A randomized, double-blind, futility clinical trial of creatine and minocycline in early Parkinson disease

The NINDS NET-PD Investigators*

Abstract—*Background:* Creatine and minocycline were prioritized for testing in Phase II clinical trials based on a systematic evaluation of potentially disease modifying compounds for Parkinson disease (PD). *Objective:* To test whether creatine and minocycline alter the course of early PD relative to a predetermined futility threshold for progression of PD in a randomized, double-blind, Phase II futility clinical trial. Agents that do not perform better than the futility threshold are rejected as futile and are not considered for further study. *Methods:* Participants had a diagnosis of PD within 5 years, but did not require medications for the management of symptoms. The primary outcome was the change in the total Unified Parkinson's Disease Rating Scale (UPDRS) score from baseline to either the time when there was sufficient disability to warrant symptomatic therapy for PD or 12 months, whichever came first. Subjects were randomized 1:1:1 to receive creatine 10 g/day, minocycline 200 mg/day, or matching placebo. The futility threshold was set as a 30% reduction in UPDRS progression based on the placebo/tocopherol arm of the Deprenyl And Tocopherol Antioxidative Therapy Of Parkinsonism (DATATOP) trial. p Values ≤ 0.1 indicate futility. *Results:* Two hundred subjects were randomized to the three groups. Neither creatine ($p = 0.96$) nor minocycline ($p = 0.66$) could be rejected as futile based on the DATATOP futility threshold. The rate of progression for the calibration placebo group fell outside the 95% CI for the DATATOP historical control. In a sensitivity analysis, based on the threshold derived from the calibration placebo group, again neither drug could be rejected as futile. Tolerability was 91% in the creatine group and 77% in the minocycline group. Common adverse events included upper respiratory symptoms (26%), joint pain (19%), and nausea (17%). *Conclusions:* Both creatine and minocycline should be considered for definitive Phase III trials to determine if they alter the long term progression of Parkinson disease (PD). Additional factors must be weighed before selecting agents for Phase III trials, including safety, tolerability, activity, cost, and availability of these two agents in comparison with other agents currently in development for PD.

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Creatine and minocycline were prioritized for clinical testing in Parkinson disease (PD) based on a systematic review of potentially neuroprotective compounds. This review considered the quality and consistency of preclinical and clinical data.[1] Both drugs are neuroprotective in preclinical models of PD, are bioavailable with oral administration,[2] and penetrate the blood–brain barrier.[3-5]

Creatine monohydrate is a dietary supplement that has generally been used for improving performance in athletes. There have been no major safety or tolerability problems with oral supplementation of creatine in doses as high as 20 g per day for short periods.[2] Creatine plays an important role in mitochondrial energy production. Creatine is converted to phosphocreatine and can transfer a phosphoryl group to ADP to make ATP, thereby buffering intracellular energy stores. There is evidence of mitochondrial dysfunction in PD, with deficits in complex I activity in platelets of patients with early PD[6,7] and in postmortem substantia nigra pars compacta (SNpc) tissue of more advanced patients.[8] Oral supplementation with creatine has been shown to protect against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) induced dopamine depletion in mice[9,10] and is protective in transgenic rodent models of Huntington disease (HD)[11,12] and amyotrophic lateral sclerosis (ALS).[13,14]

Minocycline is a semi-synthetic second generation tetracycline used for treating a variety of infections. It has been used chronically in diverse conditions such as acne[15] and rheumatoid arthritis.[16] Minocycline exerts anti-inflammatory effects independent of antimicrobial effects. The loss of dopaminergic neu-

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*The NINDS NET-PD Investigators are listed in the Appendix.

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rons in the SNpc is associated with an inflammatory response mediated by glial activation. Dopaminergic neurons are highly susceptible to microglial mediated injury which may promote neurodegeneration.[17] Minocycline was shown to be protective in preclinical studies in the MPTP model of PD,[18,19] and transgenic models of HD[20] and ALS,[14,20,21] although there are reports of negative results in an HD[22] transgenic model and exacerbation of MPTP toxicity.[23]

Based on this information we conducted a randomized, double-blind, futility clinical trial of creatine and minocycline, in parallel, in early PD. Our goal was to test whether creatine and minocycline had the potential to alter the short-term course of early PD relative to a predetermined threshold for progression of PD. Futility trials are a type of Phase II clinical trial that have been used successfully in cancer research for many years.[24,25] Futility trials are intended to eliminate agents that show low potential for further development.[24,26] Agents found to be futile in comparison to the threshold would not be considered for further clinical testing. Agents that are not found to be futile do not automatically advance to Phase III clinical trials, but receive consideration for further testing based on the overall profile including safety, tolerability, and activity. A discussion of the methods, use, and interpretation of futility trials is presented in a companion article.[27]

Methods. *Organization.* This multicenter clinical trial was organized by the Clinical Trials Coordination Center (CTCC) at the University of Rochester, the Department of Biostatistics, Bioinformatics, and Epidemiology at the Medical University of South Carolina, and National Institute of Neurologic Disorders and Stroke. National Institute of Neurologic Disorders and Stroke sponsored the trial. The Steering Committee developed the protocol and consent forms with the participating sites and guided the implementation of the trial. The protocol and consent were approved by a National Institute of Neurologic Disorders and Stroke appointed Oversight Board (OSB), an independent Data Safety Monitoring Board (DSMB), and the institutional review boards of each of the participating sites. The DSMB monitored the safety, data integrity, and progress of the trial.

Participants. Participants were men and women age 30 and over who had a diagnosis of PD but did not require medications for the management of their symptoms. Two of three cardinal manifestations of PD (tremor, rigidity, and bradykinesia) were required; these findings had to be asymmetric. The diagnosis of PD must have been made within 5 years of randomization. Women of childbearing potential were required to use adequate birth control and have a negative pregnancy test at baseline. Subjects were excluded if they had any secondary causes of parkinsonism, such as drug induced parkinsonism or structural lesions; had atypical parkinsonian syndromes; gait freezing or impairment in postural reflexes; had prior stereotaxic surgery for PD; used creatine, minocycline, or any investigational agent within 90 days prior to randomization; had known hypersensitivity to creatine or minocycline; used CoQ_{10} in doses greater than 300 mg 90 days prior to randomization; or had any clinically significant medical condition that could interfere with the subject's ability to safely participate in the study or to be followed.

Study design and randomization. A single arm futility study design was used to assess each of the study drugs, creatine and minocycline. We included a placebo arm for calibration, to verify and update the historical control assumptions used in sample size estimation.[28] Eligible subjects were randomly assigned in a 1:1:1 fashion to receive 1) 10 g/day of creatine monohydrate and placebo minocycline, 2) placebo creatine monohydrate and 200 mg/day of minocycline, or 3) placebo creatine monohydrate and placebo minocycline. The primary futility analysis was at 12 months of follow-up, but each subject was followed for 18 months for additional safety information. Subjects and investigators were kept blinded to treatment group. On January 25, 2005, the 12 month database was locked and the primary analyses were conducted.

Study intervention. Creatine was administered as 5 g sachets mixed with 8 ounces of liquid taken twice a day and minocycline was administered as 100 mg capsules taken twice a day. Both were taken with meals. Creatine and matching placebo were provided by The Avicena Group, Inc., and minocycline and matching placebo were purchased from Medicis Pharmaceuticals Corp.

Outcome measures. The primary, prespecified outcome measure was the change in the total Unified PD Rating Scale (UPDRS) score from baseline to either the time at which there was sufficient disability to warrant symptomatic therapy for PD or 12 months, whichever came first. Disability was assessed by the site investigator, based on impairment in ambulation, activities of daily living, and occupational status. Investigators were trained on this endpoint using case vignettes and retrospectively each decision to initiate therapy was reviewed by members of the Steering Committee and the DSMB. The mean change in total UPDRS for each treatment group was compared to a prespecified futility threshold of a 30% reduction in the historically derived change in the total UPDRS, which was based on the placebo arm of a previous clinical trial.[26] Tolerability was defined as the proportion of subjects taking study drug for the full 12 months. All severe adverse events (SAEs) were reviewed by the study medical monitor and an independent medical monitor. Both the site investigator and the medical monitors assessed the potential relationship between SAEs and study drug.

Study procedures. At the screening visit, the purpose and potential risks and benefits were explained to potential subjects and each subject gave written informed consent. Subjects then had a baseline medical history, physical examination, and underwent the UPDRS. Blood was obtained for serum chemistry and complete blood count. Participants were re-evaluated at 1, 3, 6, 9, and 12 months ($\pm$6 days) after the baseline visit using the battery of clinical scales and blood was drawn again at 6 and 12 months.

Sample size and statistical analysis. The sample size estimation was based on data from patients on placebo/tocopherol participating in the Deprenyl and Tocopherol Antioxidant Therapy of Parkinsonism trial (DATATOP),[29] a large cohort of newly diagnosed patients with PD similar to our planned study population. The DATATOP study met the Pocock criteria for the use of historical controls.[30] The observed mean change from baseline of total UPDRS in placebo/tocopherol patients (13 months $\pm$ 30 days) was 10.65 (SD 10.4). The threshold value was defined as 30% less progression on the total UPDRS than the 10.65 unit change in DATATOP, or 7.46. A sample size of 58 per group provides power greater than 85% to reject the null hypothesis of non futility if in fact the true mean total UPDRS worsening is greater than the threshold of 7.46 at the design alternative of 10.65. As with most clinical studies, a certain degree of noncompliance (including subject withdrawal or lost-to-follow-up) was expected. Assuming the noncompliance rate to be minimal at 5%, the required sample size was increased to 65 per treatment arm to account for the noncompliance in the intent-to-treat analysis.[31] For each study arm, the set of statistical hypotheses tested was as follows: H_0: $\Delta_i \leq 7.46$ vs H_a, $\Delta_i > 7.46$ (=10.65), where Δ_i is the mean change score (total UPDRS at 12 months or at the time of initiation of symptomatic therapy – total UPDRS at baseline) for the treatment arm i and 7.46 is the maximum mean increase (worsening) in the score between baseline and 12 months sufficient to warrant further evaluation of the drug in the Phase III trial. The hypothesis was tested with a one-sample t test at one-sided alpha level of 0.10. If the null hypothesis was rejected ($p \leq 0.1$) then the drug would be considered futile for further testing in a Phase III trial.

A secondary analysis of the primary outcome was planned, if the mean change in the total UPDRS score observed in the calibration placebo group falls outside of the 95% CI of the historical control mean change score of 10.65 ($\pm$1.02). The historical rate derived from DATATOP would be updated by incorporating the information from the calibration placebo group using Bayesian methods to derive a posterior mean. The futility threshold would be recomputed as 70% of this posterior mean and a one-sample t test would be performed for each active treatment arm.

Analysis of the primary outcome was conducted under the

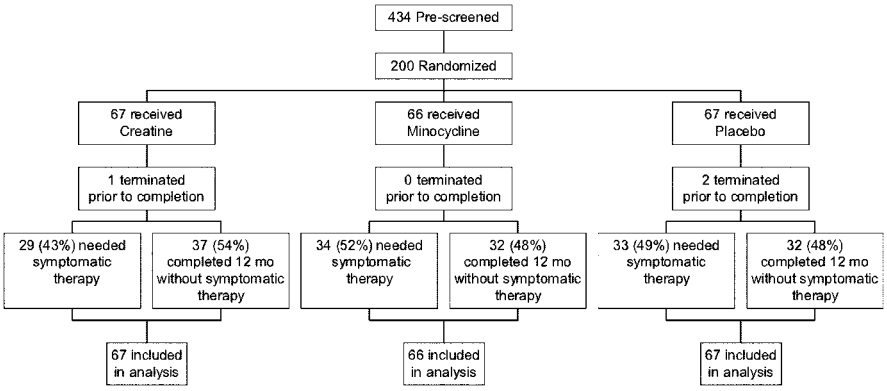

Figure 1. Flow diagram from screening to study completion (time until 12 months or need for symptomatic therapy, whatever comes first). Values were imputed due to missing visits for one creatine and one placebo patient and for those terminating prior to completion listed above. No imputation was required for the two minocycline and one creatine patients who dropped out after initiation of symptomatic therapy. Reasons for dropping out included the following: malaise, death (creatine), cardiac arrhythmia, lack of efficacy (minocycline), and colon cancer, depression (placebo). Of the 434 prescreened, 77 declined (major reasons being travel requirements, family's advice, or doctor's advice), 76 were excluded (major reasons being exclusionary medications or PD was too advanced), and the remaining 81 were identified as potential subjects (via chart review) but never screened. Seven signed inform consent but did not enroll (see text).

intent-to-treat principle where all randomized subjects are included in the analyses. For the small proportion of subjects who were lost to follow-up, we imputed their UPDRS change scores using the worst change score observed within their respective treatment groups. Exploratory analyses included multiple imputation to account for missing values and a sensitivity analysis in which we used a 30% reduction from the observed calibration placebo value to recompute the futility threshold value. No two-sample comparisons were made between placebo and treatment groups as the study was not designed or powered for this type of analysis. A two sample comparison would be underpowered compared to the planned futility analysis.

Results. *Subjects enrolled.* Between June and November of 2003, 434 potential participants were identified and prescreened for eligibility. Of these, 207 (48%) participants met study entry criteria and consented to further screening at the 45 participating sites. Three potential study subjects were found to be ineligible and four did not enroll for unknown reasons. The remaining 200 eligible subjects were randomized to one of three treatment groups (figure 1). The treatment groups were similar at baseline on demographic variables and total UPDRS and UPDRS subscores (table 1).

Futility. Compliance with study visits was high and only two patients in the creatine group and no patients in the minocycline group had missing values requiring imputation. The mean change (SD) in total UPDRS from either baseline to 12 months or the time at which symptomatic therapy was needed was 5.6 (8.69) for the creatine group and 7.09 (8.71) for the minocycline group (table 2) (figure 2). The observed progression in both the creatine and minocycline groups did not exceed the predetermined futility threshold. Therefore, the null hypothesis that the means were less than or equal to the threshold value of 7.46 (30% less than the 10.65 DATATOP historical rate of progression) could not be rejected for creatine ($p = 0.96$) or minocycline ($p = 0.63$). Creatine and minocycline could not be rejected as futile using this analysis and therefore met the criteria for consideration for further clinical testing. Using multiple imputation instead of worst change score for the group to account for missing observations yielded similar results.

The calibration placebo group mean change of 8.39 (9.76) fell outside the 95% CI for the DATATOP historical control of 9.63 to 11.67. As planned in our design, the historical control rate was updated using the observed placebo information. With this update, the threshold value decreased to 7.2. Against this comparison, neither creatine

Table 1 *Baseline characteristics*

	Creatine, n = 67	Minocycline, n = 66	Placebo, n = 67
Male, n (%)	47 (70)	39 (59)	40 (60)
White, n (%)	62 (93)	63 (95)	63 (94)
Hispanic, n (%)	3 (4)	1 (2)	2 (3)
Age, y (SD)	61.5 (10.6)	64.8 (10.5)	60.7 (9.8)
Duration PD, y (SD)	0.78 (1.06)	0.57 (0.64)	0.64 (0.59)
Total UPDRS (SD)	23.9 (9.07)	24.4 (9.74)	22.8 (9.63)
UPDRS Mental (SD)	1.13 (1.29)	1.52 (1.81)	1.13 (1.19)
UPDRS Motor (SD)	16.4 (6.77)	16.5 (7.19)	15.6 (7.01)
UPDRS ADL (SD)	6.33 (3.07)	6.38 (3.6)	6.03 (3.45)
Hoehn and Yahr (SD)	1.43 (0.5)	1.58 (0.5)	1.46 (0.5)
Schwab and England ADL (SD)	92.7 (5.25)	92.5 (6.4)	94.2 (4.81)

PD = Parkinson disease; UPDRS = Unified Parkinson Disease Rating Scale; ADL = activities of daily living.

Table 2 *Primary outcome: change in total Unified Parkinson Disease Rating Scale (UPDRS) from baseline to 12 months or need for symptomatic therapy (whichever comes first)*

Outcome/treatment group	Mean (SD)	95% CI
Primary analysis*		
Total UPDRS		
Creatine	5.6 (8.69)	(3.48, 7.72)
Minocycline	7.09 (8.71)	(4.95, 9.23)
Placebo (Calibration)	8.39 (9.76)	(6.01, 10.8)
DATATOP Placebo/Tocopherol	10.65 (10.4)	(9.63, 11.67)
Secondary outcomes		
Motor UPDRS		
Creatine	3.27 (6.65)	(1.65, 4.89)
Minocycline	3.98 (5.92)	(2.53, 5.44)
Placebo	5.34 (6.82)	(3.68, 7.01)
Mental UPDRS		
Creatine	0.33 (1.66)	(–0.08, 0.73)
Minocycline	0.38 (2.04)	(–0.12, 0.88)
Placebo	0.81 (1.87)	(0.35, 1.26)
ADL UPDRS		
Creatine	2.21 (3.09)	(1.46, 2.96)
Minocycline	2.73 (3.42)	(1.89, 3.57)
Placebo	2.60 (3.74)	(1.68, 3.51)
Hoehn & Yahr	0.39 (0.52)	(0.26, 0.52)
Minocycline	0.38 (0.72)	(0.2, 0.56)
Placebo	0.43 (0.74)	(0.25, 0.61)
Schwab & England (investigator)		
Creatine	–4.8 (6.12)	(–6.3, –3.3)
Minocycline	–7.6 (9.33)	(–9.9, –5.3)
Placebo	–7.6 (8.59)	(–9.7, –5.5)

Worst change score for the group is used to impute missing values.

* Primary analysis compares each treatment to the futility threshold, or 70% of historical control, which equals 7.46. Secondary analyses included an updated futility threshold of 7.02 based on the calibration group and a sensitivity analysis with a futility threshold of 5.87.

ADL = activities of daily living.

(p = 0.93) nor minocycline (p = 0.54) could be rejected as futile. Additionally, an exploratory sensitivity analysis was performed based on the calibration placebo group. Using only data from the placebo group, the threshold value was recomputed as 30% less than 8.39 and the futility threshold decreased to 5.87. With a threshold of 5.87, neither creatine (p = 0.6) nor minocycline (p = 0.13) could be rejected as futile, although minocycline was close to the prespecified alpha level of 0.10.

Combining all three arms of the study, 96 (48%) subjects required symptomatic therapy during the course of the trial (see figure 1). Subjects requiring symptomatic therapy had greater changes in their UPDRS scores than those who completed 12 months without the addition of symptomatic therapy. The 104 (52%) subjects who did not receive symptomatic therapy (or terminated prior to completion) had a mean change of 4.35 (8.83) on their total UPDRS score over 12 months compared to 12.36 (8.86) for the 22 subjects starting levodopa and 8.98 (8.84) for the 47 subjects starting dopamine agonists. The observed changes in the total UPDRS were largely driven by changes in the motor subscore and to a lesser extent the ADL subscore (see table 2).

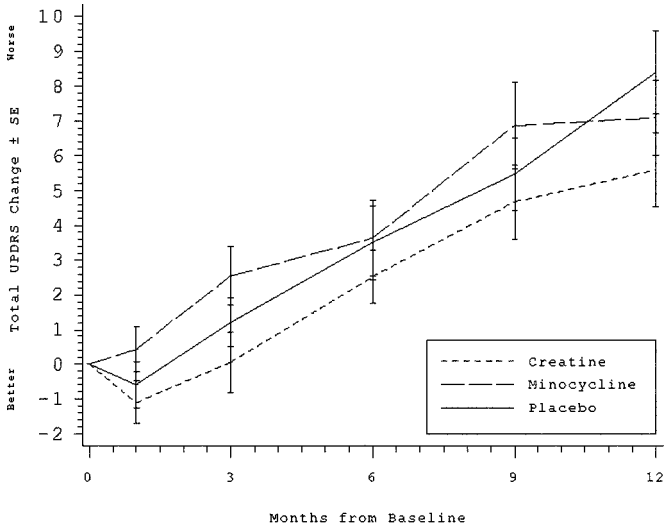

Figure 2. Change from baseline in Total Unified Parkinson Disease Rating Scale over time. Excludes visits conducted after patients needed symptomatic treatment, and carries forward the need for symptomatic therapy visit. Missing visits are imputed with worst change score for the group. Bars represent standard errors of the means at 1, 3, 6, 9, and 12 months.

Safety and tolerability. Creatine, minocycline, and the matching placebo formulations were generally well tolerated, although minocycline was less well tolerated than creatine. Study drug was prematurely discontinued in 5 cases (7%) in the creatine arm, 14 (21%) in the minocycline arm (figure 3), and 4 (6%) in the calibration placebo arm. There were 8 patients with dose reductions and 8 patients with temporary suspensions in the creatine group, 15 patients with dose reductions, and 15 patients with temporary suspensions in the minocycline group, and 11 patients with dose reductions and 8 patients with temporary suspensions in the placebo group, some of whom eventually discontinued study treatment.

The three most commonly reported adverse events across the three treatment groups were upper respiratory symptoms (26%), joint pain (19%), and nausea (17%) (table 3). There were seven cases of tooth discoloration and four cases of skin discoloration, all in the minocycline group, but only one case of tooth discoloration led to discontinuation of medication. There were six incidents of elevated serum creatinine in the creatine group; three of these, occurring in two subjects, were judged to be clinically significant. Adverse events occurring with a frequency greater than 5% are reported in table 3.

Fourteen SAEs occurred during the study. Five occurred in the creatine group (cardiomyopathy, coronary artery disease, fatal motorcycle accident, myocardial infarction, and spinal stenosis surgery). Six occurred in the minocycline group (two cases of coronary artery disease,

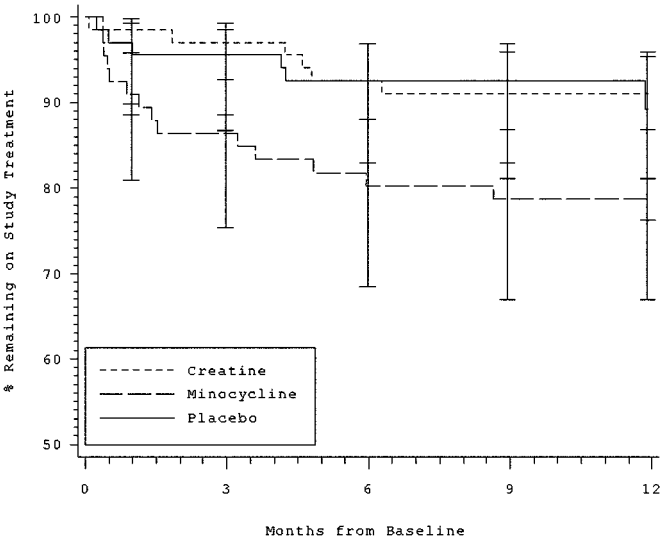

Figure 3. Kaplan–Meier estimate of time to permanent discontinuation of study treatment. Bars represent the 95% pointwise CIs. The minocycline group had more discontinuations early, but then slowed after 3 months.

two cases of pneumonia, syncope, and squamous cell carcinoma). Three occurred in the calibration placebo group (colon cancer, pneumonitis, renal calculus). Of the events in the two active treatment groups, only the squamous cell carcinoma in the minocycline group was coded by blinded investigators as possibly related to the study interventions. None of the SAEs was judged as definitely or probably related by the independent medical monitor.

Discussion. This randomized, double-blind, futility trial showed that neither creatine nor minocycline could be rejected as futile in a 12-month evaluation of the clinical progression of PD. The observed mean changes in total UPDRS scores for creatine and minocycline were not significantly greater than the futility threshold values. Based on these findings, both creatine and minocycline merit further consideration for Phase III clinical trials.

The effects of creatine on UPDRS progression were robust to a range of threshold values, whether based on the historical control data, updated historical control, or calibration placebo group. The mean progression in the minocycline group was actually above the futility threshold based on the calibration placebo group (5.87) in the sensitivity analysis. However, the minocycline group cannot be rejected as futile. This is because the minocycline group mean falls close enough to the threshold value that it is still below the rejection region of the distribution of

Table 3 *Adverse events occurring in more than 5% of subjects in any one treatment group*

Event (WHO term)	Creatine, no. (%)	Minocycline, no. (%)	Placebo, no. (%)	Total, no. (%)
Joint pain	13 (19)	12 (18)	12 (18)	37 (19)
Dizziness	9 (13)	15 (23)	4 (6)	28 (14)
Headache	7 (10)	10 (15)	6 (9)	23 (12)
Tremor aggravated	5 (7)	3 (5)	3 (4)	11 (6)
Depression	5 (7)	9 (14)	4 (6)	18 (9)
Irregular sleep	5 (8)	10 (15)	6 (9)	21 (11)
Constipation	6 (9)	9 (14)	5 (7)	20 (10)
Gastroesophageal reflux	2 (3)	5 (8)	2 (3)	9 (5)
Nausea	11 (16)	16 (24)	7 (10)	34 (17)
Upper respiratory symptoms	17 (25)	13 (20)	21 (31)	51 (26)
Back pain	1 (1)	6 (9)	6 (9)	13 (7)
Fatigue	2 (3)	8 (12)	4 (6)	14 (7)
Edema	8 (12)	9 (14)	8 (12)	25 (13)
Fall	3 (4)	7 (11)	5 (7)	15 (8)
Diarrhea	4 (6)	3 (5)	1 (1)	8 (4)
Serum creatinine increased	6 (9)	0 (0)	0 (0)	6 (3)
Hypertension	0 (0)	2 (3)	4 (6)	6 (3)
Rash	1 (1)	4 (6)	2 (3)	7 (4)
Skin/tooth discoloration	0 (0)	11 (17)	0 (0)	11 (6)
Balance difficulty	0 (0)	4 (6)	0 (0)	4 (2)
Heartburn	0 (0)	4 (6)	1 (1)	5 (3)
Dry mouth	2 (3)	5 (8)	1 (1)	8 (4)
Hypercholesterolemia	1 (1)	4 (6)	0 (0)	5 (3)
Anemia	0 (0)	4 (6)	2 (3)	6 (3)
Influenza-like symptoms	2 (3)	4 (6)	1 (1)	7 (4)

the futility threshold. This is reflected in the p value of 0.13, which is close to the significance level of 0.1 for concluding that the drug is futile. The threshold for futility used in this study was a 30% reduction in PD progression measured by the UPDRS. While other thresholds could be chosen, this decision was based on effects seen in previous trials and clinical judgment about the magnitude of a meaningful effect.[26]

There was a one point improvement in total UPDRS evident after 1 month of creatine treatment (see figure 2). This could be interpreted as a short-term or "symptomatic" effect that may not be sustained. However, creatine would not be rejected as futile even if the one-point change were discounted and the analysis were conducted using a change in creatine of 6.84 (8.54) on the total UPDRS ($p = 0.25$). Further follow-up would determine if the slowed rate of progression seen in the last 3 months of the study in the minocycline group (see figure 2) is sustained, but the primary, prespecified futility analysis was at 12 months. These futility trials were not designed to determine long-term results, but to reject agents that show no potential for success in long-term Phase III trials.

Creatine was well tolerated and 91% of subjects continued creatine throughout the 12 months of the study. The volume of the creatine suspension was not problematic for compliance and there were no serious renal complications in the creatine arm. Seventy-six percent of subjects tolerated minocycline for the entire study. Subjects who discontinued minocycline generally did so within the first 30 to 60 days due to gastrointestinal discomfort (see figure 3). Tooth discoloration in the minocycline arm occurred more commonly than expected from previous trials[16] and clinical use[32,33] but only led to discontinuation of drug in one case. Since we added a discussion on tooth discoloration to the informed consent during the trial, it is possible that the investigators were unblinded for those participants with tooth discoloration. If investigators were expecting minocycline to be effective, the potential unblinding could have the effect of inflating the positive results for minocycline. It is also possible that taking a placebo in addition to the active agent may have reduced tolerability and compliance although patients with PD commonly take multiple medications in both clinical studies and routine care.

The calibration placebo rate of progression fell outside the 95% CI for the DATATOP historical rate. This finding may be due to sampling variability or measurement error. Recent trials, such as the Coenzyme Q_{10} in Early PD trial (QE2) published in 2002,[34] showed a rate of progression nearly identical to DATATOP in early, untreated PD subjects. In contrast, a trial of the MAO-B inhibitor lazabemide published in 1996 showed a 12-month rate of progression of 8.1 units on the total UPDRS.[35] This suggests some variability in observed UPDRS progression that is not due to temporal practice or cohort effects.

Another explanation for the observed difference between our placebo group and DATATOP is a systematic difference in the types of subjects or how they were cared for in the study. The baseline characteristics in the three groups were similar to the DATATOP placebo/tocopherol cohort in age, sex, race, and ethnicity. The total UPDRS score at entry for DATATOP was 25.4 (11.6) compared to 23.68 (9.46) overall in our study. The study cohort had an average time from diagnosis of PD to randomization of 0.66 years (0.8) compared to a somewhat longer disease duration, 1.2 (1.1) years, for DATATOP. We performed a secondary analysis selecting DATATOP placebo patients with characteristics (age, duration of PD, and baseline UPDRS) similar to participants in this futility trial. These analyses gave a similar mean change in UPDRS as obtained from the analyses using the entire group of DATATOP placebo subjects. It is possible that the clinical care of early PD in this study was different from the clinical care in DATATOP and the QE2 trial. In this study subjects starting levodopa had an average change in total UPDRS of 12.36 (8.86) compared to 16.3 (10.7) for DATATOP. The change in the readiness to use levodopa may be due to the results of the earlier vs later levodopa trial (ELLDOPA).[36] The ELLDOPA trial may have changed some investigators' prior belief that levodopa hastens the progression of early PD and may have thereby reduced the amount of progression needed to trigger the decision to initiate levodopa therapy. The initiation of dopamine agonists, which were not a treatment option for the DATATOP endpoint, was associated with an even smaller 8.3 unit change in total UPDRS scores. The exact reasons for the difference in the placebo rate of progression remain unclear. A second futility study with different agents that is currently in progress will help determine if the discrepancy between our placebo group and DATATOP are due to sampling and measurement variability or more systematic differences in clinical practice.

The use of historical or other external controls has been a controversial issue, especially when these types of controls are used to replace randomized Phase III trials. However, in this study, we are looking for indications to conduct Phase III trials. See the companion article by Tilley et al.[27] for more discussion of this issue. Concerns about sampling variability or cohort effects prompted the inclusion of a calibration placebo group in this study. Most futility trials in cancer, where this design is used most commonly, do not include controls[37] since the expected control rate (usually tumor recurrence) is well-established. But some authors have advocated for calibration control arms in futility studies as a check or calibration of the historical rate.[28] Given these results of this study the use of a calibration placebo group should be considered in future futility studies in PD. Based on the 65 subjects in the calibration

placebo group, it would be premature to abandon the progression rate from DATATOP, which was based on nearly 400 subjects. But the calibration placebo group allowed us to consider a range of futility threshold values. Data from the placebo group were used to update the historical rate by calculating a Bayesian posterior mean and provided a lower futility threshold for the sensitivity analysis. The study was not intended or powered, however, to make direct comparisons between the placebo group and active arms.

The effects of creatine on UPDRS progression were robust to the range of threshold values tested. The magnitude of effect seen with creatine is comparable to the effect seen with 1,200 mg day of Coenzyme Q_{10} in QE2.[34] The similarity is intriguing since both agents are thought to support aspects of mitochondrial function. The evidence supporting a role for mitochondrial dysfunction in the pathogenesis of PD is multifaceted, including MPTP models and other environmental toxins,[38] deficits in complex I in platelets[6,7,39] and nigral tissue,[8] and genetic mutations such as DJ-1[40,41] and PINK1.[42] Taken together with the results of the Coenzyme Q_{10} trial, this study suggests that interventions that augment mitochondrial function and ameliorate oxidative stress may hold promise in PD.

This study was not designed to determine if either agent is actually effective in slowing the clinical progression of PD. Randomized, placebo controlled, Phase III clinical trials that focus on clinically meaningful outcomes will be needed to prove or disprove the clinical efficacy of these agents. Therefore, neither creatine nor minocycline should be used clinically for treating PD based on the results of this study. The conclusion from this futility trial is that these agents at the doses studied merit consideration for Phase III trials. Other doses of creatine or minocycline could be tested using this Phase II design to estimate the dose–response relationship and determine the most promising dose for further study. Several additional factors must be weighed before selecting agents for Phase III trials, including the observed safety, tolerability, activity, cost, and availability of these two agents in comparison with other agents currently being tested in Phase II trials.

In addition to identifying therapies to consider for a large simple Phase III efficacy trial, the futility study provided other valuable information. If the futility study had not been completed, the estimate used for the placebo mean in subsequent trials could have been an overestimate of the expected increase in UPDRS and could have led to incorrect sample size estimates for Phase III trials. The futility study showed that de novo patients with PD can be enrolled rapidly, in substantial numbers. Specific issues in performance, such as low minority recruitment, were identified and will be addressed before future trials begin. Since recruitment, retention, simplicity, and consistency of data collection are critical elements of success for future trials, this futility testing phase should improve the likelihood that a long term Phase III trial can be successfully conducted.

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References

1. Ravina BM, Fagan SC, Hart RG, et al. Neuroprotective agents for clinical trials in Parkinson's disease: a systematic assessment. Neurology 2003;60:1234–1240.
2. Persky AM, Brazeau GA. Clinical pharmacology of the dietary supplement creatine monohydrate. Pharmacol Rev 2001;53:161–176.
3. Sora I, Richman J, Santoro G, et al. The cloning and expression of a human creatine transporter. Biochem Biophys Res Commun 1994;204:419–427.
4. Tarnopolsky M, Parise G, Fu MH, et al. Acute and moderate-term creatine monohydrate supplementation does not affect creatine transporter mRNA or protein content in either young or elderly humans. Mol Cell Biochem 2003;244:159–166.
5. Jonas M, Cunha BA. Minocycline. Ther Drug Monit 1982;4:137–145.
6. Parker WD, Jr., Boyson SJ, Parks JK. Abnormalities of the electron transport chain in idiopathic Parkinson's disease. Ann Neurol 1989;26:719–723.
7. Krige D, Carroll MT, Cooper JM, et al. Platelet mitochondrial function in Parkinson's disease. The Royal Kings and Queens Parkinson Disease Research Group. Ann Neurol 1992;32:782–788.
8. Schapira AH, Cooper JM, Dexter D, et al. Mitochondrial complex I deficiency in Parkinson's disease. J Neurochem 1990;54:823–827.
9. Matthews RT, Ferrante RJ, Klivenyi P, et al. Creatine and cyclocreatine attenuate MPTP neurotoxicity. Exp Neurol 1999;157:142–149.
10. Klivenyi P, Gardian G, Calingasan NY, et al. Additive neuroprotective effects of creatine and a cyclooxygenase 2 inhibitor against dopamine depletion in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mouse model of Parkinson's disease. J Mol Neurosci 2003;21:191–198.
11. Andreassen OA, Dedeoglu A, Ferrante RJ, et al. Creatine increase survival and delays motor symptoms in a transgenic animal model of Huntington's disease. Neurobiol Dis 2001;8:479–491.
12. Ferrante RJ, Andreassen OA, Jenkins BG, et al. Neuroprotective effects of creatine in a transgenic mouse model of Huntington's disease. J Neurosci 2000;20:4389–4397.
13. Klivenyi P, Ferrante RJ, Matthews RT, et al. Neuroprotective effects of creatine in a transgenic animal model of amyotrophic lateral sclerosis. Nat Med 1999;5:347–350.
14. Zhang W, Narayanan M, Friedlander RM. Additive neuroprotective effects of minocycline with creatine in a mouse model of ALS. Ann Neurol 2003;53:267–270.
15. Garner SE, Eady EA, Popescu C, et al. Minocycline for acne vulgaris: efficacy and safety. Cochrane Database Syst Rev 2003:CD002086.
16. Tilley BC, Alarcon GS, Heyse SP, et al. Minocycline in rheumatoid arthritis. A 48-week, double-blind, placebo-controlled trial. MIRA Trial Group Ann Intern Med 1995;122:81–89.
17. Hirsch EC, Breidert T, Rousselet E, et al. The role of glial reaction and inflammation in Parkinson's disease. Ann NY Acad Sci 2003;991:214–228.
18. Du Y, Ma Z, Lin S, et al. Minocycline prevents nigrostriatal dopaminergic neurodegeneration in the MPTP model of Parkinson's disease. Proc Natl Acad Sci USA 2001;98:14669–14674.
19. Wu DC, Jackson-Lewis V, Vila M, et al. Blockade of microglial activation is neuroprotective in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine mouse model of Parkinson disease. J Neurosci 2002;22:1763–1771.
20. Chen M, Ona VO, Li M, et al. Minocycline inhibits caspase-1 and caspase-3 expression and delays mortality in a transgenic mouse model of Huntington disease. Nat Med 2000;6:797–801.
21. Kriz J, Nguyen MD, Julien JP. Minocycline slows disease progression in a mouse model of amyotrophic lateral sclerosis. Neurobiol Dis 2002;10:268–278.
22. Smith DL, Woodman B, Mahal A, et al. Minocycline and doxycycline are not beneficial in a model of Huntington's disease. Ann Neurol 2003;54:186–196.
23. Yang L, Sugama S, Chirichigno JW, et al. Minocycline enhances MPTP toxicity to dopaminergic neurons. J Neurosci Res 2003;74:278–285.
24. Herson J. Predictive probability early termination plans for phase II clinical trials. Biometrics 1979;35:775–783.
25. Gehan EA. Update on planning of phase II clinical trials. Drugs Exp Clin Res 1986;12:43–50.
26. Elm JJ, Ravina B, Shannon K, et al. A responsive outcome for Parkinson's disease neuroprotection futility studies. Ann Neurol 2005;57:197–203.
27. Tilley BC, Palesch YY, Kieburtz K, et al. Optimizing the ongoing search for new treatments for Parkinson disease: using futility designs. Neurology 2006;66:628–633.
28. Herson J, Carter SK. Calibrated phase II clinical trials in oncology. Stat Med 1986;5:441–447.
29. Effect of deprenyl on the progression of disability in early Parkinson's disease. The Parkinson Study Group. N Engl J Med 1989;321:1364–1371.
30. Pocock SJ. The combination of randomized and historical controls in clinical trials. J Chronic Dis 1976;29:175–188.
31. Friedman L, Furberg C, DeMets D. Fundamentals of Clinical Trials. 2nd ed. Littleton, MA: John Wright-PSG Inc., 1985:94.
32. McKenna BE, Lamey PJ, Kennedy JG, Bateson J. Minocycline-induced staining of the adult permanent dentition: a review of the literature and report of a case. Dent Update 1999;26:160–162.
33. Cheek CC, Heymann HO. Dental and oral discolorations associated with minocycline and other tetracycline analogs. J Esthet Dent 1999;11:43–48.
34. Shults CW, Oakes D, Kieburtz K, et al. Effects of coenzyme Q10 in early Parkinson disease: evidence of slowing of the functional decline. Arch Neurol 2002;59:1541–1550.
35. Effect of lazabemide on the progression of disability in early Parkinson's disease. The Parkinson Study Group. Ann Neurol 1996;40:99–107.
36. Fahn S, Oakes D, Shoulson I, et al. Levodopa and the progression of Parkinson's disease. N Engl J Med 2004;351:2498–2508.
37. Green SBJ, Crowley J. Clinical trials in oncology. London: Chapman & Hall, 1997:44–47.
38. Kindt MV, Heikkila RE, Nicklas WJ. Mitochondrial and metabolic toxicity of 1-methyl-4-(2′-methylphenyl)-1,2,3,6-tetrahydropyridine. J Pharmacol Exp Ther 1987;242:858–863.
39. Haas RH, Nasirian F, Nakano K, et al. Low platelet mitochondrial complex I and complex II/III activity in early untreated Parkinson's disease. Ann Neurol 1995;37:714–722.
40. Bonifati V, Rizzu P, van Baren MJ, et al. Mutations in the DJ-1 gene associated with autosomal recessive early-onset parkinsonism. Science 2003;299:256–259.
41. Canet-Aviles RM, Wilson MA, Miller DW, et al. The Parkinson's disease protein DJ-1 is neuroprotective due to cysteine-sulfinic acid-driven mitochondrial localization. Proc Natl Acad Sci USA 2004;101:9103–9108.
42. Valente EM, Abou-Sleiman PM, Caputo V, et al. Hereditary early-onset Parkinson's disease caused by mutations in PINK1. Science 2004;304:1158–1160.