05$, n = 7; figure 2A). The mean percentage reduction in total on-period dyskinesia after treatment with nabilone compared with placebo was 22.2% ± 8.2% (see the table). There was no difference in the duration of the on period, with a mean time of 169.6 ± 24.1 minutes after levodopa and nabilone compared with 156.7 ± 16.2 minutes with levodopa and placebo ($p > 0.05$). There was no difference in the percentage on-period dyskinesia, 98.2% ± 0.1% of the total on pe-

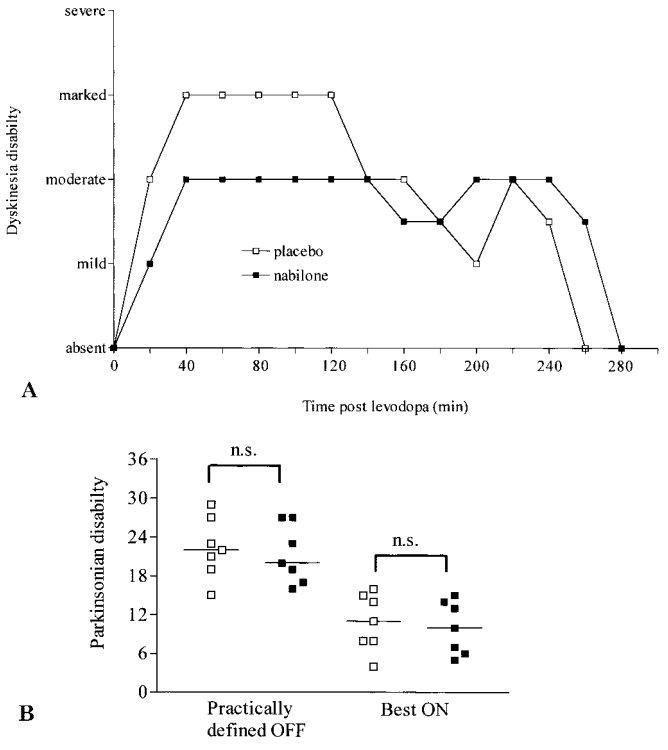

Figure 2. Effect of nabilone on levodopa-induced dyskinesia and parkinsonian disability in patients with PD. (A) Time course of levodopa-induced dyskinesia in patients with PD after administration of nabilone/placebo. Each data point represents the median dyskinesia score for the group (ranges have been removed for clarity). "Severe" represents a median score of 4, marked = 3, moderate = 2, mild = 1, absent = 0 as defined in the dyskinesia rating scale described in the text (n = 7). (B) Median parkinsonian disability after administration of nabilone/placebo in the practically defined off state and nabilone/placebo and levodopa in the best on state. Each data point represents an individual patient; the bar is the median.

riod after treatment with nabilone compared with 96.1% ± 1.7% with placebo ($p > 0.05$).

There was no difference in the Webster score in the practically defined off state (and 1 hour after nabilone/placebo administration). Thus, the median Webster score was 22 (range, 15 to 29) with nabilone compared with 20 (range, 16 to 27) with placebo (figure 2B). Two patients with painful off-period dystonia experienced symptomatic improvement of that dystonia.

Nabilone administration had no effect on the antiparkinsonian action of levodopa. The best-on scores were not significantly different, with a median score of 11 (range, 4 to 16) with levodopa and nabilone compared with 10 (range, 5 to 14) with levodopa and placebo (see figure 2B). The latency to switching on also was unchanged, with a mean time of 20.7 ± 2.5 minutes after levodopa and nabilone treatment compared with 18.3 ± 0.7 minutes with levodopa and placebo ($p > 0.05$).

All patients experienced a postural fall in systolic blood pressure in both practically defined off and best-on, but there was no significant difference between placebo and nabilone treatment. Two patients were withdrawn after nabilone treatment, one because of vertigo and the other secondary to symptomatic postural hypotension. Other adverse effects of nabilone treatment were transient and consisted of mild sedation, "floating sensation," dizziness, hyperacusis, partial disorientation, and formed visual hallucinations, and were experienced by five patients. The progress of participants through the stages of the trial is outlined in the supplemental material on the *Neurology* Web site (go to www.neurology.org and scroll down the Table of Contents to find the title link for this article).

Discussion. This study demonstrates that the cannabinoid receptor agonist nabilone can reduce GABA reuptake in the GPl and alleviate levodopa-induced dyskinesia in PD. The antiparkinsonian actions of levodopa were not reduced by nabilone. Nabilone had no antiparkinsonian action per se when assessed in the practically defined off state. The actions of SR141716A in reducing the effect of nabilone in GPl demonstrate that nabilone can stimulate cannabinoid CB_1 receptors. Although it is a matter of some debate,[4] we propose that GABA transmission is reduced in levodopa-induced dyskinesia in the GPl.[1-3] Thus, GPl is a potential site by which the aforementioned action of nabilone might have an antidyskinetic effects. However, further studies (e.g., intracerebral injections in animal models of levodopa-induced dyskinesia) will be required to resolve this issue.

These findings are in apparent contradiction to our previous reports that cannabinoid receptor antagonists have antidyskinetic actions.[2] In the absence of definitive data on the site and mechanism of action of either drug, it is difficult to resolve this paradox. However, we suggest that nabilone might act in GPl to enhance GABA transmission while SR141716A acts preferentially in the medial globus pallidus to reduce GABA transmission by blocking the actions of endogenous cannabinoids. In terms of the current model of levodopa-induced dyskinesia,[1-3] both actions would have an antidyskinetic effect.

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Motor perseveration is an early sign of Parkinson's disease

Article abstract—Perseveration in the generation of random motor behavior was examined by means of the Vienna perseverance task in groups of de novo (n = 18) and treated (n = 18) patients with early PD, and in control subjects (n = 18). In comparison with control subjects, both the de novo and treated patients with PD were relatively unable to generate random motor sequences, indicating a decreased ability to switch cortical behavioral programs in PD. An impairment of random motor generation appears to be a very early feature of PD.

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The cognitive deficit in nondemented patients with PD can be described as an inability to switch cortical behavioral programs in situations requiring the internal regulation of behavior, which leads to the perseveration of the current behavioral program. Because this type of cognitive disturbance can be found in the early phases of PD,[1] it is tempting to speculate that such cognitive disturbances may even precede the first motor deficits. In an animal model of PD, the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated monkey, cognitive disturbances are indeed present before any clear motor disturbances appear.[2] Considering the 65% loss of nigral dopaminergic neurons at the time of clinical diagnosis, as determined by means of dopamine transport SPECT,[3] a preclinical diagnosis would extend the time window available for the neuroprotective strategies that are under development.[4]

In previous studies, several tasks have been used to measure the capacity for internal guidance of behavior. Patients with PD manifest perseverative behavior on a variety of neuropsychological assessments traditionally believed to reflect frontal lobe function.[5] Most of these tasks, however, provide subjects with implicit rules and logical stimulus–response relations, whereas ideally, a task used to detect disturbances in the internal regulation of behavior would have a minimum of external cues, thereby maximizing the amount of internal (spontaneous) regulation of behavior needed to perform the task. Tasks requiring subjects to generate random behavior may be better suited to this purpose.

Most research into random behavior in PD has focused on random verbal generation of either letters[6] or numbers.[7] Because of the common use of letters and numbers in everyday life, these tasks are prone to confounding effects of prior experience with verbal or numerical tasks. A major pragmatic problem of random letter or number generation is the need to record and key the subject's response, a relatively laborious and potentially error-prone activity.

The Vienna perseverance task is a computerized version of the pointing task developed by Mittenecker and can be used to assess the ability to generate random motor behavior. Using a manual version of this task, disturbances in the generation of random motor actions have previously been found in treated patients with early PD.[8]

In the current study, the Vienna perseverance task was used to determine whether motor perseveration also is present in untreated patients with early PD. In addition, the effect of dopaminomimetic treatment on task performance was studied by comparing the de novo patients with a group of treated patients with early PD.

Methods. *Subject selection.* Groups of nondemented patients with untreated (n = 18) and treated (n = 18) idiopathic PD were selected from the outpatient clinic for movement disorders at the Vrije Universiteit Medical Center. All patients with PD were diagnosed according to the United Kingdom Parkinson's Disease Society Brain Bank criteria. Eighteen self-declared neurologically healthy subjects served as control subjects. All subjects but one of the

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