JMD
https://doi.org/10.14802/jmd.18049 / J Mov Disord 2019;12(2):91-96
pISSN 2005-940X / eISSN 2093-4939

ORIGINAL ARTICLE

Characterization of Vitamin B12 Supplementation and Correlation with Clinical Outcomes in a Large Longitudinal Study of Early Parkinson's Disease

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ABSTRACT

Objective In Parkinson's disease (PD), vitamin B12 levels are lower, and comorbid B12 deficiency has been associated with the development of neuropathy and early gait instability. Because little is known about B12 supplement use in PD, we sought to evaluate its use in a large PD cohort and, as an exploratory analysis, to determine whether baseline characteristics or disease progression differed according to B12 supplementation.

Methods We utilized data collected as part of the National Institutes of Health Exploratory Trials in PD (NET-PD) Long-term Study (LS-1), a longitudinal study of 1,741 participants. We stratified subjects into 4 groups according to daily supplement use: no B12, multivitamin (MVI) containing < 100 μg B12, B12 ≥ 100 μg, and MVI + B12 ≥ 100 μg. Clinical outcomes were assessed at 3 years for each group using the Unified Parkinson's Disease Rating Scale (UPDRS), its subscores, and selected individual questions.

Results Of the 1,147 participants who completed the 3-year visit, 41% took an MVI, 2% took B12, 3% took MVI + B12, and 54% reported taking no supplements. At 3 years, no significant differences in clinical outcomes were observed. However, there was a trend toward lower hazard ratios for developing sensory symptoms (UPDRS Item 17) in the MVI ($p = 0.08$) and B12 + MVI ($p = 0.08$) groups compared to that in the no supplement group.

Conclusion These results show that supplementation with vitamin B12 ≥ 100 μg is uncommon in early PD. The finding of a trend toward a lower hazard ratio for the development of sensory symptoms in those taking an MVI or B12 + MVI warrants further study.

Key Words Cyanocobalamin; neuropathy; neuroprotection; disease modification.

Parkinson's disease (PD) progression varies considerably between individuals.[1] The factors that underlie this variability are not well established, although later age of onset, initial symptoms of postural instability and gait difficulty, and low serum urate have been associated with a more rapid decline.[2,3]

Vitamin B12 deficiency has many features that make it a

Received: September 20, 2018 **Revised:** February 2, 2019 **Accepted:** February 21, 2019
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candidate for being an important comorbidity in PD. First, it is common, affecting 10–20% of people older than 60, and a meta-analysis has shown that B12 is lower in PD than in controls.[4] Moreover, this deficiency is well known to cause a number of neurological conditions in otherwise normal individuals, including neuropathy, gait instability, and cognitive changes.[5] Interestingly, correlations between low B12 status and PD have been described. For example, a systematic review reported that neuropathy was present in 16% of PD subjects (range 6–58%), and vitamin B12 deficiency was identified as the likely cause in the majority of cases.[6] Furthermore, a recent analysis of serum samples from the DATATOP study, a longitudinal study of early untreated PD patients, found greater worsening of gait and instability for those in the low vitamin B12 tertile (B12 < 234 pmol/mL; < 317 pg/mL) compared to those in the middle and upper tertiles.[7]

These observations raise the practical questions regarding 1) the prevalence of B12 supplementation in PD patients and 2) whether B12 supplementation started prior to or soon after a diagnosis of PD is made might slow aspects of its progression. To our knowledge, there are no studies that have specifically analyzed B12 supplementation over time in PD. Therefore, as an exploratory study, using the National Institutes of Health Exploratory Trials in PD (NET-PD) Long-term Study (LS-1) cohort, we sought to determine the prevalence of B12 supplementation in early PD and whether baseline characteristics or disease progression differed between subjects who reported consistent use of vitamin B12 supplementation compared to those who did not.

MATERIALS & METHODS

NET-PD LS-1 was a large randomized, multicenter, double-blind, placebo-controlled study designed to determine whether creatine monohydrate (10 g/day) slowed disease progression. Eligible participants had early PD of < 5 years duration and had started taking either levodopa or a dopamine agonist at least 90 days but less than 2 years prior to study entry.[8] The Institutional Review Boards of the participating sites approved this study, and all subjects provided written informed consent. After the baseline visit, subjects were monitored with annual visits for up to six years. The study was halted before all subjects completed the 5-year endpoint after it was determined that no difference would emerge between the treatment arms. The main findings are published.[8]

To quantify the amount of B12 supplementation consumed by participants, we reviewed the concomitant medication records for vitamin B12, B complex, and multivitamin (MVI) use, including supplement brand name (when available), dose, frequency, and start and end dates. To include subjects with "consistent" supplement (or nonsupplement) regimens, we included for analysis only those subjects who reported MVI or B12 use ≥ 90 days prior to baseline and continued use for at least the first 1.5 years of the study. For subjects taking an unspecified MVI, we approximated the B12 dose to be 6–25 μg (the typical range in standard MVIs). For those taking specified supplements, the published dose was used, and an average daily dose was calculated according to the dose and reported frequency. Subjects were stratified according to the following groups: no B12 supplement (NoB12Supp), those who took B12 contained in an MVI (MVI), those who took ≥ 100 μg of B12 daily (B12), and those who took an MVI plus ≥ 100 μg of B12 daily (B12 + MVI). Overall group comparisons were assessed using ANOVA for continuous variables and chi-square test or Fisher's exact test for categorical variables. We used the Hochberg procedure for post hoc group comparisons when this was of interest.

We assessed the mean change in study outcomes at 3 years. Outcomes included the Unified Parkinson's Disease Rating Scale (UPDRS) (total score and the Mental, Activity of Daily Living, and Motor subscores), Parkinson's Disease Questionnaire (PDQ-39), Scales for Outcomes in Parkinson's Disease-Cognition (SCOPA-COG) (only performed at baseline and the 5-year visit), Symbol Digit Modalities Test (SDMT), and the total daily levodopa equivalent dose (LED). Because B12 deficiency has been associated with a number of neurological defects, including cognitive change, myelopathy and neuropathy, we also performed a frequency analysis according to individual components of the UPDRS, including intellectual impairment (Item 1), falls (Item 13), freezing (Item 14), walking disturbance (Item 15), sensory complaints related to parkinsonism (Item 17), disturbance of gait (Item 29) and instability (Item 30). We also calculated the ambulatory capacity score by adding individual items of the UPDRS, including falls (Item 13), freezing when walking (Item 14), walking (Item 15), gait (Item 29), and postural stability (Item 30). This score has been validated as a global measure of ambulatory function in PD.[9] Because we were specifically interested in those subjects whose condition began to change from normal (UPDRS score of 0) to abnormal (score of ≥ 1), we measured the frequency of change from 0 to > 0. In addition, we investigated any difference in supplement use by age at diagnosis by computing frequencies and means (SDs) stratified by age ranges < 50, 50–59, 60–69, and ≥ 70. The presence of diabetes mellitus (DM) was determined by reviewing the baseline concomitant medication log and identifying those used for its treatment. The use of one or more DM medications was used as a surrogate marker for a diagnosis of DM. The presence of renal failure was assessed using the estimated glomerular filtration rate (eGFR).[10] The eGFR was calculated using baseline serum

creatinine and the Modification of Diet in Renal Disease (MDRD) equation.[10] Using established clinical criteria,[10] subjects with eGFR < 60 were considered to have renal insufficiency.

To better estimate the relationship between B12 supplementation and outcomes that showed trends in the frequency analysis (noted only for sensory complaints related to parkinsonism), we used an interval-censored proportional hazard regression model to analyze group effects. In this model, we assume that sensory symptoms occurred in the time interval between the most recent visit date prior to symptom onset and the visit during which sensory symptoms were first reported. These visits were generally a year apart. For this analysis, we excluded subjects who had developed a sensory complaint before baseline and included adjustments for baseline hazard, age, gender, education, and treatment groups, using NoB12Supp as the reference.

RESULTS

Of the 1,741 subjects who enrolled in the study, 1,147 completed the 3-year visit and met the criteria for consistent B12 supplement use or avoidance. Of these, 41% took an MVI, 2% took B12 alone, 3% took MVI + B12, and 54% did not report either B12 or an MVI supplementation. At baseline, age and the frequency of non-Hispanic whites were different for the four groups, as shown in Table 1. To address whether supplement use differed according to age, we then performed an analysis segregated according to age range (< 50, 50–60, 50–69, and ≥ 70) at PD diagnosis as shown in Table 2. This analysis confirmed that the rate of B12 use was higher in older patients. For example, the use of an MVI alone varied from 32% in those < 50 to 40% in those ≥ 70, while B12 + MVI use ranged from 1% for those < 50 to 6% for those ≥ 70. When sorted by age range, the mean ages at diagnosis were not significantly different among the four supplement groups according to ANOVA. However, a separate frequency analysis showed a significant difference in the frequency of subjects in the supplement groups for the < 50, 60–69, and ≥ 70 age groups. However, subsequent pairwise comparison to the NoB12Supp group within age ranges showed a

Table 1. Baseline characteristics according to use or non-use of MVI, B12, or MVI + B12

	NoB12Supp *n* = 617 (54%)	MVI *n* = 466 (41%)	B12 *n* = 26 (2%)	B12 + MVI *n* = 38 (3%)	*p*-value
Age (yr)	60.6 ± 9.5	62.4 ± 8.6	65.3 ± 8.4	65.2 ± 7.1	< 0.001
Age at PD diagnosis (yr)	59.0 ± 9.5	60.7 ± 8.7	63.9 ± 8.6	63.6 ± 6.9	< 0.001
Years since PD diagnosis (yr)	1.6 ± 1.1	1.6 ± 1.1	1.3 ± 1.1	1.5 ± 1.1	0.56
Years since diagnosis to DA tx (yr)	1.1 ± 1.1	1.2 ± 1.1	0.9 ± 1.1	1.1 ± 1.1	0.57
UPDRS total	24.9 ± 10.2	25.1 ± 10.3	27.6 ± 15.4	27.8 ± 11.4	0.25
UPDRS mental	1.2 ± 1.3	1.2 ± 1.3	1.3 ± 1.3	1.6 ± 1.4	0.40
UPDRS ADL	6.8 ± 3.7	6.8 ± 3.6	7.2 ± 4.6	7.6 ± 3.3	0.59
UPDRS motor	17.0 ± 7.6	17.1 ± 7.7	19.1 ± 11.9	18.7 ± 8.8	0.34
Ambulatory capacity	1.6 ± 1.4	1.6 ± 1.3	2.2 ± 2.4	1.7 ± 1.4	0.10
PDQ-39 summary	12.8 ± 10.3	11.3 ± 8.6	13.5 ± 12.0	12.9 ± 9.7	0.08
SCOPA COG	30.5 ± 5.2	30.8 ± 5.0	29.0 ± 5.3	30.3 ± 5.4	0.34
SDMT	45.4 ± 10.9	45.4 ± 10.9	44.5 ± 12.3	41.8 ± 15.1	0.27
Total daily LED	371.8 ± 213.6	370.6 ± 256.0	473.4 ± 320.3	366.1 ± 295.2	0.19
Female	204 (33.1)	171 (36.7)	10 (38.5)	16 (42.1)	0.46
Non-Hispanic white	543 (88.0)	446 (95.7)	23 (88.5)	36 (94.7)	< 0.001
Education > bachelor	191 (31.0)	164 (35.2)	9 (34.6)	12 (31.6)	0.53
UPDRS Item 1, intellectual > 0	203 (32.9)	147 (31.6)	11 (42.3)	15 (39.5)	0.54
UPDRS Item 13, falls > 0*	33 (5.4)	30 (6.4)	5 (19.2)	4 (10.5)	0.03
UPDRS Item 14, freezing > 0*	67 (10.9)	56 (12.0)	3 (11.5)	6 (15.8)	0.72
UPDRS Item 15, walking > 0	437 (70.8)	333 (71.6)	16 (61.5)	23 (60.5)	0.38
UPDRS Item 17, sensory > 0	229 (37.1)	143 (30.7)	6 (23.1)	14 (36.8)	0.09
UPDRS Item 29, gait > 0	227 (36.8)	177 (38.0)	15 (57.7)	17 (44.7)	0.15
Use of diabetes medication*	57 (9.24)	42 (9.01)	4 (15.38)	4 (10.53)	0.63
eGFR < 60*	100 (16)	49 (10.58)	4 (15.38)	7 (19.44)	0.03

Data are presented as a mean ± SD or number (percentage). F test was used for continuous variables and chi-square test was used for categorical variables unless otherwise noticed (*Fisher's exact test was used). MVI: multivitamin, PD: Parkinson's disease, DA tx: dopamine agonist therapy, UPDRS: Unified Parkinson's Disease Rating Scale, ADL: Activity of Daily Living, PDQ-39: Parkinson's Disease Questionnaire, SCOPA-COG: Scales for Outcomes in Parkinson's Disease-Cognition, SDMT: Symbol Digit Modalities Test, LED: daily levodopa equivalent dose, eGFR: estimated glomerular filtration rate.

Table 2. Mean age and frequency of MVI, B12, or MVI + B12 use by age range

Age at diagnosis	NoB12Supp *n* = 617 (54%)	MVI *n* = 466 (41%)	B12 *n* = 26 (2%)	B12 + MVI *n* = 38 (3%)	*p*-value
< 50 yrs					
Number of subjects	99 (66)‡	48 (32)‡	2 (1)	2 (1)	0.02*
Age	44.3 ± 4.6	44.73 ± 4.6	47.5 ± 2.1	48.0 ± 1.4	0.52†
50–59 yrs					
Number of subjects	219 (58)	146 (39)	6 (1)	7 (2)	0.07*
Age	54.9 ± 2.8	55.12 ± 2.9	55.5 ± 3.2	56.3 ± 3.6	0.51†
60–69 yrs					
Number of subjects	209 (48)	200 (46)	9 (2)	18 (4)	0.01*
Age	64.1 ± 2.8	64.11 ± 2.8	64.22 ± 3.4	63.4 ± 2.9	0.77†
≥ 70 yrs					
Number of subjects	90 (49)	72 (40)	9 (5)	11 (6)	0.01*
Age	73.4 ± 3.1	73.6 ± 3.2	72.8 ± 1.8	1.4 ± 1.9	0.16†

Data are presented as a number (percentage) or mean ± SD. *group comparison of number using Fisher's exact test for each age subgroup, †group comparison of age using ANOVA for each age subgroup, ‡$p = 0.038$ pairwise comparison by Hochberg test. MVI: multivitamin.

Table 3. Clinical outcomes at 3 years according to use or non-use of MVI, B12, or MVI + B12

	No supplement (*n* = 617)	MVI (*n* = 466)	B12 (*n* = 26)	B12 + MVI (*n* = 38)	*p*-value
Changes in study outcome					
UPDRS total	5.7 ± 11.7	6.3 ± 12.1	7.7 ± 17.1	5.1 ± 14.8	0.71
UPDRS mental	0.5 ± 1.6	0.5 ± 1.7	0.8 ± 2.3	0.3 ± 1.4	0.58
UPDRS ADL	2.1 ± 4.4	2.3 ± 4.6	3.5 ± 7.0	2.1 ± 5.9	0.39
UPDRS motor	3.1 ± 8.5	3.4 ± 8.7	3.4 ± 10.5	2.7 ± 9.6	0.89
Ambulatory capacity	0.7 ± 2.0	0.9 ± 2.2	1.2 ± 3.1	0.8 ± 2.6	0.63
PDQ-39 summary	4.5 ± 10.1	4.4 ± 9.6	8.8 ± 12.9	4.3 ± 10.6	0.19
SDMT	-0.1 ± 9.1	-0.5 ± 10.0	-3.6 ± 13.1	2.1 ± 13.4	0.13
Total daily LED	299.3 ± 361.7	279.0 ± 350.0	260.8 ± 392.6	258.8 ± 406.8	0.73
Third year UPDRS items					
UPDRS Item 1, intellectual > 0	270 (43.8)	192 (41.2)	11 (42.3)	18 (47.4)	0.79
UPDRS Item 13, falls > 0	67 (10.9)	58 (12.5)	6 (23.1)	6 (15.8)	0.22
UPDRS Item 14, freezing > 0	138 (22.4)	124 (26.6)	9 (34.6)	5 (13.2)	0.08
UPDRS Item 15, walking > 0	480 (77.8)	353 (75.8)	19 (73.1)	26 (68.4)	0.52
UPDRS Item 17, sensory > 0	245 (39.7)	159 (34.1)	8 (30.8)	12 (31.6)	0.21
UPDRS Item 29, gait > 0	312 (50.6)	237 (50.9)	17 (65.4)	22 (57.9)	0.41
UPDRS Item 30, instability > 0	129 (20.9)	115 (24.7)	6 (23.1)	11 (29.0)	0.39

Data are presented as a mean ± SD or number (percentage). F test was used for continuous variables and chi-square test was used for categorical variables. MVI: multivitamin, PD: Parkinson's disease, DA tx: dopamine agonist therapy, UPDRS: Unified Parkinson's Disease Rating Scale, ADL: Activity of Daily Living, PDQ-39: Parkinson's Disease Questionnaire, SDMT: Symbol Digit Modalities Test, LED: daily levodopa equivalent dose.

statistically lower frequency in the MVI group for the age < 50 group, using the Hochberg test ($p = 0.038$). Finally, there was a higher rate of falls in the B12 group compared to that in other groups at baseline.

The upper panel in Table 3 shows the mean change in study outcomes as well as the percent change in the frequency of developing specified UPDRS values > 0 according to MVI or B12 use at the 3-year endpoint. The main finding of this analysis is that no difference was observed between groups for major outcomes, including total UPDRS, its subscores, or SDMT.

The lower panel of Table 3 shows the frequencies for developing intellectual change, falls, freezing, change in walking, sensory symptoms, gait findings, and postural instability. Although these outcomes did not show significant differences, there was a trend for a lower rate of developing sensory symptoms in both the B12 and B12 + MVI groups (30.8% and 31.6%, respectively) compared to the NoB12Supp group (39.7%). Other outcomes, such as the development of freezing, showed a trend toward a lower rate of 13.2% for the B12 + MVI group compared to the NoB12Supp group rate of 22.4%, but this lower

Table 4. Interval censored proportional hazard regression results for not developing sensory symptoms at the 3-year visit

Group	Estimate	*p*-value	Proportional hazard ratio	95% CI of proportional hazard
MVI	-0.20	0.08	0.819	(0.657, 1.021)
B12	-0.18	0.61	0.838	(0.427, 1.644)
B12 + MVI	-0.67	0.08	0.511	(0.239, 1.091)

MVI: multivitamin, CI: confidence interval.

rate was not observed in the B12 group, which had a rate of 34.6%. The development of falls, abnormal gait, and postural instability trended higher in the B12 and B12 + MVI groups than in the NoB12Supp group.

To further investigate the trend of a lower rate of sensory symptoms according to B12 supplementation, we then performed an interval-censored proportional hazard regression analysis shown in Table 4. Although not statistically significant, this analysis shows trends of lower hazard ratios consistent with a lower rate of developing sensory symptoms for the MVI (p = 0.08) and B12 + MVI (p = 0.08) groups but not for the B12 group at 3 years.

DISCUSSION

In the NET PD study, at baseline, 41% of participants obtained some B12 supplementation using an MVI, while 5% used a higher dose (≥ 100 μg/day) supplement. These results are in line with those from a large cross-sectional study conducted in the United States that found an adult prevalence of 33% for MVI use and 6.8% for separate B12 supplementation between 2007 and 2008, the timeframe for the NET PD LS-1 enrollment.[11] In our analysis of outcomes according to B12 and MVI use or non-use at 3 years, we did not find a difference in UPDRS scores or primary subscores. Although it may be that B12 supplementation does not protect against aspects of PD progression, this negative result should be considered preliminary since this is a secondary study that examined outcomes in a small number of subjects using a B12 supplement of ≥ 100 μg/day.

Although we found that the mean age at disease onset was older in the MVI, B12, and MVI + B12 groups compared to that in the group not taking any B12 supplements, our further analysis showed that this finding may be due to "reverse causation" (i.e., older patients took B12 supplements at higher rates; therefore, the mean age of those taking B12 supplements was higher versus the conclusion that B12 supplement use delayed the onset of PD; therefore, the mean age of those taking B12 supplements was higher). The observation of higher rates of MVI and B12 use in older adults was also observed in a recent cross-sectional study of supplement use in adults.[11] The lower frequency of PD diagnosis in those younger than 50 in the MVI group compared to that in the no supplement group is interesting and bears further investigation in a future study of risk factors for PD.

In our exploratory analysis, using the UPDRS "sensory symptom" (Item 17) as a surrogate marker of neuropathy, we found a lower hazard ratio for the development of initial sensory symptoms in the B12 + MVI group at 5 years. The reason why the B12 group did not reach statistical significance, while the MVI + B12 group did, could reflect the benefit of the additional amount of B12 in the MVI in the MVI + B12 group versus the benefit of other nutrients in the MVI, such as folate or vitamin B6. Alternatively, it might be due to a type 1 error due to the small sample size.

Several studies have found higher rates of neuropathy in treated PD patients compared to controls, and B12 deficiency is the most common cause.[6] Moreover, both acute and subacute generalized neuropathies have been reported in PD patients undergoing levodopa/carbidopa intestinal gel infusion,[12] and a number of these cases have been associated with B12, B6, and/or folate deficiencies. This study provides some support for the notion that early B12 supplementation might prevent the development of sensory symptoms in PD.

This study was motivated by our recent analysis of baseline serum B12 measurements and clinical outcomes in the DATATOP study. In that analysis, greater increases in the ambulatory capacity score, consistent with greater impairment of stability, occurred in those subjects whose B12 level was in the lower tertile at study entry.[7] Unlike the DATATOP study in which subjects had not started dopaminergic treatment, in the NET-PD study, participants had already started taking either a dopamine agonist or levodopa therapy within 2 years of the baseline visit. In the NET-PD study, we found no difference in the change of ambulatory capacity scores according to the supplement groups. Moreover, examination of the components of the ambulatory score (falls, gait stability, freezing, walking, and gait) did not show a consistent advantage of B12, B12 + MVI, or MVI alone for any outcome. It is possible that clinician adjustments of dopaminergic treatment or other interventions (such as increased physical therapy) masked this aspect of disease progression related to low B12 levels. In support of this hypothesis, increases in LED at the 3-year endpoint were approximately 30 equivalents higher (although not statistically significant) in the NoB12Supp group than they were in the B12 supplement groups.

B12 must be obtained from dietary sources, and successful

absorption from the gastrointestinal tract depends on a series of steps.[5] The most common causes of B12 deficiency include 1) loss of intrinsic factor, primarily seen in the autoimmune disease pernicious anemia, 2) atrophic gastritis and associated hypochlorhydria, 3) insufficient dietary intake (particularly vegetarians), 4) commonly used drugs including proton pump inhibitors, H2 antagonists, and metformin, and 5) bacterial overgrowth of the stomach and small intestine, which can deplete available B12 for absorption. Despite the finding that B12 levels are lower in early PD than in controls,[4] a large prospective population-based study found no association between dietary intake of B12 and the development of PD.[13] However, PD patients may be more susceptible to low B12 status due to their higher rate of intestinal bacterial overgrowth, which occurs in 25−54% of PD patients and is a substantially higher rate than observed in healthy controls.[14,15]

This study has several limitations. First, it is an analysis of the NET-PD cohort, including only patients with early-treated PD. As it is a secondary analysis, subjects were not randomized according to B12 supplement groups. Additionally, subjects were analyzed according to reported supplement doses with no independent measurements of B12 serum levels. There was also a lower number of subjects treated with B12 or B12 with an MVI compared to that in other groups. The grouping of subjects into 4 groups left 2 of the 4 groups with a very small sample size that was insufficient for the attempted analysis. A "positive result" is more difficult to interpret in small subgroup sizes than it is in larger comparator subgroups. Finally, we used the UPDRS item, "sensory complaints," as a subjective measure of sensory symptoms. This question was not designed to selectively capture neuropathic defects since some sensory complaints might be central in origin. However, since B12 deficiency can cause both neuropathic symptoms in both the central and peripheral nervous systems, this may not be a significant limitation of this study.

These results show that although MVI use is common in older individuals with PD, B12 supplementation of ≥ 100 μg/day not common. Although no difference in clinical outcomes was observed, the trend toward a reduced hazard ratio for the development of sensory complaints is intriguing and deserves further study.

Conflicts of Interest

The authors have no financial conflicts of interest.

Acknowledgments

The NET-PD LS-1 Trial Investigators were supported, in part, by grants U01NS043127, U01NS043128, and U10NS44415-44555. Dr. Christine received unrestricted grants to support this work from the Ko, Tsu, and Liu families.

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