Caffeine for treatment of Parkinson disease

A randomized controlled trial

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ABSTRACT

Objective: Epidemiologic studies consistently link caffeine, a nonselective adenosine antagonist, to lower risk of Parkinson disease (PD). However, the symptomatic effects of caffeine in PD have not been adequately evaluated.

Methods: We conducted a 6-week randomized controlled trial of caffeine in PD to assess effects upon daytime somnolence, motor severity, and other nonmotor features. Patients with PD with daytime somnolence (Epworth >10) were given caffeine 100 mg twice daily ×3 weeks, then 200 mg twice daily ×3 weeks, or matching placebo. The primary outcome was the Epworth Sleepiness Scale score. Secondary outcomes included motor severity, sleep markers, fatigue, depression, and quality of life. Effects of caffeine were analyzed with Bayesian hierarchical models, adjusting for study site, baseline scores, age, and sex.

Results: Of 61 patients, 31 were randomized to placebo and 30 to caffeine. On the primary intention-to-treat analysis, caffeine resulted in a nonsignificant reduction in Epworth Sleepiness Scale score (−1.71 points; 95% confidence interval [CI] −3.57, 0.13). However, somnolence improved on the Clinical Global Impression of Change (+0.64; 0.16, 1.13, intention-to-treat), with significant reduction in Epworth Sleepiness Scale score on per-protocol analysis (−1.97; −3.87, −0.05). Caffeine reduced the total Unified Parkinson's Disease Rating Scale score (−4.69 points; −7.7, −1.6) and the objective motor component (−3.15 points; −5.50, −0.83). Other than modest improvement in global health measures, there were no changes in quality of life, depression, or sleep quality. Adverse events were comparable in caffeine and placebo groups.

Conclusions: Caffeine provided only equivocal borderline improvement in excessive somnolence in PD, but improved objective motor measures. These potential motor benefits suggest that a larger long-term trial of caffeine is warranted.

Classification of evidence: This study provides Class I evidence that caffeine, up to 200 mg BID for 6 weeks, had no significant benefit on excessive daytime sleepiness in patients with PD. *Neurology*® 2012;79:651–658

GLOSSARY

CGI-C = Clinical Global Impression of Change; **CI** = confidence interval; **EDS** = excessive daytime somnolence; **ESS** = Epworth Sleepiness Scale; **FSS** = Fatigue Severity Scale; **PD** = Parkinson disease; **SF-36** = Short Form-36; **UPDRS** = Unified Parkinson's Disease Rating Scale.

Recent attention has been drawn to the role of adenosine-receptor antagonists in Parkinson disease (PD). Caffeine is a nonselective antagonist of adenosine receptors with several intriguing links to PD. First, lifelong caffeine use has been consistently associated with lower risk of PD in prospective studies.[1] Second, there may be an effect of caffeine upon excessive daytime somnolence (EDS). EDS is often an extremely disabling manifestation, causing withdrawal from social activities, reduced concentration with resulting cognitive impairment, and sleep

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Supplemental data at www.neurology.org

Supplemental Data

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attacks. Since caffeine is commonly used in the general population to increase daytime alertness, and since patients with PD often have not used caffeine, it represents an intriguing potential treatment. Third, there is preliminary evidence that caffeine may improve motor manifestations.[2,3] Motor benefit of caffeine is consistent with numerous studies in PD animal models, with human studies documenting benefit from other adenosine 2A antagonists,[4–7] and with a recent open-label dose-escalation pilot study that found caffeine reduced motor manifestations of disease.[2]

Therefore, we designed a 6-week randomized placebo-controlled double-blind study of caffeine in PD. The principal aims were as follows:

1. To assess the utility of caffeine for EDS in PD (primary outcome).
2. To assess tolerability, motor effects, and other potential nonmotor effects of caffeine in PD (secondary outcome).
3. To help interpret the epidemiologic link between caffeine nonuse and PD risk, by understanding caffeine's effects in PD (exploratory outcome).

METHODS

Trial design. This was a 6-week randomized controlled trial assessing 100–200 mg of caffeine twice daily compared to placebo in a 1:1 ratio.

Standard protocol approvals, registrations, and patient consents. The study was approved by research ethics boards of the McGill University Health Center, the Toronto Western Hospital, and the Pontifical Catholic University. Written informed consent was obtained from all participants. This trial was registered with clinicaltrials.gov #NCT00459420.

Participants. Patients were eligible for inclusion if they had idiopathic PD with excessive daytime somnolence (defined as Epworth Sleepiness Scale score [ESS] ≥ 10[8]). Exclusion criteria included daily caffeine intake >200 mg daily (assessed by a standardized intake questionnaire[9]), active peptic ulcer disease, supraventricular cardiac arrhythmia, uncontrolled hypertension, another untreated reversible cause for EDS, use of prescribed alerting agents, premenopausal women not using birth control, dementia (Folstein Mini-Mental State Examination <24/30 with consequent activities of daily living impairment), depression (Beck Depression Inventory ≥ 15[10]), and changes to antiparkinsonian medication in the last 3 months. Patients were recruited from movement disorders clinics of McGill University Health Center, the Toronto Western Hospital, and the Pontifical Catholic University of Paraná, Curitiba.

Intervention. The intervention was caffeine vs matching placebo for 6 weeks. For the first 3 weeks, caffeine dose was 100 mg twice daily, upon awakening and immediately after lunch. After 3 weeks, dose increased to 200 mg twice daily. Dose timing was chosen to mimic habitual caffeine intake patterns in the general population, and to prevent adverse effects upon nighttime sleep (caffeine's clinical effect duration approximates 3–7 hours[9,11]). At the end of 6 weeks, patients continued 100 mg twice daily for 1 week, to prevent withdrawal symptoms. During the study period, patients were not permitted to change PD medications, and all patients were instructed to continue habitual caffeine intake.

The study was originally planned as a crossover trial with a 4-week washout period between treatments. After 15 patients were enrolled, the trial was converted to a parallel-group design because of excessive dropout in the placebo group after the first phase (3/8 patients), and because the funding agency (the Canadian Institute of Health Research) raised concerns of potential failure of caffeine to wash out within 4 weeks. Therefore the remaining 46 patients were recruited for a single-phase parallel design, and only the first phase of the 15 crossover patients was analyzed for this study (all criteria, methods, outcomes, and interventions were the same in both designs).

Outcomes. The primary outcome was the ESS. The ESS is a questionnaire in which patients are asked to report their propensity to fall asleep in 8 different situations.[12–15] Patients give responses scored from 0 to 3 (0 = no chance of dozing, 1 = slight chance, 2 = moderate chance, 3 = high chance).

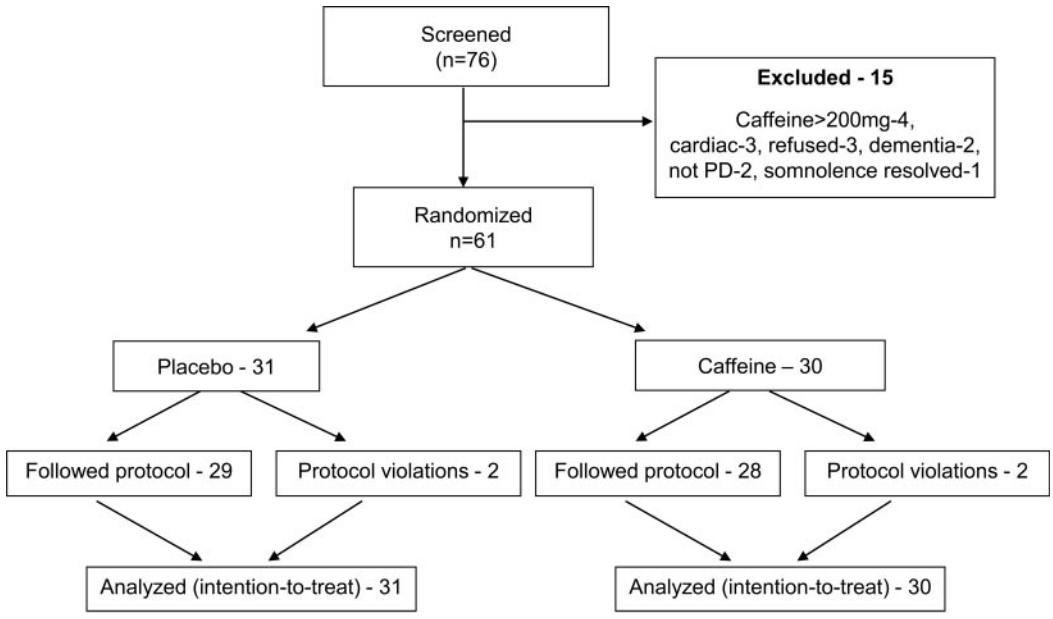
Secondary outcomes included the following:

1. Motor severity, assessed with the Unified Parkinson's Disease Rating Scale (UPDRS).[16] The UPDRS Part III was performed in the medication "on" state at each clinical visit, 2 ± 1 hours after intake of caffeine/placebo tablets.
2. Clinical Global Impression of Change (CGI-C), completed by both the examiner and the patient, with EDS as the target symptom, scored from −3 (severe worsening) to +3 (dramatic improvement).[17]
3. The Fatigue Severity Scale (FSS).[18]
4. The Pittsburgh Sleep Quality Index.[19]
5. The Beck Depression Inventory.[10]
6. The Parkinson's Disease Questionnaire–39.[20]
7. The Short Form–36 (SF-36) Quality of Life Scale.[21]
8. Tolerability and side effects of caffeine, via a structured questionnaire targeting irritability, gastrointestinal upset/pain, diarrhea, sleepiness, palpitations, anxiety, sweating, and tremulousness with open-ended reporting of other side effects.

Sample size. Sample size calculations were based on previous clinical trials using the ESS in PD[13–15] and assessing motor effects.[2] To obtain power ≥0.80, we calculated that 36 patients (18 each group) were needed to detect a change of 3 ± 2 points in the ESS (significance level = 0.05), and 52 patients (26 in each group) would detect a UPDRS part III change of 4 ± 5 points. To account for potential dropout and deviation of standard error from assumptions, 15% over requirements were recruited.

Randomization. Randomization was block randomization (block size = 4), stratified to site, and performed by study statisticians by use of PROCPLAN in SAS software and Clistat software. The randomization list was given to both central research pharmacies (in Canada and Brazil), who were not involved in outcome assessment, who prepared an individual pill pack for each patient, with only the identifying code. All patients and examiners were blinded to treatment assignment. Caffeine and placebo tablets were encapsulated to be indistinguishable in appearance; caffeine powder

Figure 1 Patient flow



PD = Parkinson disease.

or lactose were placed into identical capsules. To assess potential unblinding, patients were asked at study conclusion to guess treatment allocation, and if they felt they knew the treatment received to describe when and how they became aware.

Statistical analysis. We estimated effect of treatment (i.e., placebo vs caffeine) on the ESS (change from baseline) using Bayesian hierarchical models, adjusting for age and gender, and with random effects for study site and patient (i.e., to account for repeated measurements on the same individual). Secondary outcomes were analyzed in the same manner. Primary analysis was intention-to-treat; a separate per-protocol analysis was also conducted for the primary outcome.

Classification of level of evidence. This study represents a Class I study assessing the primary research question, that is, the effects of caffeine 200 mg twice daily upon EDS in PD as assessed by the ESS. Other secondary outcomes (e.g., CGI-C, UPDRS, ESS at 100 mg twice daily) are classified as Class II level of evidence.

Table 1 Baseline characteristics

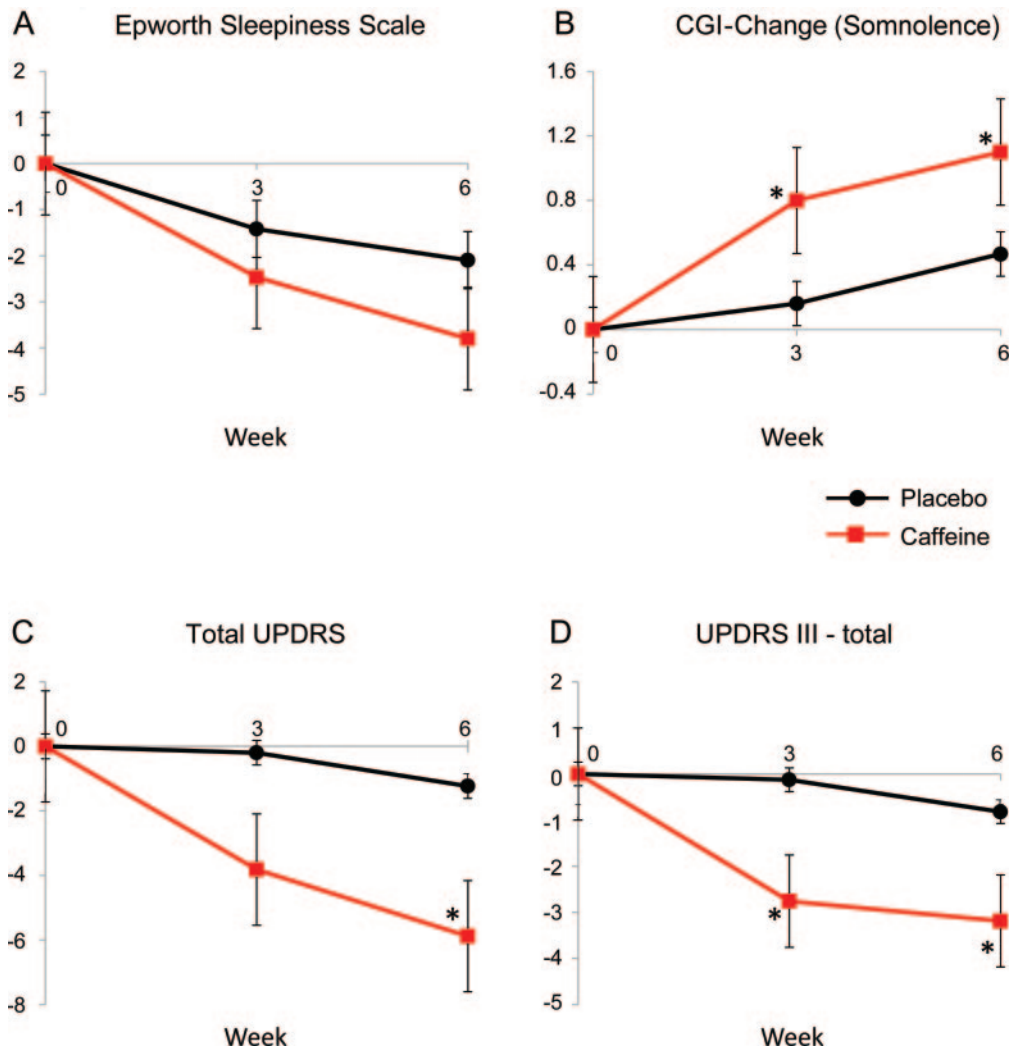
	Placebo (n = 31)	Caffeine (n = 30)
Age	67.8 (11.2)	65.2 (8.3)
Sex, % male	61	83
Disease duration, y	8.0 (4.8)	7.8 (3.5)
Levodopa dose, mg	666.9 (383.3)	686.2 (289.8)
Estimated caffeine intake, mg	70.8 (46.3)	90.7 (56.9)
Epworth Sleepiness Scale score	14.6 (3.2)	15.4 (3.0)
Pittsburgh Sleep Quality Index	6.5 ± 4.1	6.4 ± 3.9
Fatigue Severity Scale	39.5 (14.9)	39.9 (12.2)
Total UPDRS	42.0 (17.5)	41.2 (13.1)
UPDRS I	2.5 (1.9)	2.6 (2.4)
UPDRS II (on)	12.2 (5.6)	10.2 (4.5)
UPDRS III	22.5 (11.5)	23.2 (8.5)
UPDRS IV: dyskinesia	0.52 (1.3)	0.43 (0.94)
UPDRS IV: fluctuations	1.4 (1.4)	1.6 (1.9)
Beck Depression Inventory	11.5 (4.7)	10.3 (6.1)
PDQ-39	40.7 (18.7)	36.1 (19.5)
SF-36 physical score	38.0 (10.4)	40.6 (9.7)
SF-36 mental score	49.2 (8.6)	47.1 (10.9)

Abbreviations: PDQ = Parkinson's Disease Questionnaire; SF = Short Form; UPDRS = Unified Parkinson's Disease Rating Scale.

RESULTS Patient flow is presented in figure 1. A total of 76 patients were screened, and 61 patients randomized. Four protocol violations occurred: 1 patient (placebo) reduced the dose of dopamine agonist against instructions (resulting in an ESS reduction of 7 points), a second (placebo) halved dopamine agonist dose due to error by his clinical pharmacist at week 1 and dropped out of the study, a third patient (caffeine) also changed medications and dropped out of the study, and the fourth (caffeine) increased coffee intake from 1 to 3 cups daily. All these patients were analyzed in the primary intention-to-treat analysis. Recruitment was carried out between April 2007 and March 2011. Patient characteristics are outlined in table 1.

Caffeine and EDS. On the primary intention-to-treat analysis at 6 weeks, ESS was reduced (−1.71 points) in the caffeine group compared to placebo; however,

Figure 2 Change in outcomes in caffeine vs placebo



(A) Epworth Sleepiness Scale, (B) Clinical Global Impression (CGI)-Change, (C) total Unified Parkinson's Disease Rating Scale (UPDRS), (D) UPDRS part III. Shown are the changes in major outcomes of interest in caffeine and placebo over the 6-week trial. Caffeine dose at week 3 = 100 mg BID, and at week 6 = 200 mg BID. Baseline values are set at 0. Error bars indicate standard error. * Significant difference from placebo, $p < 0.05$.

confidence intervals (CI) (credible intervals) crossed 0 (95% CI −3.57, 0.13) (figure 2, table 2). Similarly, caffeine 100 mg BID (i.e., week 3) resulted in a nonsignificant decrease in ESS (−1.06 points, CI −2.61, 0.50). After exclusion of the 4 protocol violations, there was a significant reduction in ESS points (−1.97 points, CI −3.87, −0.05) at week 6.

On other somnolence outcomes, the CGI-C improved significantly by 0.64 points (95% CI 0.16, 1.13) at week 6. The PSQI was unchanged (−0.29; −1.42, 0.84); no individual components of the PSQI were different between caffeine and placebo. There was no change in FSS (−2.85; −7.73, 2.06).

Caffeine and motor manifestations. On examination, UPDRS III scores at week 6 were reduced (−3.15 points; −5.5, −0.8) in the caffeine group compared to placebo (figure 2, table 2). Similarly, 100 mg BID reduced UPDRS (−2.96 points; −0.67, −5.27). The overall UPDRS was reduced −4.69 points in the caffeine group (CI −7.7, −1.6) at week 6, without significant differences in UPDRS parts I or II. We found no significant difference in fluctuations or dyskinesia with caffeine (note that only 34/61 [56%] had fluctuations and 14/61 [23%] had dyskinesia at baseline). On analysis of UPRDS III subcomponents, there were significant changes in bradykinesia (−1.70 points; −3.1, −0.3) and rigidity (−1.01 points; −2.0, −0.7). Caffeine did not increase action tremor (−0.13 points; −0.3, −0.6).

Other secondary outcomes. There was no difference between groups in depression or PDQ-39 (table e-1 on the *Neurology*® Web site at www.neurology.org).

Table 2 Sleep and motor outcomes

	Week 3 caffeine vs placebo difference (95% CI)	Week 6 caffeine vs placebo difference (95% CI)
Epworth Sleepiness Scale	−1.06 (−2.61, 0.50)	−1.71 (−3.57, 0.13)
CGI-C: somnolence	+0.63 (0.25, 1.01)[a]	+0.64 (0.16, 1.13)[a]
Pittsburgh Sleep Quality Index	0.30 (−0.81, 1.40)	−0.29 (−1.42, 0.84)
Fatigue Severity Scale	−3.08 (−6.88, 0.73)	−2.85 (−7.73, 2.06)
UPDRS II	−0.18 (−1.34, 0.90)	−0.67 (−1.88, 0.56)
UPDRS III: total	−2.96 (−5.27, −0.67)[a]	−3.15 (−5.50, −0.83)[a]
UPDRS III: rest tremor	−0.32 (−0.73, 0.10)	−0.28 (−0.83, 0.27)
UPDRS III: action tremor	−0.11 (−0.52, 0.29)	−0.13 (−0.33, 0.60)
UPDRS III: bradykinesia	−0.97 (−2.50, 0.56)	−1.70 (−3.10, −0.31)[a]
UPDRS III: limb bradykinesia	−0.88 (−2.15, 0.38)	−1.22 (−2.47, 0.03)
UPDRS III: rigidity	−1.25 (−2.11, −0.39)[a]	−1.01 (−1.98, −0.68)[a]
UPRDS III: gait	−0.12 (−0.84, 0.60)	−0.28 (−1.16, 0.59)
UPDRS IV: dyskinesia	0.04 (−0.31, 0.38)	0 (−0.35, 0.35)
UPDRS IV: fluctuations	−0.07 (−0.56, 0.43)	−0.41 (−1.05, 0.22)
Total UPDRS	−3.69 (−7.46, 0.06)	−4.69 (−7.77, −1.60)[a]

Abbreviations: CI = confidence interval/credible interval; CGI-C = Clinical Global Impression of Change (somnolence); UPDRS = Unified Parkinson's Disease Rating Scale.
[a] Significant at $p < 0.05$.

There was an improvement in the general health component of the SF-36 (+5.0; 1.3, 8.7) without significant changes in other SF-36 components.

Adverse events and unblinding. There were no differences between groups in total adverse events or in any single adverse event (table 3). A total of 48% of placebo patients reported an adverse event compared to 43% of caffeine. The commonest adverse event was gastrointestinal upset (placebo = 19%, caffeine = 17%). In particular, anxiety, irritability, insomnia, or worsening of action tremor were not reported more in caffeine patients than controls; none of these adverse events were experienced by more than 6% of participants.

A total of 61% of placebo and 63% of caffeine patients guessed their treatment correctly (chance = 50%, $p = 0.07$). Two cited taste changes as a reason for possible unblinding, 1 in placebo (incorrect), 1 in caffeine (correct). Seven cited adverse events, 4 in placebo (incorrect), 3 in caffeine (correct). The commonest cited reason for possible unblinding was clinical benefit or lack thereof; 12 caffeine patients guessed they had received caffeine because they felt more alert or energetic (5 guessed placebo because they felt no change) and 11 placebo patients guessed they received placebo because they felt no change (4 guessed caffeine because of perceived improvement).

Table 3 Adverse events[a]

	Placebo (n = 31)	Caffeine (n = 30)
Reporting any event	15 (48)	13 (43.3)
Serious adverse event	1 (3) (fall)	0 (0)
Gastrointestinal	6 (19)	5 (17)
Dizziness/lightheadedness	2 (6)	2 (6)
Insomnia	1 (3)	1 (3)
Motor worsening	2 (6)	1 (3)
Anxiety	1 (3)	1 (3)
Irritability	1 (3)	2 (6)
Headache	1 (3)	2 (6)
Confusion	3 (10)	0 (0)
Worsening of tremor	0 (0)	0 (0)

[a] Values are n (%).

DISCUSSION

In this randomized controlled trial, we found no clear benefit of caffeine upon excessive daytime somnolence in PD, although there appeared to be a modest effect on per-protocol analysis. However, we found improvement in motor manifestations, with a 3.2-point improvement on the UPDRS part III, and 4.7-point improvement on the total UPDRS.

On analysis of the primary outcome, we found no significant benefit of caffeine on excessive somnolence. However, these results must be interpreted with caution. There was a 1.71-point improvement in the caffeine group that was statistically borderline on intention-to-treat, and significant on per-protocol analysis. The withdrawal/reduction of dopamine agonists by 2 placebo patients, with corresponding drops in ESS score (of 7 and 1 points), likely biased results substantially. Also, although the ESS has been validated in PD,[22] and successfully used in previous clinical trials of somnolence in PD,[13–15] it is possible that negative results could be due to limitations of the instrument. In particular the CGI-C, with somnolence as the target symptom, demonstrated significant (but small) improvement. Whereas the ESS only assesses episodes of actual sleep, the CGI-C is a global scale which can incorporate other sensations, e.g., fighting sleep and mental fogginess, which are important features of somnolence in PD. There is often poor correlation between subjective and objective measures of sleepiness in PD, and patients with PD may even be unaware of a daytime nap soon after it occurs.[12,23] Therefore, objective measures, such as the maintenance of wakefulness or Multiple Sleep Latency Test, would have been of interest—however, in addition to adding participant burden, these tests have not been validated in PD, and may not reflect the somnolence experienced by patients in daily life. Regardless of statistical significance, the

point estimate of difference in ESS remains small, so the clinical significance of any change is unclear.

This study has also found evidence that caffeine can improve motor manifestations of disease. Numerous lines of evidence have suggested potential beneficial effects of caffeine on PD. Caffeine's principal mechanism of action is antagonism of the adenosine-2A (A2A) receptor, which is involved in striatopallidal neuronal activity in the indirect pathway.[4,24] Adenosine receptors are colocalized as heteromers with dopaminergic D2 receptors, inhibiting effects of dopaminergic transmission.[25,26] Numerous animal studies have found motor improvement in toxin-induced models of PD,[27] in dopamine-deficient mice,[28] and in drug-induced parkinsonism[29] with caffeine. Caffeine may also increase bioavailability and prolong the clinical effect of levodopa[30] (note that the clinical effect of caffeine may persist even after levodopa levels decline, suggesting that the D2 receptor interactions are also important). Two early small-scale human studies evaluated caffeine as a potential symptomatic agent in PD, and found no effect.[31,32] However, these were limited by very atypical dosing (e.g., 1,000 mg acute dose), or a single assessment in time. A recent study documented improvement in gait akinesia with 100 mg caffeine daily in patients with PD with gait freezing.[3] Very recently, we found a UPDRS reduction with caffeine in an open-label dose escalation pilot study using similar doses to the current trial.[2]

Of note, there is increasing interest in the role of newer A2A antagonists for treatment of motor PD. Recent trials of istradefylline and preladenant have demonstrated modest (1–1.2 hour) reductions in off time, and modest (1.1 to 3.2 points) improvements in UPDRS part III.[6,7,33,34] Although methodologic and patient population differences preclude direct comparison to our results, the effects of these newer antagonists upon UPDRS appear to be broadly similar to what we found with caffeine. Given caffeine's dramatically lower cost and well-established long-term safety profile, the advantage of the newer A2A antagonists relative to caffeine remains to be established.

In epidemiologic studies, there is compelling evidence that caffeine nonuse is associated with PD. Relative risks in large cohort studies range from 0.45 to 0.89,[35] and a meta-analysis suggested a relative PD risk of 0.72 (95% CI 0.62, 0.84) for coffee intake vs no coffee intake.[1] This inverse correlation is also present with tea and is not present with decaffeinated coffee, suggesting that caffeine itself is responsible.[36,37] However, despite extensive documentation of this relationship between caffeine and PD, we lacked basic information to interpret these findings, mainly because we did not understand the effects of caffeine in PD. Although a true neuroprotective benefit is an important potential explanation, our findings suggest that other possibilities may also explain this relationship. The absence of a clear effect of caffeine on somnolence could suggest that reverse causality is important—patients in prodromal PD stages could lose the beneficial effects of caffeine upon alertness and wakefulness, and so spontaneously stop taking caffeine. Prospective epidemiologic studies (in which intake is assessed years before PD onset) argue against this, but depend upon assumptions of a relatively short prodromal phase of PD (i.e., $<$15–20 years). Second, caffeine's effect on motor manifestations suggests that symptomatic benefit could partially explain the epidemiologic findings; caffeine might delay onset of motor symptoms, resulting in an apparent protective effect. It is unclear if the modest symptomatic benefit we found would be of sufficient amplitude to produce such robust epidemiologic findings—studies of UPDRS progression in early PD suggest that a 5-point total UPDRS reduction would only delay diagnosis by approximately 6 months.[38] Given that PD lasts a decade or more, this would presumably not translate to a 30%–40% reduction in prevalence. Note, also, that symptomatic and neuroprotective effects may not be mutually exclusive; some have suggested that early symptomatic treatment, by preventing maladaptive compensatory mechanisms in striatal structures, could also be neuroprotective.[39]

Some limitations of this study should be noted. The motor and quality of life benefits were secondary outcomes of the study, and therefore should be viewed as exploratory. Also, for these outcomes, selection of subjects with daytime sleepiness may have produced results not representative of other patients with PD. The study was not designed or powered to examine caffeine's effects upon fluctuations or dyskinesia, as only a subset of our patients had these features at baseline. A total of 15/61 patients in this study were originally enrolled into a crossover study and the first phase of their study is included; however, all trial procedures in the first phase were exactly the same as the parallel group study, so reliability should not be affected by their inclusion. To enhance generalizability and recruitment, we did not demand that all patients have no baseline caffeine intake—it is possible that some changed habitual caffeine intake during the 6-week study without notifying investigators. With a 2 $\pm$ 1 hour window during which patients were examined after caffeine intake, there was some variability in assessment time of UPDRS part III relative to caffeine. Although patients did not guess treatment allocation significantly better than chance, the point estimate exceeded

50%. It appears that any possible unblinding did not seem to be related to capsule appearance, taste changes, or adverse events; patients who guessed correctly generally did so because they recognized clinical benefits or lack of them. We did not ask investigators to guess treatment allocation, so cannot rule out unrecognized investigator unblinding. Importantly, the duration of the study was short—given caffeine's tachyphylactic properties (at least for somnolence), effects may lessen over the long term. Therefore, our findings must be confirmed in separate longer-term trials explicitly designed to assess effects in early disease, and in patients with fluctuations.

AUTHOR CONTRIBUTIONS

R.B. Postuma was responsible for study concept, obtaining funding, acquisition of data, analysis and interpretation of data, and drafting of the manuscript. A.E. Lang was responsible for obtaining funding, acquisition of data, interpretation of data, and manuscript revision. Renato Munhoz was responsible for acquisition of data, interpretation of data, and manuscript revision. Katia Charland was responsible for statistical analysis and manuscript revision. Amelie Pelletier was responsible for generation of data, interpretation of data, and manuscript revision. Mariana Moscovich was responsible for acquisition of data and manuscript revision. Luciane Filla was responsible for acquisition of data and manuscript revision. Debora Zanatta was responsible for statistical assistance, interpretation of data, and manuscript revision. Silvia Rios-Romenets was responsible for acquisition of data and manuscript revision. Robert Altman was responsible for acquisition of data and manuscript revision. Rosa Chuang was responsible for acquisition of data and manuscript revision. Binit Shah was responsible for acquisition of data and manuscript revision.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. **Go to Neurology.org for full disclosures.**

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