Multicenter randomized clinical trial of donepezil for memory impairment in multiple sclerosis

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ABSTRACT

Objectives: The goal of this study was to determine if memory would be improved by donepezil as compared to placebo in a multicenter, double-blind, randomized clinical trial (RCT).

Methods: Donepezil 10 mg daily was compared to placebo to treat memory impairment. Eligibility criteria included the following: age 18–59 years, clinically definite multiple sclerosis (MS), and performance ≤½ SD below published norms on the Rey Auditory Verbal Learning Test (RAVLT). Neuropsychological assessments were performed at baseline and 24 weeks. Primary outcomes were change on the Selective Reminding Test (SRT) of verbal memory and the participant's impression of memory change. Secondary outcomes included changes on other neuropsychological tests and the evaluating clinician's impression of memory change.

Results: A total of 120 participants were enrolled and randomized to either donepezil or placebo. No significant treatment effects were found between groups on either primary outcome of memory or any secondary cognitive outcomes. A trend was noted for the clinician's impression of memory change in favor of donepezil (37.7%) vs placebo (23.7%) ($p = 0.097$). No serious or unanticipated adverse events attributed to study medication developed.

Conclusions: Donepezil did not improve memory as compared to placebo on either of the primary outcomes in this study.

Classification of evidence: This study provides Class I evidence which does not support the hypothesis that 10 mg of donepezil daily for 24 weeks is superior to placebo in improving cognition as measured by the SRT in people with MS whose baseline RAVLT score was 0.5 SD or more below average. *Neurology*® 2011;76:1500–1507

GLOSSARY

AChEI = acetylcholinesterase inhibitor; **AD** = Alzheimer disease; **BAMA** = Brief Assessment of Memory and Attention; **BRB** = Brief Repeatable Battery; **CI** = confidence interval; **CMDI** = Chicago Multiscale Depression Inventory; **D-KEFS** = Delis-Kaplan Executive Functions System; **EDSS** = Expanded Disability Status Scale; **MACFIMS** = Minimal Assessment of Cognitive Function in Multiple Sclerosis; **MS** = multiple sclerosis; **MSNQ** = Multiple Sclerosis Neuropsychological Questionnaire; **NNH** = number needed to harm; **NNT** = number needed to treat; **OFQ** = Occupational Functioning Questionnaire; **PP** = primary progressive; **RAVLT** = Rey Auditory Verbal Learning Test; **RCT** = randomized clinical trial; **RR** = relapsing-remitting; **SP** = secondary progressive; **SRT** = Selective Reminding Test; **WRAT 3** = Wide Range Achievement Test 3.

Cognitive dysfunction is a common problem in multiple sclerosis (MS), affecting approximately 50% of individuals with the disease.[1,2] Cognitive impairment is associated with unemployment, increased caregiver burden, and decreased quality of life.[3] Verbal memory dysfunction is among the most commonly affected cognitive domains observed in MS[1,2] and is specifically associated with vocational disability.[2,4]

There is some suggestion that disease-modifying therapies improve cognitive functioning in MS,[5] but the benefit is limited and there is little evidence for effective symptomatic treatments.[6]

Supplemental data at www.neurology.org

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Acetylcholinesterase inhibitors (AChEI) are a promising option for treating MS-associated cognitive impairment.[6] MS does not involve a selective reduction of cholinergic neurons as in Alzheimer disease (AD), but there is evidence of reduced cholinergic activity in MS.[7] In addition, lesions targeting cholinergic pathways have been found to correlate with memory impairment in MS.[8] Some, but not all, small randomized clinical trials (RCTs) in MS have been positive.[9-13] The largest study was a single-center placebo-controlled RCT of 69 participants, which showed that donepezil relative to placebo improved verbal memory ($p = 0.043$) and self-reported memory ($p = 0.006$).[9] However, a more recent study comparing rivastigmine to placebo in 60 patients with MS showed no treatment effect.[13] The goal of the current study was to determine whether prior suggestions of the efficacy of donepezil on verbal memory[9] could be confirmed in a larger multicenter study.

METHODS

Study population. Participants were enrolled from 5 Northeastern United States hospital-based MS centers from June 2005 to October 2008. Eligibility criteria included a clinically definite MS diagnosis,[14] age from 18 to 59 years, and Expanded Disability Status Scale (EDSS) score ≤7.0.[15] Participants could not have received steroids within 4 weeks of screening. All MS subtypes were eligible. Participants had to score ≤0.5 SD below age- and gender-corrected normative data on the Rey Auditory Verbal Learning Test (RAVLT).[9,16] Concurrent use of antidepressants, antispasticity agents, and disease-modifying therapies were permitted. Participants had to agree to maintain stable doses of all medications to the extent possible. Benzodiazepine use was a basis for exclusion as these medications can affect cognition.[17] Other exclusion criteria included prior use of donepezil, a current diagnosis of major depression, current alcohol or substance abuse, and history of any other neurologic or medical condition that could adversely affect cognition.

Standard protocol approvals, registrations, and patient consents. An institutional review board at each site approved the study. All participants provided written informed consent. The clinical trial is registered with clinicaltrials.gov (protocol ID: Teva186557-1).

Study design. This RCT used a 24-week double-blind, parallel-group design, as previously used in MS,[9] and as commonly used in AD[18,19] and vascular dementia.[20] The initial dose was 5 mg donepezil daily, increased to 10 mg daily at week 4.[18,21] Participants were administered neuropsychological tasks and questionnaires at week 0 (baseline) and week 24. Testing typically required 2 to 3 hours with breaks provided as needed. The treating neurologist assessed each patient during the study visits. A separate evaluating clinician performed a structured interview to assess cognition at baseline and at the end-of-study visit. Medication compliance and adverse events were monitored by telephone at weeks 8, 12, 16, and 20, and in-person visits with the treating neurologist at weeks 4 and 14.

Randomization. Using a random number generator, participants were assigned by the pharmacist at the Stony Brook University Hospital site to receive either donepezil or placebo in a 1:1 ratio, using a randomization scheme stratified by gender, MS type (relapsing-remitting [RR], secondary progressive [SP], primary progressive [PP]), and study site (Stony Brook, Rochester, Buffalo, Rhode Island, Dartmouth). The pharmacists at each site were the only individuals informed of the randomization assignments and were responsible for labeling study drug and maintaining a master list linking patients with treatment assignments. All other research staff and participants were masked regarding treatment assignment. Masking of active and placebo treatments was preserved by creating capsules that appeared identical.

Power. The study was powered on the basis of the findings for the primary outcome in a prior clinical trial with donepezil in MS (change in Selective Reminding Test [SRT] sum of recall).[9] With sample sizes of 34 and 35 (placebo and donepezil), the previous RCT showed a placebo mean change of 0.68 ± 6.34 (mean ± SD) and donepezil mean change of 4.57 ± 9.05, yielding $t(67) = 2.06$, 2-tailed p value 0.043. With a proposed sample size of 144 with 10% attrition leaving 130 completers ($n_1 = n_2 = 65$), and standard deviations of 6.34 and 9.05, power was estimated to be 82.5% for an effect of 4 points (2-sided test, 5% type I error rate). With actual sample sizes of 61 for donepezil and 59 for placebo, there was a modest decrease in power to 79.1%.

Study hypotheses. The primary hypotheses were that donepezil would enhance verbal learning and memory more than placebo on the SRT, and that persons on donepezil would be more likely to report improved memory after treatment. Secondary hypotheses were that, compared to placebo, donepezil would enhance performance on other neuropsychological tasks (e.g., assessing attention, information processing speed, executive functions), and that evaluating clinicians and significant others would report more general cognitive improvement in persons randomized to donepezil.

Outcome measures. There were 2 primary outcome measures: change in total recall on the SRT and self-reported memory change. The SRT measure of verbal learning and memory is part of the widely used Brief Repeatable Battery (BRB).[22] The SRT was chosen because it assesses cognitive processes most commonly impaired in MS,[1] and has previously responded favorably to donepezil in MS.[9,23] Secondary neuropsychological outcomes included the other BRB tasks,[22] plus 2 measures from the Minimal Assessment of Cognitive Function in Multiple Sclerosis (MACFIMS),[24] Judgment of Line Orientation,[25] and Delis-Kaplan Executive Functions System (D-KEFS) Sorting Test.[26]

Secondary self report outcome measures included a participant's impression of overall cognitive (not just memory) change, and impressions of memory and cognitive functioning from the perspective of the participant's partner (when available) and the evaluating clinician. The evaluating clinician's ratings were based upon their structured interview assessing the participant's cognitive functioning at baseline and 24 weeks, which included the administration of a clinician version of 2 questionnaires assessing a participant's reported cognitive abilities, the Multiple Sclerosis Neuropsychological Questionnaire (MSNQ),[27] and a brief 5-item questionnaire we designed called the Brief Assessment of Memory and Attention (BAMA). The MSNQ and BAMA were administered at weeks 0 and 24. At the 24-week visit, the

MSNQ and BAMA were modified to ask about change from study baseline. The evaluating clinician was allowed only to ask about cognitive functioning and was specifically masked to any adverse events that the participant might have experienced due to study medication. Additional secondary questionnaire measures completed by the participants included the Chicago Multiscale Depression Inventory (CMDI),[28] and a self-report measure designed for this study, the Occupational Functioning Questionnaire (OFQ), which was used to assess disability and whether their disability was due in part to mental challenges that they attribute to MS.

Statistical analysis. All statistical analyses were performed on all participants randomized to either donepezil or placebo using an intention-to-treat principle. A last-observation-carried-forward imputation strategy was used for missing data. There were 2 primary analyses: one for SRT change score and one for self-reported memory improvement. The SRT analysis used linear regression to compare differences in SRT change between the donepezil and placebo groups. Change score was the dependent variable and the independent variables were drug treatment, baseline SRT score, and the stratification variables of gender and MS type. Additional analyses controlled for any significant baseline differences between groups. Analyses of other continuous outcome variables used a similar approach. Group difference on the categorical primary outcome of self-reported memory improvement was analyzed by the χ^2 test, as were other categorical outcomes. All statistical tests were 2-tailed. A p value of <0.05 was considered significant. Analyses were performed with SAS, version 9.2, and PASW Statistics 17.0 software. There was no interim analysis.

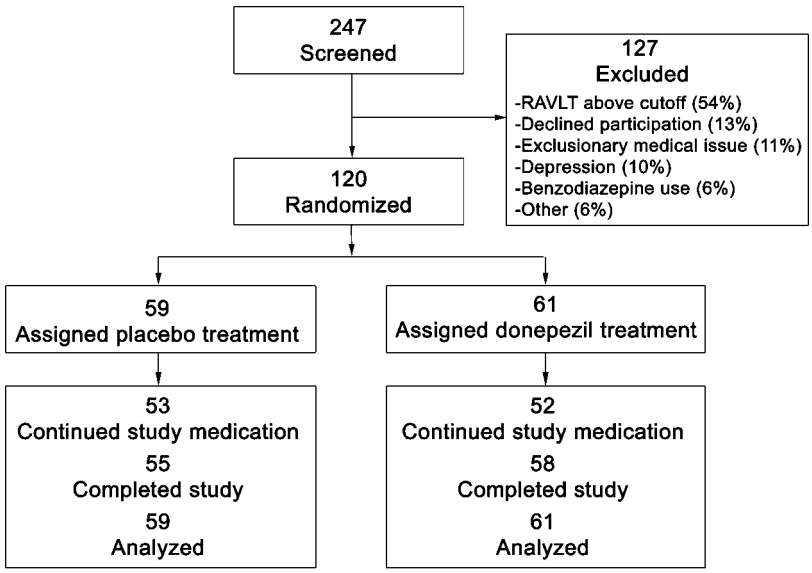
RESULTS Study population and baseline characteristics. As shown in the figure, a total of 247 individuals with MS were screened for the study and 120 were enrolled. The most common reasons for not meeting eligibility criteria are shown in the figure. Of the 120 enrolled participants, 113 completed their final visit and data collection.

While the eligibility criterion for memory function required that subjects perform at least 0.5 SD below norms on the RAVLT,[16] the mean impairment of enrolled subjects was 1.7 ± 0.9 SD below norms, similar to a prior donepezil study in MS.[9] A total of 42.5% of enrolled participants performed below fifth percentile of published norms (1.65 SD or more below the mean).[29]

As shown in table 1, the 2 groups did not differ significantly on most demographic or baseline features. However, the donepezil group had more years of education ($p = 0.027$) and higher reading scores on the Wide Range Achievement Test 3 (WRAT 3) ($p = 0.026$).[30] The groups were well-matched on most disease characteristics (e.g., MS subtypes, EDSS). There were no differences between groups in the use of anticholinergic medications (e.g., tricyclic antidepressants). However, the donepezil group had a longer self-reported disease duration as measured from symptom onset ($p = 0.039$). Self-report on the OFC indicated that a total of 38% of those on placebo and 44% of those on donepezil were on disability. OFC responses also indicated that cognitive challenges associated with MS contributed to disability in 76% of the placebo and 65% of the donepezil group.

On the SRT (see table 1), the placebo group had a baseline mean score that was nonsignificantly lower than in the donepezil group. The mean performance of the placebo group on the SRT was 2.4 ± 1.3 SD below an age- and education-matched healthy control group (from Stony Brook) while the donepezil group was 2.2 ± 1.4 SD below these healthy controls. On the overall BRB battery, the donepezil group was 1.3 (SD = 0.80) and the placebo group 1.5 (SD = 0.90) SD below healthy controls. No baseline differences between the donepezil and placebo groups reached significance on any of the neuropsychological test measures or questionnaires.

Figure Subject flow



RAVLT = Rey Auditory Verbal Learning Test.

Efficacy. As shown in table 2, there was no significant treatment effect for the primary neuropsychological outcome measure (change in total recall on the SRT) or any other neuropsychological measure. Results for the primary neuropsychological outcome were no different in a secondary analysis that controlled for the additional covariates of years of education, WRAT 3 reading score, age, and study site, in addition to the primary analysis covariates of gender, MS type, and baseline SRT total score. Results remained nonsignificant when week 24 SRT was used as the dependent variable instead of the change in total recall. Results also remained nonsignificant when week 0 SRT was eliminated as a covariate while retaining

Table 1 Summary of participant characteristics at baseline

Characteristics	Placebo (n = 59)	Donepezil (n = 61)
Demographics		
Mean age, y, ± SD	47.3 ± 8.9	46.2 ± 7.5
Women, n (%)	48 (81)	45 (74)
Mean education, y, ± SD[a]	13.2 ± 2.0	14.0 ± 2.2
MS characteristics		
Mean EDSS ± SD	3.74 ± 1.98	3.96 ± 1.78
MS subtypes, n (%)		
RR	37 (63)	38 (62)
SP	19 (32)	18 (30)
PP	3 (5)	5 (8)
Years since symptom onset[a]	11.8 ± 8.0	14.9 ± 8.2
Years since diagnosis	9.4 ± 7.6	11.3 ± 7.7
Concomitant medications, n (%)		
Interferon-β	24 (41)	28 (46)
Glatiramer acetate	9 (15)	18 (30)
Anticholinergic medications[b]	10 (17)	14 (23)
Nontricyclic antidepressants	26 (44)	23 (38)
Anticonvulsant medication	14 (24)	12 (20)
Cognitive characteristics		
Mean WRAT 3 reading score ± SD[a]	45.0 ± 6.5	47.1 ± 3.5
Mean MSNQ patient total ± SD	30.3 ± 10.5	30.2 ± 10.8
Mean MSNQ clinician total ± SD	25.5 ± 10.3	25.7 ± 9.9
Mean SRT ± SD	36.0 ± 9.80	38.0 ± 8.7
Median SRT (range)	36.0 (16-60)	40.0 (19-57)
Mean RAVLT ± SD	37.5 (7.3)	35.6 (6.7)
Median RAVLT (range)	39.0 (17-49)	36.0 (18-47)
Primary occupational role, n (%)		
Paid worker	21 (36)	15 (25)
Disabled	26 (44)	23 (38)
Cognitive challenges contribute to disability	20 (76% of disabled)	15 (65% of disabled)
Psychological characteristics		
Mean CMDI mood sum + SD	17.0 + 7.7	17.5 + 8.0
Mean CMDI mood T score + SD	54.2 + 14.0	55.2 + 14.5
Mean FSS total + SD	4.9 + 1.5	5.3 + 1.4
Mean AES total + SD	31.7 + 7.7	31.5 + 8.6

Abbreviations: AES = Apathy Evaluation Scale Self Report; CMDI = Chicago Multiscale Depression Inventory; EDSS = Expanded Disability Status Scale; FSS = Fatigue Severity Scale; MS = multiple sclerosis; MSNQ = Multiple Sclerosis Neuropsychological Screening Questionnaire; PP = primary progressive; RAVLT = Rey Auditory Verbal Learning Test; RR = relapsing remitting; SP = secondary progressive; SRT = Selective Reminding Test; WRAT 3 = Wide Range Achievement Test 3.

[a] $p < 0.05$.

[b] Anticholinergic medications: tricyclic antidepressants, anticholinergic bladder medications (oxybutynin, tolterodine).

SRT change as the dependent variable. Overall, both groups improved slightly on the SRT total score. There were also no group differences found in χ^2 analyses that compared the proportion of subjects in each group who displayed a reliable change in their

Table 2 Mean ± SD (95% CI) performance of the donepezil and placebo groups on the SRT primary outcome and other neuropsychological tasks at week 0, week 24, and week 24-0

	Week 0		Week 24		Week 24-0		Effect size (week 24-0)
	Placebo	Donepezil	Placebo	Donepezil	Placebo	Donepezil	
SRT	36.0 ± 9.8 (33.5, 38.6)	38.0 ± 8.7 (35.7, 40.2)	37.7 ± 11.5 (34.7, 40.7)	39.6 ± 8.7 (37.4, 41.8)	1.7 ± 7.2 (−0.2, 3.6)	1.6 ± 7.5 (−0.3, 3.6)	0.54
10/36	16.6 ± 5.6 (15.1, 18.1)	17.5 ± 5.0 (16.3, 18.8)	18.2 ± 5.0 (16.9, 19.5)	17.1 ± 5.1 (15.8, 18.4)	1.6 ± 4.6 (0.4, 2.8)	−0.4 ± 5.0 (−1.7, 0.8)	−1.63
SDMT	38.0 ± 13.7 (34.4, 41.6)	39.2 ± 11.8 (36.1, 42.2)	40.0 ± 14.6 (36.2, 43.8)	39.8 ± 11.7 (36.8, 42.8)	2.0 ± 6.4 (0.3, 3.6)	0.6 ± 6.4 (−1.0, 2.2)	−1.01
PASAT 2 + 3 sec	57.4 ± 24.0 (51.2, 63.7)	61.7 ± 23.2 (55.8, 67.6)	60.9 ± 26.3 (54.1, 67.8)	65.5 ± 23.9 (59.3, 71.6)	3.5 ± 12.0 (0.4, 6.6)	3.8 ± 12.5 (0.6, 7.0)	0.90
COWA	27.9 ± 9.1 (25.6, 30.3)	29.6 ± 9.0 (27.3, 31.9)	28.5 ± 9.7 (26.0, 31.1)	30.6 ± 10.4 (27.9, 33.3)	0.6 ± 6.0 (−1.0, 2.1)	1.0 ± 7.4 (−0.9, 2.9)	0.92
D-KEFS Sort	6.7 ± 2.9 (6.0, 7.5)	6.9 ± 2.6 (6.2, 7.6)	7.2 ± 2.7 (6.5, 7.9)	7.5 ± 2.8 (6.8, 8.2)	0.5 ± 2.5 (−0.2, 1.1)	0.6 ± 2.4 (−0.0, 1.2)	0.23
JOLO	19.5 ± 5.4 (18.1, 20.9)	20.6 ± 5.9 (19.1, 22.1)	20.1 ± 5.0 (18.8, 21.4)	21.2 ± 5.7 (19.8, 22.7)	0.6 ± 3.0 (−0.2, 1.4)	0.6 ± 3.4 (−0.3, 1.4)	0.10

Abbreviations: 10/36 = 10/36 Spatial Recall Test; CI = confidence interval; COWA = Controlled Oral Word Association letter fluency total; D-KEFS Sort total = Delis-Kaplan Executive Function System Sorting total; JOLO = Judgment of Line Orientation total; PASAT = Paced Auditory Serial Addition Test 2 & 3 form total; SDMT = Symbol Digit Modalities Test total; SRT = Selective Reminding Test total.

Table 3 Percent of individuals in each group who reported improvement in memory or overall cognition

Impression of change measure	Placebo	Donepezil
Participant's impression of memory change	35.6	36.1
Participant's impression of cognitive change	39.0	37.7
Clinician's impression of memory change	23.7	37.7[a]
Clinician's impression of cognitive change	25.4	34.4
Significant other's impression of memory change	15.3	21.3
Significant other's impression of cognitive change	15.3	23.0

[a] $p = 0.10$.

SRT total score (an increase or decrease of at least 1.96 Z score points), nor were there any χ^2 differences in reliable change on any of the other neuropsychological measures (table e-1 on the *Neurology*® Web site at www.neurology.org). Nonsignificant results were also obtained in secondary analyses of other SRT scores (consistent long-term retrieval, long-term storage, and delayed recall).

As shown in table 3, there was no significant group difference on the primary outcome measure of self-reported memory change, or on any other perceived cognitive change measure. The absolute risk reduction for self-reported memory change was 0.5%, and the number needed to treat (NNT) was 200 (1/0.5%), with a 95% confidence interval (CI) for NNT of 5.72 to infinity and a 95% CI of 6.02 to infinity for number needed to harm (NNH).[31] The only outcome measure showing a trend ($p = 0.097$) favoring donepezil was the evaluating clinician's impression of memory change, which had an absolute risk reduction of 14.0%, and an NNT that was 7.14 with a 95% CI of 37.8 to infinity for NNT and 3.3 to infinity for NNH.

The subgroup of participants not taking anticholinergic medications were no more likely to benefit from donepezil on the primary outcomes than were persons taking anticholinergic medications.

Exploratory subgroup analyses on the 51 participants with verbal memory impairment defined by performing below the fifth percentile on the RAVLT[16] showed that donepezil-treated subjects improved more on the primary outcome of SRT total recall than those on placebo ($p \leq 0.045$), plus trends favoring the donepezil group for SRT long-term storage ($p \leq 0.085$), and PASAT total score ($p \leq 0.069$).

Adverse events. No serious adverse events were attributed to the study medications. As shown in table 4, diarrhea was the only adverse event more frequent with donepezil than placebo ($p < 0.05$). Other gastrointestinal symptoms, urinary frequency, and upper respiratory infections were also reported more often by those on donepezil, but none differed significantly between the 2 groups. In contrast to a prior donepezil RCT,[9] there were no significant differences in the frequency of vivid dreams.

Table 4 No. (%) of participants experiencing each type of adverse event in each group

Symptom	Placebo	Donepezil
Gastrointestinal		
Diarrhea	3 (5)	15[a] (25)
Nausea	7 (12)	14 (23)
Vomiting	1 (2)	5 (8)
Other gastrointestinal	8 (14)	12 (20)
Neuropsychiatric		
Fatigue	9 (15)	5 (8)
Headaches	5 (8)	9 (15)
Abnormal dreams	5 (8)	12 (20)
Sleeplessness	3 (5)	8 (13)
Psychiatric distress	3 (5)	3 (5)
Other neuropsychiatric	6 (10)	8 (13)
Multiple sclerosis relapse	2 (3)	4 (7)
Bladder		
Frequency	0 (0)	5[b] (8)
Other bladder	2 (3)	4 (7)
Motor		
Weakness	5 (8)	5 (8)
Other motor	6 (10)	9 (15)
Somatosensory		
Pain	9 (15)	5 (8)
Other somatosensory	3 (5)	5 (8)
Infectious		
Upper respiratory infection	8 (14)	17[b] (28)
Infection other	4 (7)	6 (10)
Other		
Dermatologic	7 (12)	3 (5)
Musculoskeletal	2 (3)	6 (10)
Metabolic	3 (5)	6 (10)
Miscellaneous	5 (8)	4 (7)

[a] $p < 0.05$.
[b] $p < 0.10$.

Overall the study was well-blinded despite some group differences in the side effect profile. A total of 30% of placebo recipients and 40% of donepezil recipients treated correctly guessed their group assignment.

DISCUSSION Cognitive impairment affects 40% to 60% of individuals with MS[1,2] and no medication has been consistently shown to be effective for this problem. A prior RCT in mildly impaired patients with MS showed that donepezil relative to placebo led to modestly greater improvements on a test of

verbal learning and memory.[9] However, the current study failed to confirm this benefit as donepezil did not differ from placebo in improving a test of verbal memory or self-reported memory change. Donepezil also failed to improve any of the other neuropsychological measures. This negative RCT had a multicenter design and a larger sample size than the earlier positive trial,[9] though it had the same eligibility criteria and primary outcome.

There were some baseline differences between the 2 groups in this study. The donepezil group had more years of education and performed better on the WRAT 3 reading task. However, there were no significant differences in the estimated treatment effect after controlling for these baseline differences. While disease duration was longer in the donepezil-treated group, other disease parameters including proportion of patients in each MS subgroup and mean EDSS did not differ between groups.

Why was this study negative whereas a smaller single-center RCT showed a positive treatment effect?[9] One can come to either of 2 conclusions: the medication is ineffective in MS or some aspect of the study design limited the ability to identify an actual treatment benefit. It is possible that an AChEI such as donepezil that was designed for use in AD is inappropriate for persons with MS. MS is not known to selectively damage cholinergic neurons. However, there is some evidence of decreased cholinergic activity in cerebral spinal fluid markers in MS,[7] and hippocampal damage in MS has been correlated with cognitive impairment,[32] though these findings do not mean that AChEI treatment would necessarily be therapeutic. As discussed elsewhere,[6] AChEIs have shown promise of benefit in a variety of other disorders in addition to AD, such as traumatic brain injury and Parkinson disease. There is some evidence that even healthy individuals may benefit from donepezil.[33] For example, donepezil improved performance on flight simulator tasks among healthy older airplane pilots.[21] Nonetheless, it is possible that the mechanisms underlying cognitive impairment in MS preclude any treatment effect from AChEIs.

It is also possible that the benefit of donepezil in MS is more modest than initially estimated, and therefore difficult to reliably demonstrate with a sample of the current size. The power estimation for the present sample was derived from the results of an earlier clinical trial in MS with donepezil,[9] and it is possible that those results represent an unusually large effect for MS. The current sample size of approximately 60 per treatment group is substantially smaller than that used in standard AD clinical trials, with sample sizes ranging from approximately 160[18] to 270.[19] Conversely, if the effects of donepezil are particularly small, then it could call into question the clinical or real-world benefit of the medication.

Another characteristic that might have influenced the present results is the choice of cognitive screening criterion. The inclusion cutoff on the RAVLT memory task was relatively mild, requiring participants to score at least one-half SD below norms. The subgroup analysis of subjects with more impaired RAVLT performance (below the fifth percentile on the RAVLT) did reveal a positive treatment effect on the primary outcome measure and showed a trend on 2 secondary cognitive outcomes. It is possible that if the entire sample had met this criterion of baseline memory impairment a positive treatment with donepezil might have been observed. Nonetheless, the participants in the current study were as impaired as those in the prior positive trial.[9]

The trend favoring donepezil for the clinician's impression of memory change is interesting, but should not be overinterpreted given the multiple secondary outcome measures that were examined. Nonetheless, the use of a structured interview to guide the clinician's impression of change may have enhanced the sensitivity of clinicians' ability to detect improvement. This type of outcome should be further explored in future clinical trials for cognitive impairment in MS.

Cognitive impairment has proven to be very difficult to treat and with the results of this trial there are no medications that have consistently shown efficacy in MS-associated cognitive impairment. RCTs with symptomatic therapy using a different AChEI (rivastigmine)[13] or other agents such as pemoline,[34] amantadine,[34] ginkgo biloba,[35] and amphetamine[36] have also failed to show a consistent benefit on primary cognitive outcomes.

Overall, this was a negative study due to the failure of donepezil compared to placebo to improve memory functioning or other cognitive abilities (in the overall sample). Future studies with more effective agents are clearly needed to treat cognitive impairment in MS.

AUTHOR CONTRIBUTIONS

Statistical analysis was conducted by Dr. L.R. Muenz and D. He.

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DISCLOSURE

Dr. Krupp has served on scientific advisory boards for Acorda Therapeutics Inc., Genentech, Inc., Pfizer Inc, Novartis, and sanofi-aventis; served on speakers' bureaus for Bayer Schering Pharma, Biogen Idec, Teva Pharmaceutical Industries Ltd., and EMD Serono, Inc.; serves as a consultant for Leerink Swan, Gerson Lehrman Group, Guidepoint Global; and has received research support from Biogen Idec, EMD Serono, Inc., Acorda

Therapeutics Inc., BioMS Medical, Teva Pharmaceutical Industries Ltd., Novartis, Genentech, Inc., the NIH, the National Multiple Sclerosis Society, the Montel Williams Foundation, the Lourie Foundation, and the Slomo and Cindy Silvian Foundation. Dr. Christodoulou has received research support from Cephalon, Inc., the NIH, and the National Multiple Sclerosis Society. P. Melville, W.F. Scherl, and L.-Y. Pai report no disclosures. Dr. Muenz serves on scientific advisory boards for Teva Pharmaceutical Industries Ltd., Neuren Pharmaceuticals Limited, and the National Heart, Lung, & Blood Institute; has served as a biostatistical consultant for Capstone Therapeutics, DJO Surgical, Georgetown University, Johns Hopkins University, Lightlab Imaging Inc., Musculoskeletal Clinical Regulatory Advisers LLC, NanoBio Corp., Nephrogenex Inc., Neuren Pharmaceuticals Limited, New York University, Oakwood Laboratories LLC, Oceana Therapeutics Inc., Sigma-Tau Pharmaceuticals, Inc., SUNY Stony Brook, VGX Pharmaceuticals, LLC, and Westat, Inc.; and has served as a biostatistical consultant for Capstone Therapeutics, ChemoCentryx, ClinData Services, The Center for Mind-Body Medicine, DJO Surgical, Lightlab Imaging Inc., Musculoskeletal Clinical Regulatory Advisers LLC, Nabi Biopharmaceuticals, Nephrogenex Inc., New York University, Oakwood Laboratories LLC, Oceana Therapeutics Inc., Provident Clinical Research & Consulting Inc., Sigma-Tau Pharmaceuticals, Inc., SUNY Stony Brook, and VGX Pharmaceuticals, LLC. Dr. Benedict serves on scientific advisory boards for Merck Serono, Biogen Idec, Bayer Schering Pharma, Novartis, and Pfizer Inc; serves on the editorial boards of *Multiple Sclerosis*, *Neuropsychology*, and the *International Journal of MS Care*; receives royalties from Psychological Assessment Resources; has received speaker honoraria from Biogen Idec, Pfizer Inc, Abbott, Bayer Schering Pharma, Merck Serono, and Teva Pharmaceutical Industries Ltd.; and receives research support from Shire plc, Biogen Idec, the NIH, and the National Multiple Sclerosis Society; and has given expert testimony in several personal injury trials. Dr. Goodman has served as a consultant for and received funding for travel from Acorda Therapeutics Inc., Actelion Pharmaceuticals Ltd, Avanir Pharmaceuticals, Bayer Schering Pharma, Biogen Idec, EMD Serono, Inc., Genentech, Inc., Genzyme Corporation, Pfizer Inc, and Teva Pharmaceutical Industries Ltd.; and receives research support from Acorda Therapeutics Inc., Bayer Schering Pharma, Biogen Idec, EMD Serono, Inc., Genentech, Inc., Genzyme Corporation, Novartis, Teva Pharmaceutical Industries Ltd., the NIH, and the Montel Williams Foundation. Dr. Rizvi serves on a scientific advisory board for Bayer Schering Pharma; serves as a consultant for Bayer Schering Pharma, Biogen Idec, Teva Pharmaceutical Industries Ltd., Acorda Therapeutics Inc., Merck Serono, and Pfizer Inc; serves on speakers' bureaus for Biogen Idec, Teva Pharmaceutical Industries Ltd., Bayer Schering Pharma, Acorda Therapeutics Inc., and Merck Serono; and receives research support from Biogen Idec, Bayer Schering Pharma, Teva Pharmaceutical Industries Ltd., Genentech, Inc., UCB, and the NIH. Dr. Schwid has received research support from Bayer Schering Pharma, Biogen Idec, Merck Serono, Teva Pharmaceutical Industries Ltd., and the National Multiple Sclerosis Society. Dr. Weinstock-Guttman serves on a scientific advisory board for the National Multiple Sclerosis Society; has received funding for travel from Biogen Idec, Teva Pharmaceutical Industries Ltd., EMD Serono, Inc., and Pfizer Inc, and Novartis; serves on the editorial board of aan.com; serves as a consultant for Biogen Idec, Teva Pharmaceutical Industries Ltd., EMD Serono, Inc., Pfizer Inc, sanofi-aventis, and Novartis; serves on speakers' bureaus for Biogen Idec, Teva Pharmaceutical Industries Ltd., EMD Serono, Inc., Pfizer Inc, and Novartis; and receives research support from Biogen Idec, EMD Serono, Inc., Teva Pharmaceutical Industries Ltd., Cyberonics, Inc., Novartis, the NIH, and the National MS Society. Dr. Westervelt serves as an Associate Editor for *Archives of Clinical Neuropsychology*; receives publishing royalties for *Practitioner's Guide to Evaluating Change with Neuropsychological Assessment Instruments* (Kluwer Academic/Plenum Publishers, 2000); and receives research support from the NIH/NINDS. Dr. Wishart serves on a scientific advisory board for and has received funding for travel from Bayer Schering Pharma; and receives research support from Teva Pharmaceutical Industries Ltd., Bayer Schering Pharma, Merck Serono, Genzyme Corporation, the NIH, the US Department of Defense, the National MS Society, and the Dartmouth Center for Clinical and Translational Science.

APPENDIX

The Data and Safety Monitoring Committee (DSMC): Stuart Cook, MD, Nicholas LaRocca, PhD, and Daniel F. Heitjan, PhD.

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