Low dose niacin versus placebo in the treatment of Parkinson's Disease: A Randomized Controlled Trial

Chandramohan Wakade (cwakade@augusta.edu)
Augusta University College of Allied Health Sciences https://orcid.org/0000-0002-4348-8603
Raymond Chong
Augusta University College of Allied Health Sciences
Marissa Seamon
Augusta University College of Allied Health Sciences
Sharad Purohit
Augusta University College of Allied Health Sciences
Banabihari Giri
Augusta University College of Allied Health Sciences
John C. Morgan
Augusta University Medical College of Georgia

Research

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Abstract

Background

Parkinson's Disease (PD) patients have lower niacin levels compared to their spouses. The main objective was to study low-dose daily niacin supplementation versus placebo on motor symptoms in Parkinson's disease subjects.

Methods

A randomized, placebo-controlled, double-blind, single-center clinical trial in Parkinson's disease patients was performed in Augusta, GA, between September 2016 to September 2019. Randomized participants were 47 PD patients who received either low-dose niacin (N = 21) or placebo (N = 26) for the first six months (mean age 68.4 SD, 8.7; mean duration of disease 5.8 SD 4.9; H&Y scores between 0.5 to 4; 64% subjects were Veterans). The Veterans Affairs Pharmacy generated the randomized sequence. After the double-blind phase, all participants received open-label niacin for the next six months. All patients were evaluated at baseline, six months, and one year of treatment. The main outcome measure was the Unified Parkinson's Disease Rating Scale III (UPDRS III) scores. Secondary outcome measures were depression, sleep quality, mental flexibility and cognition, and physical fatigue.

Results

39 subjects were analyzed with low-dose niacin (N = 18) and placebo (N = 21) for the completion of the first six months (randomized, double-blind), and 31 subjects were analyzed for the completion of the next six months (open-label) with low-dose niacin (N = 14) and placebo (N = 17). Niacin treatment was not tolerated by two subjects. The baseline mean UPDRS III score was 21.3 ± 15.8 for the niacin group and 22.4 ± 11.8 for placebo. The change with six months of placebo was 0.05 [95% CI, -2.4 to 2.32], and niacin was 1.06 [95% CI, -3.68 to 1.57]. From six to twelve months, the average UPDRS III score decreased for the placebo group by 4.58 [95% CI, -0.85 to 8.30] and the niacin group by 4.63 [95% CI, 1.42 to 7.83]. Eight subjects withdrew from the study before the 6-month time point and eight more before the one-year time point due to voluntary discontinuation, flushing, or inability to continue (SARS-CoV-2 shut-down).

Conclusion

Low-dose niacin supplementation may be helpful as an adjunct therapy in improving motor function in PD.

Trial registration

Clinicaltrials.gov, NCT03462680. Registered 12 March 2018- Retrospectively registered, https://clinicaltrials.gov/ct2/show/NCT03462680?term=gpr109A&draw=2&rank=1

Background

Parkinson's disease (PD) is one of the most common movement disorders afflicting about 1% of the population above 60 and reaches 4% by age 80. A definitive diagnosis for PD requires an autopsy, and there is no cure or definitive disease-slowing therapy despite extensive investigation [1]. Sinemet (carbidopa/levodopa) remains the cornerstone of PD therapy but can lead to significant motor complications (wearing off and dyskinesia) over time [2].

Numerous pathophysiological processes interplay in PD, but neuroinflammation and mitochondrial dysfunction remain at the core of PD pathology. Niacin is, therefore, a proper choice as an adjunct therapy in PD because it is anti-inflammatory and boosts mitochondrial function, providing NAD [3–5]. Our previous data, including a recently published three-month effectiveness trial, support this finding and indicate that niacin may influence outcomes in PD [3, 6–8]. Moreover, carbidopa in Sinemet is known to deplete niacin levels in treated PD patients [9]. Despite the above-mentioned reasons and strong indications from animal models in PD, there have been no prior randomized clinical trials for supplementation of niacin in PD.

We hypothesized that niacin might improve tremor, rigidity, and overall UPDRS III scores in PD. At the end of the 6-month double-blind controlled trial, all participants enrolled received an open-label niacin supplementation for another six months (total 12 months), and then the randomization code was opened. This study reports the final analysis of 39 randomized PD patients who completed six months of the double-blind, placebo-controlled trial with an open-label niacin supplementation for six additional months. Participants were assessed by UPDRS III, Trail-making Test (TMT), Stroop test, Geriatric Depression Scale (GDS), Fatigue Severity Scale (FSS), Visual Analogue Fatigue Scale (VAFS), sleep pattern, and grip strength. Blood, urine, and CSF samples were tested for niacin metabolites and other biological markers but are not reported here.

Methods

Study Design and Participants

The trial was a six-month randomized, double-blind, placebo-controlled (wait-listed) over-the-counter study of 250mg daily, slow-release niacin with a subsequent six-month open-label portion. The study was a single-center trial conducted at Charlie Norwood Veterans Affairs Medical Center (CNVAMC, GA, USA) neurology clinic and Augusta University Medical Center (AUMC, GA, USA) tertiary movement disorders center (clinicaltrials.gov identifier: NCT03462680). Supplements (placebo and niacin), a room for performing outcome measures, and blood level measurements (amino acids and serotonin) were provided by the CNVAMC. Patients were tested at baseline, after six months of daily 250mg niacin or placebo, and then again after six months of open-label 250mg daily niacin. All measurements were taken by a single assessor to eliminate interrater differences. The protocol was approved by the institutional review boards at the CNVAMC and AUMC. All participants gave written informed consent prior to any study procedures.

Mild to moderately severe Parkinson's Disease patients with H&Y scores between 0.5-4 were enrolled in the study. The UK Parkinson's Disease Society Brain Bank Diagnostic Criteria [10] were used for the inclusion criteria. Subjects were previously stabilized on all Parkinson's Disease medications prior to enrollment with expected medication stability for at least six months. To be qualified for the study, subjects had scores above 24 on the mini mental state exam (MMSE), indicating no significant evidence of dementia that may confound the study. Those with other severe neurological problems, previous brain surgery, functional blindness, inability to participate in visuomotor or gait assessments, an allergy to niacin, or other severe illnesses were excluded from the study. An attending expert neurologist used clinical judgment to determine if a patient was suitable for the study, which included an optional spinal tap.

Intervention

Forty-seven patients were enrolled in the study. Patients were randomized and blinded to receive either 250 mg of niacin once daily or a placebo, in accordance with the sequestered fixed randomization schedule (Fig. 1), using balanced blocks to ensure an approximate 1:1 ratio of the two treatment arms for early-stage or late-stage patients. The CNVAMC pharmacy generated the randomized sequence for the trial. The PI, all study personnel, and study subjects were blinded to this randomization. The code was not revealed to the investigators until the study was completed in April 2020.

Outcomes of the study

The primary outcome of the study was a change in the UPDRS III scores from baseline to six months and then one year. Rejection of the null hypothesis occurs when the mean score at twelve months is less than baseline. Based on pilot data, the margin of superiority representing the minimal clinically meaningful change in score, δ, is 5. This value is consistent with the expected median annual rate of decline in the UPDRS III score of + 5.5 points [11, 12]. Secondary outcomes included depression rating by the GDS, fatigue rating by the FSS and VAFS, mental resilience measured by TMT A and B, the difference between TMT-B and TMT-A was considered as a measurement of cognitive flexibility [13], cognitive ability and mental fatigue through the Stroop Test, overall cognitive function by MMSE (which excluded those who displayed dementia as a score < 24), amino acid and serotonin levels, and physical strength and fatigue through a grip strength test. There were no changes made during the course of the trial period.

Statistical Analysis

The sample size of 39 patients was determined by power analysis to give 80% power ($\alpha = 0.05$) to detect a reduction of 2.5 points in UPDRS III scores after six-month treatment [11, 12]. For a significance level (α) of 5%, and a power ($1-\beta$) of 80%, an expected standard deviation of the difference between pairs of data is 3.9, and the minimum sample size was 13 participants per group. Our study sample was substantially increased to take into account potential dropouts or any unexpected increase in variability.

Data for all participants was captured into an Excel sheet (Microsoft Excel v2016) for subsequent analysis. Outcomes of all 39 participants who completed the 6-month trial were analyzed according to

their randomization groups, comparing differences between treatments and differences between time points of baseline, six months, and one year.

One outlier was removed from UPDRS III scores based on the ordinary least-squares regression test (Q = 10%). All other outcome data had no outliers removed by the robust regression and outlier removal test [14]. Mean, standard deviations or standard error, and ranges were calculated for all numerical data. Categorical data were presented as counts and percentages. Statistical differences were tested between the treatment groups and time points by ANOVA with Tukey's posthoc corrections for primary outcomes. P-values were not corrected for the multiple comparisons between placebo and niacin for the secondary outcomes.

Differences were considered significant when $p \leq 0.05$; all p values were two-sided. All analyses were performed using Prism (v8.0, Graphpad, San Deigo, CA, USA).

Results

Participant Characteristics

Between 2016–2019, 47 participants were enrolled at the CNVAMC and randomly assigned to the placebo (n = 26) or 250 mg daily niacin (n = 21) group (Fig. 1). The mean age was 68.4, with a mean duration of the disease being 5.8 years (Table 1). Forty-four were Caucasian, three were African American, and eight of the 47 were women. The H&Y score of all patients ranged between 0.5-4.0. Thirty-four subjects were rated early-stage (H&Y < 2.5), while thirteen were classified as late-stage (H&Y ≥ 2.5). Twenty-five (64.1%) subjects were Veterans (Table 1).

Table 1
Demographic and baseline clinical characteristics of the participants (n = 47).

		Treatment Groups	
Characteristics	Total (n = 47)	Placebo (n = 21)	Niacin (n = 18)
Sex, N (%)			
Men	35 (89.7)	19 (48.7)	16 (41.0)
Women	4 (10.3)	2 (5.1)	2 (5.1)
Race/ethinicity, N (%)			
Non-Hispanic White	46 (92.3)	18 (46.2)	18 (46.2)
Non-Hispanic Black	3(7.7)	3 (7.7)	0 (0)
Veteran status, N (%)			
Veterans	25 (64.1)	15 (38.7)	10 (25.6)
Non-Veterans	14 (35.9)	6 (15.4)	8 (20.5)
Age, mean (SD), y	68.4 (8.7)	68.0 (10.7)	68.2 (6.0)
Duration of PD, mean (SD), y	5.8 (4.9)	5.6 (4.2)	6.0 (6.0)
Age of Onset, mean (SD), y	62.3 (9.4)	61.6 (10.9)	63.3 (7.2)
Disease Stage, N (%)			
Early (H&Y < 2.5)	28 (71.8)	14 (35.9)	14 (35.9)
Late (H&Y ≥ 2.5)	11 (28.2)	7 (17.9)	4 (10.2)
UPDRS III scores, mean (SD)	21.9 (15.3)	22.4 (11.8)	21.3 (15.8)
Medications, mg/day			
Sinemet intake, N (%)	35 (89.7)	20 (51.3)	15 (38.5)+,
Levodopa dosage, mean (range)	485.5 (200–1000)	488.9 (300–1000)	480.8 (200–800)
H&Y staging, mean (range)	2.0 (0.5-4)	2.2 (1.5-4)	1.8 (0.5-4)
UPDRS III – Unified Parkinson's Disease Rating Scale III, H&Y - Hoehn and Yahr Scale for Parkinson's Disease Staging. Levodopa dosage was determined as mg/day.			
+Medication information on two subjects in the niacin group was not available.			

Thirty-five subjects were on Sinemet as their primary Parkinson's medication throughout the study, with five patients changing their dose during the open-label phase of the study. Other medications or supplements taken by subjects included Trihexyphenidyl (n = 2), Donepezil (n = 1), Simvastatin (n = 1),

Diclofenac (n = 1), Temazepam (n = 1), Aspirin (n = 7), Ropinirole (n = 8), Rasagiline (n = 9), Pramipexole (n = 13), Amantadine (n = 1), Vitamin D3 (n = 2), multivitamin (n = 5), and Vitamin C (n = 1).

The 6-month follow-up was completed by 39 of the 47 enrolled patients. Eight of the 39 patients did not complete the optional 6-month open-label portion of the study (Fig. 1). Those who discontinued the study did so due to the flushing effect of niacin (n = 2), voluntary discontinuation (n = 7), or the SARS-CoV-2 shut-down of clinical research (n = 7). Although both groups took niacin from six to twelve months, the group who took the placebo for the first six months will continue to be referred to as the placebo group for this study.

Primary Outcome: UPDRS III

Six months of 250mg niacin vs placebo

The mean UPDRS III scores at baseline for placebo (22.4 ± 11.8) and niacin (21.3 ± 15.8) groups were comparable (Fig. 2A and Table 2). The mean changes in UPDRS III scores at six months for niacin (1.06 [95% CI, -3.68 to 1.57]) and placebo (0.05 [95% CI, -2.4 to 2.32]) groups were not significant. At six months, no significant changes were noted in rigidity, bradykinesia, or resting tremor in either placebo or niacin-treated subjects. However, the changes in the mean scores between baseline and 6-months were observed in both the groups for these variables. Average scores for rigidity non-significantly decreased in the placebo (0.14 [95% CI, -0.14 to 0.42]) and niacin (0.03 [95% CI, -0.26 to 0.31]) groups. The average score for resting tremor changed by 0.05 [95% CI, -0.54 to 0.64] in the placebo group and by -0.17 [95% CI, -0.49 to 0.16] in the niacin treated group. Mean scores for bradykinesia changed by 0.07 [95% CI, -0.35 to 0.49] in the placebo group and by -0.39 [95% CI, -1.42 to 0.65] in the niacin group (Table 2).

Table 2: Comparison of the motor and cognitive scores between treatment groups during the randomized period.

	Baseline Values, Mean (SD)		6-month change (Randomized, placebo-controlled trial)		
Variable, units	Placebo Group	Niacin Group	Placebo Group Change	Niacin Group Change	Between Group Difference
UPDRS III Scores	22.4 ± 11.8	21.3 ± 15.8	-0.05 (-2.4-2.32)	-1.06 (-3.68-1.57)	1.13 (-10.40-12.65)
Rigidity	1.69 ± 2.23	1.5 ± 1.92	0.14 (-0.14-0.42)	0.03 (-0.26-0.31)	0.19 (-1.47-1.85)
Resting Tremor	4.52 ± 2.87	3.11 ± 2.82	0.05 (-0.54-0.64)	-0.17 (-0.49-0.16)	1.4 (-0.87-3.7)
Bradykinesia	4.5 ± 4.6	4 ± 4.5	0.07 (-0.35-0.49)	-0.39 (-1.42-0.65)	0.5 (-3.15-3.7)
Cognitive flexibility	73.38 ± 57.11	79.42 ± 62.46	-3.04 (-28.04-21.96)	5.44 (-30.78-41.67)	-6.04 (-54.93-42.85)
Grip Strength, PSI					
First affected hand	305.09 ± 105.26	297.04 ± 125.68	5.88 (-14.19-25.94)	-22.56 (-53.54-8.43)	8.05 (-132.3-148.4)
Non (or later) affected hand	300.43 ± 80.49	284.1 ± 123.09	3.73 (-35.11-42.56)	-31.67 (-63.74-0.39)	16.33 (-110-142.7)
FSS	36.65 ± 13.02	40.28 ± 11.99	-0.06 (-2.5-2.37)	1.78 (-5.5-9.05)	-3.63 (-13.79-6.53)
VAFS	5.4 ± 2.23	5.17 ± 2.23	-0.22 (-0.97-0.53)	-0.44 (-1.74-0.85)	0.23 (-1.58-2.05)
REM sleep, %	15.19 ± 12.1	22.5 ± 13.36	-6.26 (-11.05--1.47)*	1.39 (-5.42-8.2)	-7.31 (-17.62-3.0)
GDS	6.2 ± 5.87	7.89 ± 7.31	0.25 (-0.53-1.03)	1.17 (-1.75-4.08)	-1.69 (-7.14-3.76)
Stroop 3 trial	8.13 ± 6.64	6.18 ± 7.92	-0.59 (-3.17-1.99)	-2.19 (-5.93-1.54)	1.96 (-4.16-8.08)
Walk and Turn, s	11.47 ± 3.46	10.33 ± 3.16	0.44 (-1.08-1.96)	0.18 (-0.61-0.96)	1.14 (-1.61-3.88)
Valine, mg/dL	229.33 ± 51.78	245.64 ± 33.42	1.83 (-27.05-30.72)	-0.71 (-35.17-33.74)	-16.31 (-57.55-24.93)
Tyrosine, mg/dL	73.93 ± 14.77	64.93 ± 16.28	8.82 (-2.2-19.84)	-0.5 (-10.82-9.82)	9.01 (-5.75-23.76)
Tryptophan, mg/dL	60.87 ± 11.39	53.5 ± 10.81	7.48 (-0.39-15.34)	-0.07 (-6.1-5.96)	7.37 (-3.13-17.86)
Serotonin, mg/dL	89.56 ± 60.5	84.21 ± 68.17	25.34 (5.79-44.89)*	1.21 (-17.82-20.25)	5.35 (-55.03-65.72)

Phenylalanine, mg/dL	74.47 ± 12.59	73.07 ± 9.74	3.74 (-8.48-15.97)	-1.64 (-8.62-5.33)	1.40 (-9.23-12.02)
Leucine, mg/dL	136.87 ± 38.75	143.07 ± 27.71	9.26 (-15.26-33.77)	-4.64 (-28.45-19.16)	-6.21 (-38.02-25.61)
Isoleucine, mg/dL	72.14 ± 24.2	73.36 ± 15	4.03 (-14.21-22.26)	-4.79 (-19.34-9.77)	-1.21 (-20.89-18.47)

All the study personnel and patients were blinded to the group assignment. Treatment group assignment code was disclosed at the completion of the study in April 2020. VAFS: Visual analog severity scale, GDS: Geriatric depression scale, FSS: fatigue severity scale. Values presented are Mean±SD or Mean (95% CI). *p<0.05

Six to Twelve months of 250mg niacin

At the 12-month visit, the mean UPDRS III scores decreased by 4.58 [95% CI, 0.85 to 8.3] points in placebo compared to the 6-month visit (Table 3). In the niacin group, the mean UPDRS III scores decreased by 4.63 [95% CI, 1.42 to 7.83] points (Table 3). At the 12-month visit, rigidity scores significantly decreased in the placebo group (0.75 [95% CI, -0.01 to 1.51], p = 0.05), while no changes were observed in the niacin group (0.008 [95% CI, -0.47 to 0.49]). No significant changes were observed in resting tremor scores for placebo (0.92 [95% CI, -0.12 to 1.96]) or niacin (0.1 [-0.56 to 0.76]) groups. Bradykinesia scores significantly reduced in the placebo (1.13 [95% CI, 0.25 to 2.02]) and niacin (1.21 [95% CI, 0.36 to 2.06]) groups at the 12-month visit compared to the 6-month visit (Table 3).

Table 3
Comparative differences in motor and cognitive scores during open-label trial.

Clinical	**6–12 month change (open-label niacin treatment)**		
Variable, units	Placebo Group Change	Niacin Group Change	Between Group Difference at 6MO
UPDRS III Scores	4.58 (0.85–8.30)*	4.63 (1.42–7.83)*	0.12 (-12.29-12.53)
Rigidity	0.75 (-0.01-1.51)*	0.008 (-0.47-0.49)	0.08 (-1.522-1.673)
Resting Tremor	0.92 (-0.12-1.96)	0.1 (-0.56-0.76)	1.20 (-1.17-3.57)
Bradykinesia	1.13 (0.25–2.02)*	1.21 (0.36–2.06)*	0.04 (-3.74-3.82)
Cognitive flexibility	-15.18 (-40.6-10.24)	4.9 (-27.8-37.6)	2.44 (-47.02-51.91)
Grip Strength, PSI			
First affected hand	-23.58 (-79.14-31.98)	-80.3 (-176.2-15.65)	-20.38 (-167.4-126.7)
Non (or later) affected hand	-11.84 (-56.59-32.92)	-54.72 (-128.8-19.38)	-19.07 (-152.8-114.7)
FSS	2.89 (-1.62-7.4)	4.36 (1.59–7.13)*	-1.79 (-11.91-8.34)
VAFS	-0.76 (-1.75-0.24)	-0.39 (-0.92-0.14)	0.008 (-1.88-1.89)
REM sleep, %	1.92 (-7.2-11.03)	-4.32 (-10.32-1.68)	0.34 (-11.09-11.77)
GDS	1.08 (-1.12-3.28)	1.37 (-0.5-3.23)	-0.77 (-5.53-3.99)
Stroop 3 trial	-0.78 (-5.47-3.91)	-0.78 (-2.85-1.28)	0.35 (-4.9-5.61)
Walk and Turn, s	0.75 (-0.53-2.02)	1.72 (0.59–2.84)*	0.87 (-1.95-3.69)
Valine, mg/dL	4.29 (-32.51-41.08)	21.07 (-16.01-58.15)	-18.86 (-52.4-14.69)
Tyrosine, mg/dL	1.83 (-11.66-15.31)	4.57 (-5.33-14.47)	-0.32 (-13.74-13.11)
Tryptophan, mg/dL	-4.11 (-12.97-4.75)	4.29 (-4.75-13.32)	-0.18 (-10.28-9.92)
Serotonin, mg/dL	-18.11 (-37.97-1.75)	-13.36 (-58.77-32.06)	-18.78 (-77.83-40.27)
Phenylalanine, mg/dL	-0.85 (-12-10.3)	2.43 (-9.35-14.21)	-3.99 (-18.11-10.12)

Six to 12 months, all the participants were given 250mg niacin once a day. All the study personnel and patients were blinded to the group assignment. Treatment group assignment code was disclosed at the completion of the study in April 2020.

Values presented are Mean (95% CI). *$p < 0.05$

Clinical	6–12 month change (open-label niacin treatment)		
Leucine, mg/dL	-1.75 (-29.99-26.5)	14.86 (-9.31-39.02)	-20.1 (-44.43-4.23)
Isoleucine, mg/dL	1.26 (-14.45-16.97)	8.64 (-4.48-21.77)	-10.03 (-26.28-6.230)
Six to 12 months, all the participants were given 250mg niacin once a day. All the study personnel and patients were blinded to the group assignment. Treatment group assignment code was disclosed at the completion of the study in April 2020.			
Values presented are Mean (95% CI). *p < 0.05			

Baseline to Twelve months

Compared to baseline, a trend towards reductions in the mean UPDRS III scores was observed in the placebo (4.52 [95% CI, -0.16 to 9.21]) and niacin (3.57 [95% CI, -1.02 to 8.16]) groups (Table 4). At twelve months, scores for rigidity (0.90 [95% CI, -0.05 to 1.84]) and resting tremor (0.97 [95% CI, -0.16 to 2.09]) showed slight, non-significant decreases in the placebo group. Compared to baseline, bradykinesia scores at twelve months decreased in the placebo (1.21 [95% CI, 0.19 to 2.23]) and niacin (0.82 [95% CI, -0.004 to 1.65]) groups (Table 4).

Table 4
Differences in motor and cognitive scores between baseline and 12-month visit.

	12- month change		
Clinical Variable, units	Placebo Group Change	Niacin Group Change	Between Group Difference
UPDRS III Scores	4.52 (-0.16-9.21)	3.57 (-1.019-8.16)	0.17 (-10.66-11.01)
Rigidity	0.90 (-0.05-1.84)	0.04 (-0.43-0.5)	-0.67 (-2.25-0.91)
Resting Tremor	0.97 (-0.16-2.09)	-0.07 (-0.94-0.81)	0.38 (-2.18-2.94)
Bradykinesia	1.21 (0.19–2.23)*	0.82 (-0.004-1.65)*	0.12 (-3.34-3.57)
Cognitive flexibility	18.22 (-42.79-6.35)	10.35 (-17.7-38.39)	22.52 (-36.72-81.77)
Grip Strength, PSI			
First affected hand	-17.71 (-62.17-26.75)	-102.9 (-218.8-13.14)	-77.1 (-186.4-32.22)
Non (or later) affected hand	-8.12 (-56.34-40.13)	-86.4 (-187.8-15.05)	-61.96 (-181.5-57.59)
FSS	2.83 (-2.15-7.81)	6.14 (-1.59-13.86)	-0.32 (-12-11.37)
VAFS	-0.98 (-2.2-0.25)	-0.83 (-2.16-0.49)	0.38 (-1.84-2.59)
REM sleep, %	-4.34 (-11.45-2.76)	-2.93 (-11.11-5.26)	-5.9 (-20.57-8.78)
GDS	1.33 (-1.01-3.66)	2.53 (-1.56-6.62)	-0.48 (-5.24-4.28)
Stroop 3 trial	-1.37 (-5.41-2.67)	-2.98 (-7.73-1.78)	0.35 (-6.45-7.14)
Walk and Turn, s	1.19 (-0.38-2.76)	1.89 (0.55–3.23)*	1.84 (-0.39-4.07)
Valine, mg/dL	6.12 (-29.16-41.4)	20.36 (-17.62-58.33)	-2.07 (-38.5-34.35)
Tyrosine, mg/dL	10.65 (1.19–20.1)*	4.07 (-8.28-16.42)	2.43 (-7.98-12.84)
Tryptophan, mg/dL	3.37 (-5.21-11.94)	4.21 (-3.69-12.12)	8.21 (-1.54-17.97)
Serotonin, mg/dL	7.23 (-24.06-38.51)	-12.14 (-49.59-25.31)	-14.02 (-58.56-30.51)
Phenylalanine, mg/dL	2.9 (-6.82-12.61)	0.79 (-10.03-11.6)	-0.71 (-12.62-11.19)
Leucine, mg/dL	7.51 (-18.63-33.65)	10.21 (-21.1-41.53)	-3.5 (-29.45-22.45)

The study personnel were blinded to the group assignment, the randomization code was revealed at the completion of the study.

Values presented are Mean (95% CI). *p < 0.05

	12- month change		
Isoleucine, mg/dL	5.29 (-8.82-19.39)	3.86 (-10.4-18.12)	-2.64 (-16.11-10.82)
The study personnel were blinded to the group assignment, the randomization code was revealed at the completion of the study.			
Values presented are Mean (95% CI). *p < 0.05			

A significant decrease occurred across both groups over a treatment period of one year (p = 0.012), but no significant differences were found between treatments at any time point (Fig. 2D and Table 2).

Secondary Outcomes

Six months of 250mg niacin vs placebo

Of all the secondary outcomes, no significant differences were observed for FSS, VAFS, GDS, Stroop test, or walk and turn time (Table 2). Serum levels of amino acids valine, tyrosine, tryptophan, phenylalanine, leucine, and isoleucine were also not different between the treatment groups. Sleep efficiency or percentage of light sleep, deep sleep, or awake time also did not show any significant differences for this portion of the study (Table 2).

The difference between TMT-B and TMT-A is a measurement of cognitive flexibility while removing the factors of motor and visuoperceptual deficits. The change in cognitive flexibility between baseline and six months was not significant between treatment groups. The difference between the treatment groups at six months was 2.44 [95% CI, -47.02 to 51.91] (Table 2).

Grip strength, a measure of motor function and muscle energetics, in the affected or first-affected hand did not show significance (Table 2) between the placebo and niacin-treated group. However, in the niacin-treated group, grip strength increased by 22.56 [95% CI, -53.54 to 8.43] pounds/square inch (PSI) compared to placebo (5.88 [95% CI, -14.19 to 25.94] PSI). During the same time, the unaffected hand (without tremor or with tremor appearing in this hand later in the disease) showed a similar change in grip strength in the niacin group (31.67 [95% CI, -63.74 to 0.39] PSI) vs. placebo (3.73 [95% CI, -35.11 to 42.56] PSI) (Table 2).

The percentage of sleep measured as rapid eye movement (REM) sleep changed significantly by 6.26% [95% CI, -11.05 to -1.47] with placebo, but non-significantly decreased with niacin by 1.39% [95% CI, -5.42 to 8.2]. Blood serotonin levels significantly decreased in placebo by 25.34 [95% CI, 5.79 to 44.89] while staying relatively the same between baseline and six months of niacin supplementation (Table 2).

Six to Twelve months of 250mg niacin

FSS scores at twelve months decreased by 4.36 [95% CI, 1.59 to 7.13] points in the niacin-treated group. Additionally, the average time for walk and turn was significantly reduced in the niacin-treated group by

1.72 [95% CI, 0.59 to 2.84] seconds. No other secondary outcome measures showed significant differences between six to twelve months (Table 3).

Baseline to Twelve months

Compared with baseline, at twelve months, grip strength, FSS, VAFS, sleep, GDS, valine, serotonin, tryptophan, phenylalanine, leucine, and isoleucine did not show any significant differences between the treatment time and groups (Table 4). The mean change in time difference between TMT-B and TMT-A scores for placebo was 18.2 [95% CI, -42.79 to 6.35] and 10.35 [95% CI, -17.7 to 38.39] for the niacin group (Table 4).

The change in walk and turn time was lowered in both the niacin (1.89 [95% CI, 0.55 to 3.23]) and placebo (1.19 [95% CI, -0.38 to 2.76]) groups. Plasma tyrosine levels significantly decreased in placebo group (10.65 [95% CI, 1.19 to 20.1] mg/dL) compared to niacin treated group (4.07 [95% CI, -8.28 to 16.42] mg/dL) (Table 4).

Adverse Events

Adverse events were similar between the niacin and placebo groups. Out of 47 recruited patients, Eight patients dropped out during the first six months, and eight more dropped out before the one-year time point. The flushing effect of niacin occurred in and caused discontinuation for two patients, one in each group. Unrelated injuries occurred in one patient in the niacin group and one in the placebo group, although neither resulted in discontinuation of the study. One patient complained of leg cramps at the end of the study but was likely due to dehydration rather than supplement intake as assessed by the neurologist. No other adverse events were reported. Seven patients could not complete the study due to the SARS-CoV-2 shut-down, and all other dropouts voluntarily discontinued the study.

Discussion

In this single-center, double-blind, placebo-controlled, randomized clinical trial comprising of patients with early- and late-stage PD, supplementation of a single daily dose of niacin for twelve months improved the rigidity, bradykinesia, and overall UPDRS III scores. To our knowledge, this is the first trial where niacin (a form of vitamin B3) is tested at a low dose for PD in a randomized, placebo-controlled, double-blind, prospective trial. A 250mg daily dose of niacin produced negligible or no flushing symptoms when consumed after meals as instructed. Our previous preliminary studies helped us decide the low dose for niacin [7, 8]. Different low-dose regimens, longer duration of intervention, multi-center trials, and inclusion of niacinamide would be pertinent future investigations.

Numerous studies have attempted either raising NAD levels or directly providing NAD in PD. Niacin remains a natural source for NAD and acts on the niacin receptor GPR109A, unlike other forms of vitamin B3 [7]. Niacin supplements and agonists of the niacin receptor are shown to be neuroprotective and lead to enhanced motor function in animal models of PD (BHB, niacinamide, PINK1 fruit fly study) [5, 15, 16].

In a serendipitous finding, a high-dose niacin supplement was observed to reduce bradykinesia and rigidity in a PD case report [17].

In this study, both the niacin-treated group and placebo group demonstrated a significant decrease in UPDRS III scores from six to twelve months when taking the open-label niacin supplement. Both groups, when comparing baseline to one year, demonstrated a trending reduction in UPDRS III scores. Individual components of the UPDRS III showed improvements in gait, finger tapping, rising from a chair, posture, and rapid alternating movements after niacin treatment. A significant decrease in rigidity was observed in the placebo-treated group from six months to one year when they received niacin. Although the overall tremor score did not show any significance in the niacin-treated group, individual limb tremor scores decreased in the niacin-treated group.

Similar to UPDRS III and rigidity, one year of 250mg of daily niacin and six months of niacin with the placebo group demonstrated significant improvements in bradykinesia scores compared to baseline. Also, six to twelve months of open-label niacin showed significantly better bradykinesia scores. Since some of the scores began higher (although insignificant) in the placebo group than niacin, such as with resting tremor, then there is more room for improvement; this may have contributed to the significant changes with only six months of niacin during the open-label portion for the placebo group opposed to the niacin group in the first six months.

Almost all reported secondary measures demonstrated a trend towards improvement over the one-year period. However, serotonin levels and the FSS scores stood out. Serotonin levels were significantly down in the placebo-treated group but not in the niacin-treated group. The FSS scores were significantly better in the niacin-treated group but not the placebo group. Both of these findings may explain the reporting of increased mood by PD subjects who received niacin for one year.

Study Strengths

It is a novel approach utilizing an over-the-counter vitamin supplement at a low dose in PD. The commonly used therapies for PD subjects do not currently include niacin. The placebo control was used for the first six months, and codes were not broken until patients completed the 12-month study. The flushing effect of niacin was negligible and did not deter the PD patients from the study. The PD patients and caregivers were very enthusiastic after the 6-month open-label niacin supplementation. Dropout rates were low. A single rater captured the motor outcome scores for all of the subjects, which extended higher confidence in the reliability of the outcomes.

Study Limitations

The sample size is small. We did not titrate the dosages of niacin. The clinical trial recruited patients primarily through the CNVAMC. Due to veterans and PD patients being predominantly men, we were only able to recruit eight women. Therefore, the potential gender bias was not adequately addressed. In addition, the sample population was primarily Caucasian (only three African American subjects).

Many outcome scores within the trial were self-reported surveys, including the FSS, VAFS, and GDS, although the groups were not found to be different at baseline. Furthermore, one year of niacin supplementation may be necessary to find significant differences from placebo, so a longer placebo-controlled study should be performed in the future.

Conclusions

Among the PD patients, treatment with low-dose daily niacin supplementation compared to placebo resulted in significantly improved motor function outcomes. These findings support the use of low-dose niacin supplementation in PD as an adjunct therapy to the typically prescribed medications. Multi-center clinical trials with a larger PD patient population, titration of niacin dosages for longer durations, and inclusion of other forms of vitamin B3 (niacinamide) are warranted for further confirmation. Although this trial is limited by its small sample size, it illustrates the potentially beneficial effects of niacin on rigidity, bradykinesia, and overall UPDRS III scores in PD.

Abbreviations

PD: Parkinson's Disease; UPDRS III: Unified Parkinson's Disease Rating Scale III; NAD: Nicotinamide adenine dinucleotide; TMT-A: Trail-making Test A; TMT-B: Trail-making Test-B; GDS: Geriatric Depression Scale; FSS: Fatigue Severity Scale; VAFS: Visual Analogue Fatigue Scale; CSF: Cerebro-spinal fluid; VA: Veterans Affairs; MMSE: mini-mental state exam; H&Y: Hoehn and Yahr Score; CI: Confidence Interval; PSI: Pounds per Square Inch; REM: Rapid Eye Movement; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; GPR109A: G-protein Receptor 109A; BHB: β-hydroxybutyrate; PINK1: PTEN (phosphatase and tensin homolog)-induced kinase1.

Declarations

Ethics approval and consent to participate: The study was approved by the IRB at CNVAMC and Augusta University. All subjects or their legally authorized caregivers signed informed consents.

Consent for Publication: Not applicable

Availability of data and materials: Upon reasonable request, de-identified individual participant data will be available beginning 9 months and ending 36 months following the publication of this article. Proposals may be submitted up to 36 months following publication of this article.

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Author contributions: CW and RC developed the concept and designed the study. CW, RC, MS, SP, and BG performed experiments. RC, SP, and MS analyzed the data. CW, MS, and SP drafted the manuscript. CW, RC, JCM, MS, and SP coordinated sample selection and collected biobank archive info. CW, RC, JCM, MS, and SP jointly wrote the final version of the manuscript. All authors critically revised the manuscript and approved the final version.

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References

1. Collaborators GBDPsD. Global, regional, and national burden of Parkinson's disease, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol. 2018;17:939–53.
2. Schrag A, Quinn N. Dyskinesias and motor fluctuations in Parkinson's disease. A community-based study. Brain. 2000;123(Pt 11):2297–305.
3. Giri B, Belanger K, Seamon M, Bradley E, Purohit S, Chong R, Morgan JC, Baban B, Wakade C. Niacin Ameliorates Neuro-Inflammation in Parkinson's Disease via GPR109A. *Int J Mol Sci* 2019, 20.
4. Hellenbrand W, Boeing H, Robra BP, Seidler A, Vieregge P, Nischan P, Joerg J, Oertel WH, Schneider E, Ulm G. Diet and Parkinson's disease. II: A possible role for the past intake of specific nutrients. Results from a self-administered food-frequency questionnaire in a case-control study. Neurology. 1996;47:644–50.
5. Schöndorf DC, Ivanyuk D, Baden P, Sanchez-Martinez A, De Cicco S, Yu C, Giunta I, Schwarz LK, Di Napoli G, Panagiotakopoulou V, et al. The NAD + Precursor Nicotinamide Riboside Rescues Mitochondrial Defects and Neuronal Loss in iPSC and Fly Models of Parkinson's Disease. Cell Rep. 2018;23:2976–88.
6. Wakade C, Chong R, Bradley E, Morgan JC. Low-dose niacin supplementation modulates GPR109A, niacin index and ameliorates Parkinson's disease symptoms without side effects. Clin Case Rep. 2015;3:635–7.
7. Wakade C, Giri B, Malik A, Khodadadi H, Morgan JC, Chong RK, Baban B. Niacin modulates macrophage polarization in Parkinson's disease. J Neuroimmunol. 2018;320:76–9.
8. Chong R, Wakade C, Seamon M, Giri B, Morgan JC, Purohit S. Niacin Enhancement for Parkinson's Disease: An Effectiveness Trial. *Frontiers Aging Neuroscience* 2021.
9. Bender DA, Earl CJ, Lees AJ. Niacin depletion in Parkinsonian patients treated with L-dopa, benserazide and carbidopa. Clin Sci (Lond). 1979;56:89–93.
10. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry. 1992;55:181–4.
11. Evans JR, Mason SL, Williams-Gray CH, Foltynie T, Brayne C, Robbins TW, Barker RA. The natural history of treated Parkinson's disease in an incident, community based cohort. J Neurol Neurosurg Psychiatry. 2011;82:1112–8.
12. Poewe W. The natural history of Parkinson's disease. J Neurol. 2006;253(Suppl 7):VII2–6.

13. Kortte KB, Horner MD, Windham WK. The trail making test, part B: cognitive flexibility or ability to maintain set? Appl Neuropsychol. 2002;9:106–9.
14. Motulsky HJ, Brown RE. Detecting outliers when fitting data with nonlinear regression – a new method based on robust nonlinear regression and the false discovery rate. BMC Bioinformatics. 2006;7:123.
15. Anderson DW, Bradbury KA, Schneider JS. Broad neuroprotective profile of nicotinamide in different mouse models of MPTP-induced parkinsonism. Eur J Neurosci. 2008;28:610–7.
16. Jia H, Li X, Gao H, Feng Z, Li X, Zhao L, Jia X, Zhang H, Liu J. High doses of nicotinamide prevent oxidative mitochondrial dysfunction in a cellular model and improve motor deficit in a Drosophila model of Parkinson's disease. J Neurosci Res. 2008;86:2083–90.
17. Alisky JM. Niacin improved rigidity and bradykinesia in a Parkinson's disease patient but also caused unacceptable nightmares and skin rash–a case report. Nutr Neurosci. 2005;8:327–9.

Figures

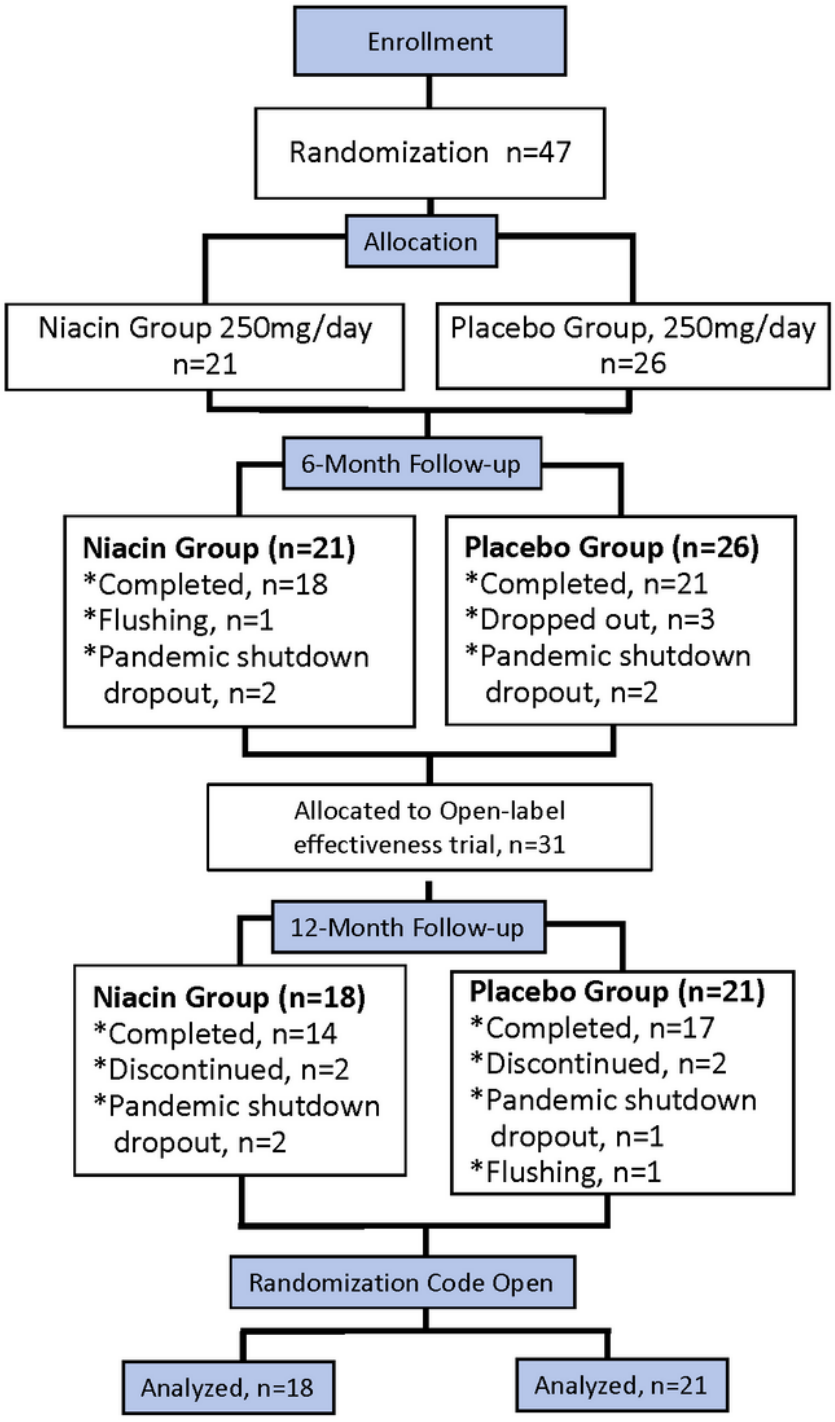

Figure 1

Flowchart showing participant flow in the Niacin for Parkinson's Disease trial. Forty-seven participants enrolled in the study were randomly placed into the placebo or niacin-treated group. Randomized double-blind portion lasted the first six months; then, a subsequent open-label niacin phase was implemented from six to twelve months.

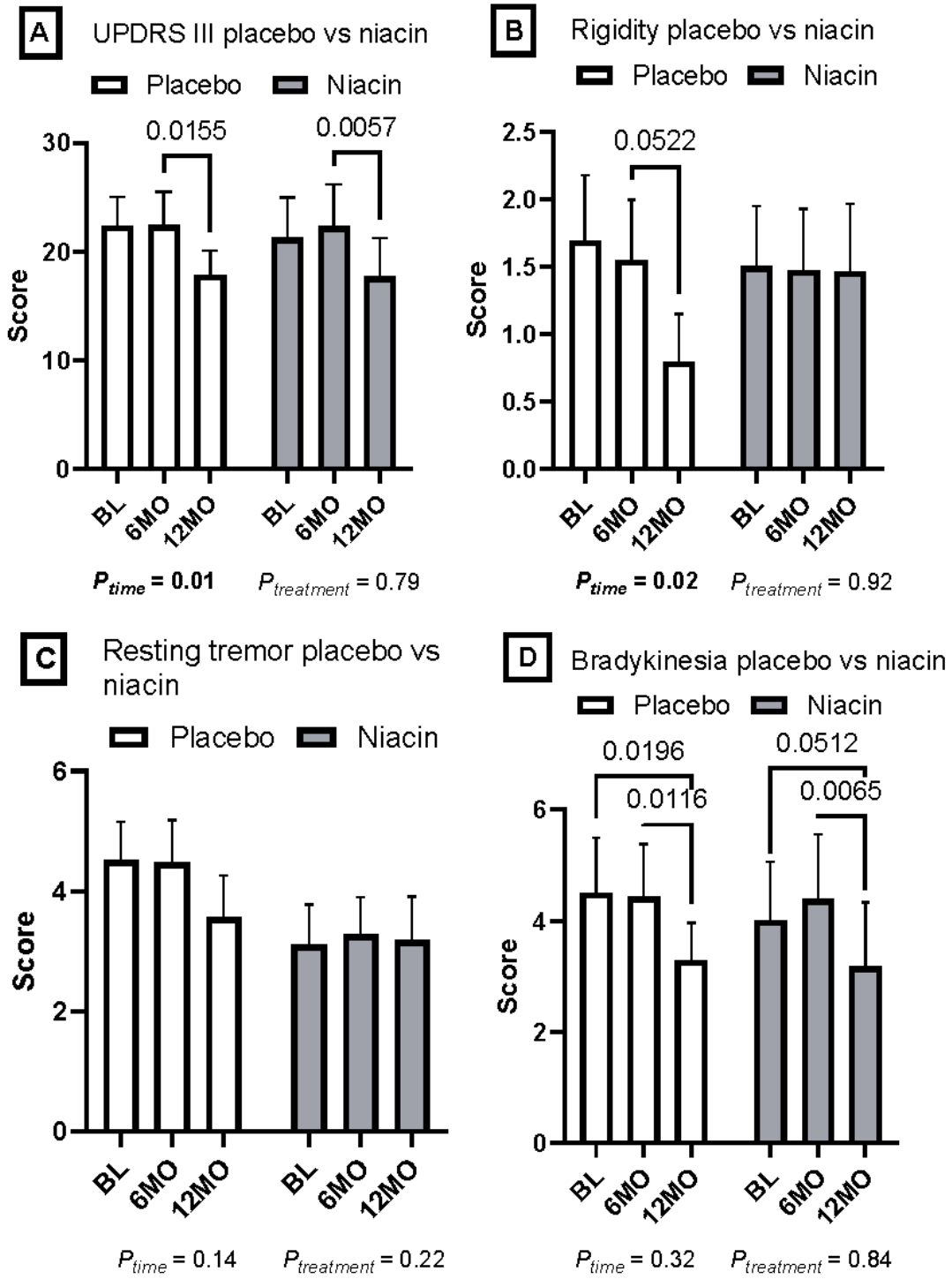

Figure 2

Mean Unified Parkinson's Disease Rating Scale III (UPDRS III) scores for two treatment groups. A) Barplot comparing changes in UPDRS III scores at baseline (BL), after six months (6MO) of placebo or niacin, and after six months of niacin thereafter (12MO) (maximum points: 108). B) Barplot of mean + SEM for rigidity scores (maximum points: 20), as a component of the UPDRS III scores, C) Barplot showing mean + SEM for resting tremor scores (maximum points: 20), as a component of UPDRS III scores, and D)

Barplot showing mean + SEM for bradykinesia scores (maximum points: 20), as a component of UPDRS III scores.

Supplementary Files

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- CONSORT2010ChecklistTN.docx