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Caffeine and Progression of Parkinson Disease

David K. Simon, MD, PhD^{*}, Christopher J. Swearingen, MS[†], Robert A. Hauser, MD, MBA[‡], Joel M. Trugman, MD[§], Michael J. Aminoff, MD, DSc^{||}, Carlos Singer, MD[¶], Daniel Truong, MD[#], and Barbara C. Tilley, PhD[†] On Behalf of the NET-D Investigators

^{*} Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA

[†] Department of Biostatistics, Bioinformatics and Epidemiology, Medical University of South Carolina, Charleston, SC

[‡] Department of Neurology, University of South Florida, Tampa, FL

[§] Department of Neurology, University of Virginia Health Sciences Center, Charlottesville, VA

^{||} Department of Neurology, School of Medicine, University of California, San Francisco, CA

[¶] Department of Neurology, Miller School of Medicine, University of Miami, Miami, FL

[#] The Parkinson's and Movement Disorder Institute, Fountain Valley, CA

Abstract

Objective—Caffeine use is negatively associated with the risk of developing Parkinson disease (PD) and is protective in animal models of PD, but the relationship between caffeine intake and rate of progression of PD is unknown. We assessed this relationship using data from 2 recent clinical trials of PD.

Methods—Data were ascertained from 2 recent 1-year clinical trials that together included 413 early PD subjects who did not require symptomatic therapy at the time of study entry. Exploratory analyses compared caffeine intake with rate of progression of PD, as measured by either the likelihood of progression to the point of requiring symptomatic therapy or by change in the total Unified Parkinson Disease Rating Scale score.

Results—Rate of progression of PD did not differ significantly between those in the highest and lowest quartiles for caffeine use for either of the primary measures or for secondary analyses of changes in scores on the motor or activities of daily living subsections of the Unified Parkinson Disease Rating Scale. Other secondary analyses yielded variable results.

Conclusions—These data do not reveal a consistent relationship between caffeine intake and rate of progression of PD by these measures, although a larger study is required for sufficient power to more fully assess this relationship.

Keywords

coffee; adenosine A_{2A} receptor; neuroprotection; disease modifying

Numerous studies of varying methodologies have demonstrated a dose-dependent negative association between caffeine intake and the risk of developing Parkinson disease (PD).^{1–4} This negative association is present for caffeinated coffee and for noncoffee sources of caffeine, but is not present for decaffeinated coffee.^{2,4} Although personality differences that

predates the onset of PD may partially account for this negative association,⁵ preclinical studies have demonstrated that caffeine and other more specific adenosine A_{2A} receptor antagonists are protective in rodent models of PD, providing a plausible biologic mechanism that might contribute to the inverse association with PD.⁶ Although adenosine A_{2A} receptor antagonists also seem to have the potential for significant symptomatic benefit in patients with PD,^{7–9} data are limited as to the association of caffeine and the rate of progression of PD. To address this question, we took advantage of data available from 2 recent multicenter clinical trials of PD that included standardized rating scales at baseline and after 1 year, thereby allowing an estimate of the rate of progression of PD, in conjunction with quantitative assessments of caffeine intake.

MATERIALS AND METHODS

Data for the current study came from 2 futility studies designed as preliminary tests of agents selected for their potential to slow the progression of symptoms of PD.^{10,11} These multicenter studies were sponsored by the National Institute of Neurological Disorders and Stroke and were organized by the Clinical Trials Coordination Center at the University of Rochester and the Department of Biostatistics at the Medical College of South Carolina. Participants included men and women aged 30 years and older with a diagnosis of PD within 5 years of study entry, but not yet requiring symptomatic therapy. The diagnosis of PD required 2 of 3 cardinal features of PD (tremor, rigidity, and bradykinesia) and asymmetric findings. In the first futility trial (FS1), 200 subjects were randomized 1:1:1 to creatine, minocycline, or placebo.¹⁰ In the second trial (FS-TOO), 213 subjects were randomized 1:1:1 to coenzyme Q10, GPI-1485 (an immunophilin ligand), or placebo.¹¹

Caffeine use questionnaires were administered at baseline to each participant in both studies and included questions regarding intake of coffee, tea, and caffeinated beverages. A 12-part questionnaire was used for the FS1 study, and an 8-part questionnaire was used for the FS-TOO study. The FS1 questionnaire focused primarily on intake of caffeinated beverages during the previous week, whereas the FS-TOO questionnaire focused primarily on average intake during the previous 6 months. The FS1 questionnaire was validated based upon a 1-week recall method (M. Schwarz-child, personal communication), whereas we are not aware of any validation studies for the FS-TOO questionnaire. The caffeine use distributions between the FS1 and FS-TOO questionnaires were different. A reliability study of the 2 questionnaires was completed before the analysis presented in this article. Although the FS-TOO questionnaire consistently reports less caffeine consumption than the FS1 questionnaire, the 2 questionnaires have strong concordance ($\rho_c = 0.714$; 95% confidence interval [CI], 0.643 to 0.773) and moderate quartile agreement (weighted $\kappa = 0.542$; 95% CI, 0.462 to 0.623).¹² Because of the differences in the methods for ascertaining caffeine use between the FS1 and FS-TOO studies, analyzing the caffeine use by quartiles allowed for a comparable primary analysis to be conducted for each study, whereas secondary analyses used the continuous caffeine measures.

At the end point of the studies (12 months after study entry or upon a determination of a need for symptomatic therapy, whichever came first), subjects were asked if their level of intake of caffeine had changed since baseline. Those answering positively were administered the caffeine questionnaire again. Although the baseline questionnaire was used for this exploratory analysis, a secondary aim in this analysis excluded subjects whose follow-up questionnaire indicated a change in caffeine intake of 25% or greater relative to the baseline questionnaire. Details regarding the questionnaires or the formula for calculating caffeine intake (mg per day) are available upon request.

The primary prespecified aim of this exploratory analysis was to compare the rates of progression of clinical features of PD for those in the highest with those in the lowest quartiles for caffeine intake (separately determined for each study; Table 1). Clinical progression of PD was measured in 2 ways. The first measure was the likelihood of requiring symptomatic therapy during the first 12 months after study entry. The second prespecified primary outcome measure was the change in the total Unified Parkinson Disease Rating Scale (UPDRS) score from baseline to either the time at which there was sufficient disability to warrant symptomatic therapy for PD (as determined by the site investigator) or 12 months, whichever came first. The UPDRS has been shown to be a measure of PD progression sensitive to short-term (12 months) change.¹³ As a secondary aim, change from baseline scores of the Motor and the Activities of Daily Living (ADL) subsections of the UPDRS were compared between the 2 quartile usage groups. Another secondary aim compared caffeine use as a continuous variable with the rate of progression of PD based on the change from baseline in the total UPDRS, and in the Motor and ADL subsections of the UPDRS. Changes in UPDRS scores and subscores were calculated as the scores at the study end point minus the scores at baseline. Because higher scores on the UPDRS represent clinical worsening, positive values for the changes in UPDRS scores correspond to clinical worsening, whereas negative values represent clinical improvement.

Statistical Methods

The primary aim examined differences in PD progression between the 2 groups defined by those subjects in the highest and lowest caffeine intake quartiles. Parkinson disease progression as determined by symptomatic therapy initiation during the first 12 months was analyzed between the 2 groups using Pearson χ^2 test. Parkinson disease progression as determined by change from baseline in outcome scores was analyzed between the groups using a Student *t* test. Linear regression models were used to assess the relationships between caffeine use measured as a continuous variable and changes in the outcome scores.

A power analysis for the primary aim was conducted before its analysis. A 2-group χ^2 test with a 0.05 2-sided significance level had 82% power to detect the difference between the highest quartile group's proportion of starting symptomatic treatment ($P_1 = 0.3$) and the lowest quartile group's proportion ($P_2 = 0.5$) when the sample size in each group is 100. This calculation assumed that a 40% ($P = 0.4$) rate of symptomatic treatment initiation for both futility studies, and that the lowest quartile group would be 25% more likely to start symptomatic treatment, whereas the highest quartile group would be 25% less likely to start symptomatic treatment. The statistical analyses were completed using SAS 9.1 (Cary, NC), and the power analysis was completed using nQuery Advisor 6.0 (Saugus, Mass).

RESULTS

Distributions of caffeine use are shown in Figure 1 and Table 1. Mean levels of caffeine intake and the cutoffs for the upper and lower quartiles seem lower in FS-TOO relative to levels in FS1, but because of differences between these 2 studies in the questionnaire used to ascertain these data, absolute levels of caffeine are not directly comparable. In FS-1 and FS-TOO, 15 (7.9%) and 16 (7.5%) of participants reported no caffeine use, respectively.

Parkinson disease progression as determined by symptomatic therapy initiation during the first 12 months and also determined by change from baseline in the total UPDRS scores were not significantly different between subjects in the highest and lowest quartiles for caffeine use when data from both studies were combined or when data from each study were analyzed separately (Table 2). No significant differences were detected in the mean changes in the motor UDPRS scores for the lowest versus highest quartiles for caffeine use. For ADL scores, those in the highest quartile for caffeine use deteriorated at a slower rate than those

in the lowest quartile for caffeine use for subjects in the FS1 study. However, this trend did not reach statistical significance ($P = 0.081$), and a nonsignificant trend in the opposite direction was seen for this secondary analysis for the FS-TOO study ($P = 0.231$), with no significant difference in the combined analysis ($P = 0.54$).

The statistical power of this study was insufficient for a definitive determination of the impact of gender on the effect of caffeine, and none of the primary or secondary analyses yielded significant results when the subgroups of men or women were analyzed separately. In the FS1 study, a nonsignificant trend toward slower decline in ADLs was observed in the highest quartile for caffeine use relative to the lowest quartile for both men ($P = 0.131$) and women ($P = 0.166$). A strong trend toward slower decline in the total UPDRS score was found among female subjects in the FS1 study in the highest quartile relative to the lowest quartile ($P = 0.053$). However, a similar trend was not observed among female subjects in the FS-TOO study ($P = 0.962$), and the combined analysis did not show a significant difference.

As an additional secondary analysis, the primary and secondary analyses were repeated after excluding any subjects whose caffeine intake changed by 25% or more from baseline to the end point of the study. This resulted in exclusion of 25 subjects from FS1 and 15 subjects from the FS-TOO study who increased caffeine use by at least 25% during the studies, and 43 subjects from FS1 and 30 from FS-TOO who decreased caffeine use by 25% or more during the studies. The repeat analyses after excluding these subjects did not alter the primary results, with the exception of a significantly slower rate of decline in the ADL scores in the FS1 study for subjects in the highest quartile for caffeine use relative to subjects in the lowest quartile ($P < 0.05$). This difference for ADL scores was not confirmed in the FS-TOO study, and the combined analysis showed no significant difference. No other differences reached statistical significance.

To assess the impact of hormonal replacement therapy (HRT) on the impact of caffeine, we also repeated the primary and secondary analyses separately for women who used or did not use HRT. Among subjects in the lowest or highest quartiles for caffeine use, only 23 of the 34 women in FS1 and 21 of the 31 women in FS-TOO used HRT, limiting the ability to assess an interaction between HRT and caffeine. Surprisingly, despite these low numbers, for the 23 women in the FS1 study who reported using HRT, the rate of decline in ADL scores was slower among those in the highest quartile for caffeine use (mean, 0.22; 95% CI, -1.84 to 2.28) compared with the rate of decline for those in the lowest quartile (mean, 2.64; 95% CI, 0.89 to 4.39) ($P = 0.064$). This finding was not reproduced among women using HRT in the FS-TOO study ($P = 0.80$), and once again, the combined analysis showed no significant difference.

In addition to the primary analyses comparing outcomes for the highest and lowest quartiles for caffeine intake, we also completed a secondary analysis of caffeine intake as a continuous variable. The change in outcome scores was modeled as the dependent variable in a linear regression model with caffeine intake, sex, and treatment group assignment as covariates. Significant interactions were detected between caffeine and the treatment groups. As a result, subgroup analyses for each treatment group were conducted (Table 3) following established guidelines.¹⁴ In the FS1 placebo group, the change in UPDRS score improved by -1.014 (95% CI, -1.726 to -0.303) for every 100 mg/d caffeine intake ($P < 0.01$). The change in the motor subscore of the UPDRS in the FS1 placebo group improved by -0.621 (95% CI, -1.101 to -0.140) for every 100 mg/d caffeine intake ($P < 0.05$), and the change in the ADL subscore by -0.337 (95% CI, -0.622 to -0.052) ($P < 0.05$). Surprisingly, in the creatine group, the change in the UPDRS score worsened by 0.934 points (95% CI, 0.029 to 1.838) for every 100 mg/d caffeine intake ($P < 0.05$). Furthermore,

the change in the ADL subscore worsened by 0.318 points (95% CI, 0.011 to 0.624) ($P < 0.05$) for every 100 mg/d caffeine intake in the GPI-1485 group. No other comparisons yielded significant results.

DISCUSSION

These data do not reveal any consistent relationship between caffeine use in early PD patients and the rate of progression of PD as measured by progression to the need for symptomatic treatment or by change in total UPDRS scores. We are aware of only a single previous study that has addressed the question of the impact of caffeine on the rate of progression of PD. A preliminary report from Schwarzschild et al¹⁵ described results from an analysis of data from the Comparison of the Agonist Pramipexole Versus Levodopa on Motor Complications of Parkinson's Disease (CALM-PD) Study, which included 5-year data from 87% of the 268 PD patients who participated in that study. No association was found between caffeine intake and rate of progression of PD as measured by the UPDRS score or by the change in striatal uptake of iodine-123-labeled 2- β -carboxymethoxy-3- β -(4-iodophenyl) tropane ([123I] β -CIT) in a subset of patients who also underwent repeat neuroimaging. A nonsignificant trend toward lower risk of dyskinesias with increasing caffeine intake was noted. The possibility of an effect of caffeine on dyskinesias could not be addressed in the current study, as patients in the FS1 and FS-TOO studies did not yet require symptomatic therapy at the time of study entry, resulting in an extremely low incidence of dyskinesias within the 1 year of study entry.

The benefit seen in the FS1 study with respect to slower progression of ADL scores among subjects in the highest quartile for caffeine use relative to the lowest quartile is potentially promising, but must be interpreted with caution. This was a secondary analysis that did not reach statistical significance, except after exclusion of subjects whose caffeine use changed by at least 25% after study entry. This led to a result of borderline significance ($P < 0.05$), and there was a nonsignificant trend in the opposite direction in the FS-TOO study.

An additional concern is that caffeine blocks adenosine A_{2A} receptors, and adenosine A_{2A} antagonists may have symptomatic benefits in PD.⁷ Therefore, a significant change in the level of caffeine use from baseline to the end of the study could lead to changes in the outcome measures because of a symptomatic effect of caffeine independent of the rate of progression of the underlying clinical features of the disease. However, because levels of caffeine intake remained stable for most subjects throughout the study, a symptomatic effect alone is unlikely to have had a significant impact on these results. Furthermore, repeat analyses after exclusion of subjects whose caffeine use changed by 25% or more during the trial did not alter any of the results, with the exception of the association of caffeine with slower worsening of the ADL score among FS1 subjects, which became stronger ($P < 0.05$). It is important to note that our study addresses the association of caffeine with the rate of clinical progression of PD, but does not address the question of symptomatic benefits of caffeine. An additional interesting observation was the strong trend toward a slower decline in the total UPDRS score among women in the FS1 study ($P = 0.053$), but again, the lack of a similar result for women in the FS-TOO study precludes a definitive conclusion.

In addition to the limitations imposed by the use of 2 different instruments to measure caffeine intake, a limitation of the current study is the lack of data regarding the dose of caffeine most likely to be beneficial in PD. A beneficial effect of caffeine on progression of PD may require levels of caffeine higher than the upper quartile cutoffs arbitrarily selected for the current study. Conversely, it is possible that even low levels of caffeine intake have a protective effect. Adenosine receptor blockade in humans occurs at caffeine doses as low as 100 mg, about 20-fold lower than doses required for phosphodiesterase inhibition, and a

dose that can be achieved by a single 6-ounce cup of coffee.^{16,17} Although the lower quartile cutoff for daily caffeine intake was less than 100 mg for both FS1 and FS-TOO, it remains possible that inclusion of subjects with low (but non-0) levels of caffeine intake in the lower quartile group may have limited our ability to detect an effect of caffeine.

A potential confounder of these analyses is the possibility that a study drug influences either the rate of progression of PD or the impact of caffeine on this outcome. For the primary analyses of the influence of caffeine on the need for initiation of symptomatic therapy, we did not account for treatment group, consistent with published findings that time to symptomatic therapy initiation seemed similar across treatment groups in the FS1 and FS-TOO studies.^{10,11} We did account for treatment group in a post hoc analysis of caffeine intake as a continuous variable on the change in UPDRS scores (Table 3). In the FS1 placebo group, the increased baseline caffeine intake was associated with a benefit with respect to the change in UPDRS score. This association was significant for the total UPDRS score ($P < 0.05$) and for the motor and ADL subscores ($P < 0.01$). However, this result was not confirmed in the FS-TOO placebo group, leaving uncertainty as to the interpretation of this finding. It is possible that the lower mean levels of caffeine intake among subjects in the FS-TOO study limited the sensitivity for detecting an effect, but comparison of levels of caffeine intake between the 2 studies is complicated by the use of different caffeine intake questionnaires. Surprisingly, increased caffeine intake was associated with a significant worsening of the change in UPDRS score among the subset of FS1 subjects in the creatine group. The reasons for such an effect are unclear, although there is evidence that caffeine counteracts some effects of creatine in muscle.^{18,19} However, this was a post hoc analysis of borderline significance ($P < 0.05$ without correction for multiple comparisons), and so a definitive conclusion is not possible. Differences in the questionnaires used in FS-1 and FS-TOO may have influenced this result, as the FS-TOO questionnaire reflected more contemporary caffeine consumption (eg, espresso, high-caffeine soft drinks, etc) than the FS-1 measure. This may lead to the FS-TOO questionnaire reflecting a different level of accuracy than the FS-1 questionnaire.

An additional reason for caution in interpreting these data is that this was not a randomized study with respect to caffeine use. A correlation of caffeine use with rate of progression of PD in certain subgroups could signify that caffeine use correlates with some other genetic or environmental factors that influence the rate of progression of PD rather than a direct effect of caffeine itself. On the other hand, the negative results for the primary analyses do not exclude a beneficial effect of caffeine on progression of PD that might be too small to be detected by a study of this size or one that might be detected only with a study of longer duration. Furthermore, it is possible that individuals who develop PD despite high levels of caffeine intake may be more likely to have other factors that adversely affect PD progression than those with low caffeine intake. Given the strength of the preclinical and epidemiological data suggesting the potential for a beneficial impact of caffeine in PD and the suggestion of an effect of caffeine in some of the secondary analyses, a larger study of sufficient duration is needed to more definitively test the relationship between caffeine use and rate of progression of PD.

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FIGURE 1.
Distributions of subjects according to levels of daily caffeine intake in the FS1 (n = 189) and FS-TOO (n = 213) studies.

TABLE 1
Distributions of Subjects for the FS1 and FS-TOO Studies According to Caffeine Use

Study	n	Baseline Caffeine (mg per day)					
		Minimum	25th Pctl	Median	75th Pctl	Maximum	Mean SD
FS1	189	0.0	85.0	187.1	340.0	1451.1	244.9 243.2
FS-TOO	213	0.0	27.2	122.8	285.9	906.3	181.4 196.5

Minimum, maximum, median, mean, and SD for caffeine use are shown for each study.
n indicates number of subjects for whom caffeine intake data were available; Pctl, percentile.

TABLE 2

Comparison of Primary Outcome Measures (Need for Symptomatic Therapy and Change in Total UPDRS Score) and Secondary Outcome Measures (Change in Motor UPDRS Score and Change in ADL-UPDRS Score) for Those in the Lowest Quartile for Caffeine Use Versus Those in the Highest Quartile for Caffeine Use

	Need for Symptomatic Therapy?		Mean Change in Total UPDRS (95% CI)	Mean Change in Motor UPDRS (95% CI)	Mean Change in ADL-UPDRS (95% CI)
	No	Yes			
FS1					
Lowest quartile, no. subjects (%)	23 (52.3)	21 (47.7)	8.1 (5.2–11.1)	4.6 (2.4–6.7)	3.0 (1.9–4.1)
Highest quartile, no. subjects (%)	24 (49.0)	25 (51.0)	6.0 (3.5–8.6)	3.9 (2.1–5.7)	1.7 (0.8–2.7)
<i>P</i>	0.751		0.279	0.626	0.081
FS-TOO					
Lowest quartile, no. subjects (%)	23 (46.9)	26 (53.1)	7.1 (4.7–9.5)	4.8 (2.9–6.7)	2.0 (1.3–2.8)
Highest quartile, no. subjects (%)	25 (47.2)	28 (52.8)	8.5 (6.1–11.0)	5.3 (3.4–7.2)	2.7 (1.9–3.4)
<i>P</i>	0.981		0.418	0.729	0.231

TABLE 3

Linear Regression Parameter Estimates of Outcome Change per 100 mg of Baseline Caffeine by Treatment Group

	n	Unit Change in Total UPDRS		Unit Change in UPDRS Motor Subscore		Unit Change in UPDRS ADL Subscore	
		Estimate	(95% CI)	Estimate	(95% CI)	Estimate	(95% CI)
FSI							
Creatine	64	0.934[*]	(0.029 to 1.838)	0.548	(-0.169 to 1.264)	0.217	(-0.121 to 0.556)
Minocycline	59	-0.432	(-1.680 to 0.816)	-0.246	(-1.091 to 0.599)	-0.194	(-0.657 to 0.270)
Placebo	66	-1.014[†]	(-1.726 to -0.303)	-0.621[*]	(-1.101 to -0.140)	-0.337[*]	(-0.622 to -0.052)
FSToo							
GPI-1485	71	0.923	(-0.168 to 2.015)	0.611	(-0.262 to 1.484)	0.318[*]	(0.011 to 0.624)
Coenzyme Q10	71	-0.149	(-1.066 to 0.768)	-0.219	(-0.917 to 0.479)	0.084	(-0.255 to 0.422)
Placebo	71	0.682	(-0.355 to 1.719)	0.387	(-0.386 to 1.161)	0.195	(-0.156 to 0.546)

Higher UPDRS scores represent a worsening of disease severity, and therefore positive unit changes represent a worsening in the rate of change in the UPDRS score with increased caffeine intake, whereas negative unit changes represent a slower rate of change. Significant differences shown in bold.

^{*} $P < 0.05$,

[†] $P < 0.01$.