

## Caffeine in Parkinson's Disease: A Pilot Open-Label, Dose-Escalation Study

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### ABSTRACT

**Introduction:** Epidemiologic studies consistently find an inverse association between caffeine use and PD. Numerous explanations exist, but are difficult to evaluate as caffeine's symptomatic effect and tolerability in PD are unknown. **Patients and Methods:** We designed an open-label, 6-week dose-escalation study of caffeine to establish dose tolerability and evaluate potential motor/nonmotor benefits. Caffeine was started at 200 mg daily and was increased to a maximum of 1,000 mg. **Results:** Of 25 subjects, 20 tolerated 200 mg, 17 tolerated 400 mg, 7 tolerated 800 mg, and 3 tolerated 1,000 mg. The most common adverse events were gastrointestinal discomfort, anxiety, and worsening/emerging tremor. At 400 mg daily, we found potential improvements in motor manifestations and somnolence (UPDRS III:  $-4.5 \pm 4.6$ ,  $P = 0.003$ ; Epworth:  $-2.0 \pm 3.0$ ,  $P = 0.015$ ). **Conclusion:** Maximum dose tolerability for caffeine in PD appears to be 100 to 200 mg BID. We found pilot preliminary evidence that caffeine may improve some motor and non-motor aspects of PD, which must be confirmed in longer term, placebo-controlled, clinical trials. © 2011 Movement Disorder Society

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Caffeine is a widely used psychostimulant with well known effects and side effects. Epidemiological studies consistently find negative correlation between caffeine intake and PD.<sup>1–8</sup> Relative risk of PD in caffeine users is reduced by approximately 30%.<sup>8,9</sup> Many theories exist to explain this finding, including (1) direct neuroprotective effect, (2) symptomatic effect that delays diagnosis (this could be disease modifying, if early symptomatic treatment has long-term benefit),<sup>10</sup> (3) reverse causality (i.e., loss of benefit or intolerability in early presymptomatic PD), or (4) residual confounding by unknown elements.<sup>6</sup>

To assess these epidemiologic findings, it is essential to define tolerability. This information is also vital for the development of future randomized, placebo-controlled, clinical trials testing symptomatic benefit or possible disease modification. To date, there have been no published dose-finding studies for caffeine use in IPD. Therefore, the aims of this study were to establish the optimal tolerated caffeine dose in PD patients and to assess potential motor and nonmotor benefits in a pilot manner.

## Patients and Methods

### Trial Design

This was a 6-week pilot open-label, dose-escalation study to investigate tolerability and clinical effects of caffeine in PD.

### Participants

Patients were recruited from the Movement Disorders Clinic at the McGill University Health Center (MUHC), and clinical data were collected at the Montreal General Hospital. The Medical Research and Ethics Committee of MUHC approved the study, and informed consent was obtained from each subject. All idiopathic PD patients (stage I–IV Hoehn and Yahr) were eligible. Exclusion criteria included daily consumption of caffeine >200 mg per day (calculated from standardized nutrition charts),<sup>11,12</sup> dementia (defined as Mini-Mental State Examination [MMSE] <26 and activities of daily living impairment secondary to cognitive loss), active peptic ulcer disease, severe intolerance or allergy to caffeine, recent changes to antiparkinsonian medication (previous 4 weeks) or anticipated modifications during the period of the study protocol, supraventricular cardiac arrhythmia, uncontrolled hypertension, current use

of prescribed alerting agents, use of lithium or clozapine, and premenopausal women not using effective methods of birth control.

### Intervention and Study Visits

Patients were provided prepackaged dosettes containing 100- or 200-mg tablets of caffeine (Wake-Ups). Dose started at 100 mg BID (upon awakening and after lunch) and was escalated weekly in 200-mg increments (i.e., 100 mg BID) until week 5. For weeks 5 and 6, the dose remained at 1,000 mg QD. Study visits were conducted at baseline and at the end of weeks 2, 4, and 6. Additional telephone follow-up for tolerability was conducted at the end of weeks 1, 3, and 5. Patients were instructed to take whatever caffeine-containing beverages they were accustomed to taking (all took <200 mg daily), without changing habitual schedule. One examiner (R.D.A.) performed baseline and all subsequent evaluations. All subjects were examined in the ON-medication state within  $2 \pm 1$  hours of last caffeine dose.

Adverse events were systematically recorded, and if a subject experienced a dose-limiting effect (defined either as any side effect with severity  $>2$  on the National Cancer Institute Scale or patient perception of intolerability),<sup>13</sup> caffeine was stopped and study evaluations were terminated.

### Outcomes

Maximal tolerated dose was defined as the last dose before experiencing a limiting adverse effect. Secondary outcomes were evaluated at every clinic visit and included the following: UPDRS I-IV,<sup>14</sup> Timed “Up and Go” (TUG),<sup>15</sup> Epworth Sleepiness Scale (ESS),<sup>16</sup> Fatigue Severity Score (FSS),<sup>17</sup> Pittsburgh Sleep Quality Index (PSQI),<sup>18</sup> Beck Depression Inventory (BDI),<sup>19</sup> Beck Anxiety Inventory (BAI),<sup>20</sup> Parkinson’s Disease Questionnaire—39 items (PDQ-39),<sup>21</sup> and the Clinical Global Impression of Improvement (CGI-I),<sup>22</sup> with overall PD severity as the target symptom.

### Analysis

The primary outcome used for power calculations was the prevalence of dose-limiting side effects. For sample-size estimation purposes, the study was powered to detect a prevalence of dose-limiting side effects of  $>0.30$  with 95% confidence. Assuming  $\alpha = 0.05$ , power = 80%, and predicted tolerability = 0.9, this study had the power to detect a probability of dose-limiting adverse effects of  $>0.30$  with 24 patients. Potential predictors of caffeine intolerance were assessed with Spearman correlation analysis. All secondary outcome analyses were analyzed with the Wilcoxon signed ranks test, when comparing each dose to baseline values. For secondary variables, analysis was per protocol.

**Table 1.** Baseline Subject Characteristics

Scale	Mean $\pm$ SD (n = 25)
Daily caffeine intake (mg)	90.8 $\pm$ 69.10
UPDRS total	43.72 $\pm$ 17.57
UPDRS III	27.96 $\pm$ 11.52
Resting Tremor (from UPDRS part III)	2.44 $\pm$ 3.21
PDQ 39 total	30.12 $\pm$ 20.48
PDQ 39—mobility subscore	8.90 $\pm$ 9.31
Timed “Up and Go” (seconds)	10.39 $\pm$ 3.04
Epworth Sleepiness Scale (ESS)	6.76 $\pm$ 4.25
PSQI overall	17.40 $\pm$ 7.58
Beck Depression Inventory	9.06 $\pm$ 6.39
Beck Anxiety Inventory	15.72 $\pm$ 11.30
Fatigue Severity Score	35.72 $\pm$ 12.47
Dyskinesia (UPDRS part IV)	0.56 $\pm$ 1.12
Fluctuations (UPDRS part IV)	1.92 $\pm$ 1.73

Subject baseline characteristics. UPDRS, Unified Parkinson’s Disease Rating Scale; PDQ, Parkinson’s Disease Questionnaire; PSQI, Pittsburgh Sleep Quality Index.

## Results

### Subject Characteristics

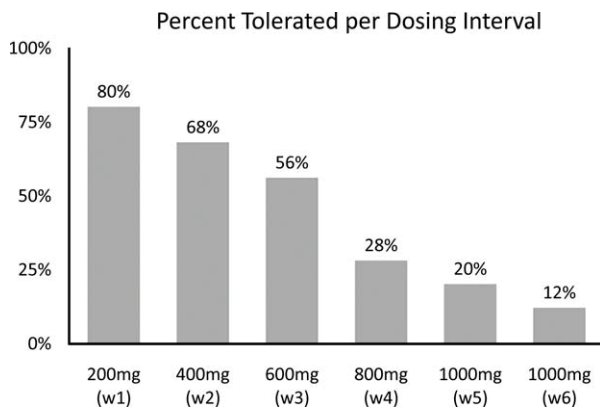
A total of 48 patients with IPD were screened during the recruitment phase between August and December 2010. Twenty-five subjects enrolled and none withdrew for reasons other than adverse effects or 6-week study completion (Supporting Fig. 1). Mean age was  $65.5 \pm 9$  years (range = 42–80), baseline caffeine consumption was  $90.8 \pm 69$  mg/day, disease duration was  $4.6 \pm 3.6$  years (range, 0.5–12 years), and L-dopa dose was  $679 \pm 259$  mg/day (range, 300–1,170). Remaining baseline subject characteristics are shown in Table 1. Twenty patients were on dopamine therapy (11 on levodopa [L-dopa] alone, 9 on L-dopa plus dopamine agonist). Thirteen took monoamine oxidase inhibitors and 2 were on no PD medications.

### Tolerability

Three patients (12%) completed the full 6-week trial, with remaining subjects withdrawing because of adverse effects. Median tolerated dose was 200 mg BID. Twenty (80%) patients tolerated 100 mg BID, 17 (68%) tolerated 200 mg BID, 14 (56%) tolerated 300 mg BID, 7 (28%) tolerated 400 mg BID, and 3 tolerated 500 mg BID (Fig. 1). The principal reasons for intolerability were nausea, dyspepsia, and malaise. Worsening parkinsonian and emerging or enhanced physiologic tremors, anxiety, and insomnia were the next bothersome side effects prompting cessation. On correlation analysis, only female sex predicted lower tolerability of caffeine (Spearman correlation coefficient = 0.550;  $P = 0.04$ ).

### Secondary Outcomes: Motor And Nonmotor Effects

For those who tolerated 200 mg BID of caffeine, there was improvement in total UPDRS ( $-7.2 \pm 5.6$ ;



**FIG. 1.** Tolerability per dosing interval. Illustrated is the percent tolerated at specified dosing interval. Dose listed as total daily milligrams of caffeine tablets. During trial, caffeine was administered in BID dosing. w denotes week of trial.

$P = 0.001$ ), UPDRS II ( $-1.8 \pm 2.74$ ;  $P = 0.02$ ), UPDRS III ( $-4.5 \pm 4.6$ ;  $P = 0.003$ ), and the PDQ-39 mobility dimension ( $-2.8 \pm 3.4$ ;  $P = 0.01$ ) (Supporting Table 1). Parkinsonian resting tremor diminished significantly over the first 2 weeks of the study ( $-1.18 \pm 2.4$ ;  $P = 0.01$ ). There was also significant improvement in PDQ-39 ( $-5.2 \pm 8.1$ ;  $P = 0.02$ ) and daytime sleepiness (Epworth Sleepiness Scale:  $-1.98 \pm 2.98$ ;  $P = 0.02$ ). Despite concerns that caffeine might worsen sleep quality, overall sleep measures improved (PSQI score:  $-3.8 \pm 6.6$ ;  $P = 0.02$ ), without worsening on any subscales. There were no significant changes in anxiety and depression scores. Clinical global overall impression of change (physician rated) improved at week 2 ( $0.74 \pm 0.66$ ;  $P = 0.02$ ). Supporting Table 2 demonstrates baseline differences between subgroups.

## Discussion

In this open-label, dose-escalation study, we found that maximal tolerability of caffeine in PD patients was between 200 and 400 mg daily. Higher doses of caffeine appear to be poorly tolerated. We found potential benefits of caffeine on motor manifestations, sleep quality, and measures of daytime sleepiness, which need to be confirmed in definitive randomized trials.

### Tolerability

To proceed with any large-scale testing of caffeine in PD, it is essential to define tolerability. We found that 80% of patients tolerated 200 mg per day and 68% tolerated 400 mg per day, with substantial decreases in tolerability at higher doses. No subjects cited worsening dyskinesia, motor fluctuations, dystonia, or other off phenomena as reasons for termination. Other than female sex, we were unable to identify PD patients at risk of intolerability (e.g., baseline anxiety, caffeine use, age, etc.); therefore, future studies may be unable to improve tolerability by excluding subgroups. The 32% drop-out rate suggests

that 400 mg may be too poorly tolerated for clinical trials. However, it should be noted that the dose escalation in our study was relatively quick (200 mg weekly), faster than new coffee drinkers may increase intake. Also, because they were enrolled in a clinical tolerability study, patients may have been more vigilant for side effects than if taking caffeinated beverages on a day-to-day basis. In future studies, slower dose escalation or further dividing of doses (e.g., TID) may improve tolerability.

### Motor and Nonmotor Effects

Recognizing the limitations of a pilot open-label study, we have found potential motor and nonmotor benefits of caffeine in PD. These results corroborate clinical and laboratory evidence of enhanced motor state with adenosine antagonism.<sup>23–32</sup> Numerous adenosine 2A receptor antagonists are currently being investigated for potential use in PD. Caffeine is a nonspecific adenosine-receptor antagonist, which has the considerable advantage of negligible cost and very well-established safety profile. However, before caffeine can be considered as a therapeutic agent, the effects must be confirmed in larger trials, including the potential for tachypylaxis of motor effects over a longer evaluation period.

### Limitations

As this was an open-label trial, apparent benefits could have been the result of placebo effect. This limitation also applies to the tolerability findings—patients may have been anticipating side effects more than if caffeine administration was blinded. To maximize generalizability, we selected broad inclusion criteria, and it is possible that there were subgroups of patients who had different tolerability and clinical effect. Although we instructed patients not to change caffeine intake, we did not systematically monitor subjects' nonstudy caffeine consumption during the study. Because of poor tolerability, we were unable to confidently assess the effects of caffeine at doses exceeding 400 mg per day. Finally, one cannot be certain whether caffeine acts independently upon basal ganglia or by enhancing L-dopa pharmacokinetics.<sup>33</sup>

## Conclusion

In conclusion, this open-label, dose-escalation study demonstrates dose-dependent tolerability of caffeine in PD patients, with the best tolerated dose approximating 200 to 400 mg daily. There may be potential benefits upon motor state, apparently without worsening of sleep. Longer term, placebo-controlled, blinded, clinical trials of caffeine in PD are warranted to substantiate these preliminary findings. ■

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