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Efficacy of acetylcholinesterase inhibitors for cognitive impairment in multiple sclerosis: A systematic review and meta-analysis

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Abstract

Background & Objective: Multiple Sclerosis (MS) is a chronic demyelinating condition characterized by a myriad of neurologic deficits. The prevalence rate of Cognitive impairment (CI) ranges from 40 to 60 percent among community-dwelling individuals with MS. Cholinergic dysfunction is one of the different mechanisms proposed to cause CI, supporting the use of acetylcholinesterase inhibitors (AChEIs) in certain conditions. The study aims to determine the safety and efficacy of acetylcholinesterase inhibitors in multiple sclerosis patients with cognitive impairment through a review of randomized clinical trials. *Methods:* Using the updated PRISMA guidelines, we searched MEDLINE by PubMed, Cochrane Central Register for Controlled Trials (CENTRAL), ClinicalTrials.gov website, Google Scholar, and HERDIN Database for relevant studies until November 15, 2022. *Results:* A total of 73 records were identified and five studies were included in the analysis. Pooled evidence shows that AchEIs (donepezil 10 mg/day or rivastigmine 10 mg/day for 12 to 14 weeks) did not significantly improve Paced Auditory Serial Addition Test (PASAT) score for information processing and sustained attention and the Selective Reminding Test (SRT) score for verbal memory. Another study using the Weschler Memory Scale (WMS) also did not show significant improvement in their scores. However, a recent trial that used the Everyday memory questionnaire (EMQ), prospective and retrospective memory questionnaire (PRMQ), and the Digit span test (DST) showed significant difference between pre- and post-intervention mean scores in the donepezil group ($p<0.001$). The physical and mental health scores of the Multiple Sclerosis Quality of Life questionnaires (MSQOL) significantly improved in MS patients receiving donepezil. Both donepezil and rivastigmine were associated with non-serious adverse events.
Conclusion: The use of AchEIs among MS patients does not significantly improve objective measures of cognition but has positive impact on subjective scales of cognition (EMQ and PRMQ). AchEIs were shown to improve patients' quality of life. AchEIs are safe and well tolerated among MS patients.

Keywords: Multiple sclerosis, cognitive impairment, acetylcholinesterase inhibitors, donepezil, rivastigmine

INTRODUCTION

Multiple Sclerosis (MS) is a chronic demyelinating condition characterized by a myriad of neurologic symptoms. The estimated number of people with MS worldwide has increased to 2.8 million in 2020 with a global prevalence of 35.9 per 100,000 people.[1] The prevalence rate of cognitive impairment (CI) in MS ranges from 40 to 60 percent among community-dwelling individuals with MS.[2–4] A study by Amato *et al*[4] showed an increase in the proportion of CI patients with MS in a 10 year follow up from 26% to 56%. Cognitive domains are variably affected depending on the site and volume of the lesion/s. Several studies

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have elucidated, however, that some cognitive domains are affected more frequently than others. Memory, information processing efficiency, executive functioning, attention, and processing speed are most commonly implicated[3]. Recent studies have shown that memory deficits result from impaired encoding rather than impairment in the retrieval of information.[5,6]

Cognitive impairment in MS was previously considered a form of subcortical dementia.[5] Unlike other subcortical dementias, MS is not characterized by a disconnection between cortical and subcortical functions[7] Newer studies have shown that both the grey matter and subcortical networks are affected in MS and the complexity of the pathophysiology of CI in MS gives rise to its diverse clinical presentation[8,9] Cognitive impairment has been demonstrated in all stages and subtypes of MS but more frequent and severe deficits are reported in secondary progressive MS (SPMS) than in relapsing-remitting MS(RRMS).[10]

Several mechanisms were implicated in the occurrence of cognitive impairment in MS patients. Demyelination, axonal loss, and grey matter plaques have been assumed to contribute to cognitive impairment.[11] Inflammatory diseases such as Diffuse Systemic lupus erythematosus (SLE) and dementia associated with HIV infection served as models that will explain the likely causes of CI in MS[12] Studies have shown that MS patients with cognitive impairment have some form of cholinergic dysfunction[13,14] A post-mortem study in 2011 of 15 patients with MS revealed 80% of them had partial or complete demyelination of the hippocampus. There was a clear reduction in Choline Acetyltransferase (ChAT) activity and protein expression. These findings suggest that there is an imbalance in the hippocampal cholinergic transmission and reduced synthesis of acetylcholine.[15] Acetylcholinesterase inhibitors (AChEIs) inhibit the degradation of acetylcholine leading to increased levels in the synapse. Studies reviewed the positive effect of these drugs on several diseases causing dementia, such as Alzheimer's disease (AD)[16], Vascular dementia (VaD)[17,18], and Lewy body dementia (LB/DLB).[19] The study aims to determine the safety and efficacy of AChEIs in people with MS in terms of improvement in cognitive function and quality of life.

METHODS

This review followed the updated PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) consensus guidelines.[20]

Eligibility criteria

We included randomized, double-blind, placebo-controlled trials that determined the efficacy of AChEIs among patients with MS regardless of subtype, defined by the Mcdonald Criteria 2001[21] or 2017.[22,23] Studies that employed AChEIs as an intervention compared to placebo were included. All studies were primary research, reported in English and with the available full-text article. Studies were required to report cognitive outcome measures and to involve daily administration of the study drug.

We excluded studies using other designs such as quasi-experimental, cross-over studies, prospective or retrospective cohort, case-control, and cross-sectional designs. We also excluded studies that administered a single dose of the drug. The following patient characteristics were not considered in selecting the studies for review: age, sex/gender, ethnicity, disease types, disease severity, and disease activity. Previous or current use of other medications for MS was also not considered.

The primary outcome of this review was the effect on cognitive function in MS patients with CI. Secondary outcome measures considered were the effects on the quality of life and adverse events.

Search methods for identification and selection of studies

Articles were searched until November 15, 2022. The following databases were searched: MEDLINE by PubMed, Cochrane Central Register for Controlled Trials (CENTRAL), ClinicalTrials.gov website, Google Scholar, and HERDIN Database. We used the following terms for the search strategy: ("multiple sclerosis" OR "ms") AND ("cognitive impairment") OR ("memory disorders" OR ("memory" AND "disorders") OR "memory disorders" OR ("memory" AND "impairment") OR "memory impairment")) AND ("acetylcholinesterase inhibitors" OR "galantamine" OR "rivastigmine" OR "donepezil".

Two authors (MCF and LGD) assessed all the identified records based on the titles and abstracts identified using the screening criteria. Articles that passed the screening were retrieved in full text and were evaluated by authors (MCF and LGD) using the predetermined eligibility criteria. Disagreements were resolved by consulting with a

different author either JAC, SGV, MLC, or ERA. Those studies that satisfied the eligibility criteria were included in this review.

Data extraction, assessment of risk of bias, and analysis of data

The following data were extracted from the eligible articles included in this review: study characteristics (authors, year of publication) (2) participant demographics (sample size, sex, age, years of education); (3) trial design (including details of the treatment and the control group); (4) eligible outcomes.

We evaluated studies included in the review using the Cochrane Risk of Bias Tool.[24] The tool assesses six aspects of trial methodology that could potentially introduce different sources of bias: sequence generation, allocation concealment, blinding of participants and study personnel, blinding of outcome assessments, incomplete outcome data, and selective outcome.

Descriptive statistics were used to summarize data. Continuous outcomes were expressed as mean differences (MD) and standard deviations. Mean Difference (95% Confidence Interval) and Odds ratio were the effect size used for continuous and dichotomous outcomes respectively. The null hypothesis was rejected at 0.05 α-level of significance while homogeneity assumptions were rejected at 0.05 α-level of significance. A funnel plot was used to measure the publication bias of the studies included in the analysis while a Forest plot was used to illustrate the overall effect of the model. Review Manager 5.0 was used for data analysis.

RESULTS

Included studies

There were a total of 73 records identified through database searching. An additional 4 studies were identified through citation searching, all of them have no available abstract or full text hence they were excluded. Five records were duplicates. 68 were screened and 59 records were excluded, 23 were review articles, 12 articles used a different intervention, 10 articles focused on other diseases, 3 were animal studies, 3 were commentaries, 2 were unpublished terminated trials, 2 focused on other components of MS, 1 is a diagnostic study, 1 is an unpublished completed trial and the other was a case report. The remaining nine records were subjected to eligibility testing and four records were excluded. Five studies were included in the qualitative and quantitative analysis. Figure 1 shows the PRISMA Flow diagram. Study demographics and other information were summarized in Table 1.

Characteristics of the population in the included studies

A total of 430 patients were analyzed in the five trials.[25–29] The majority of the participants were female and with a relapsing-remitting subtype. Table 2 summarizes the characteristics of the population of the five trials. One trial[26] did not report the types of MS according to the intervention given however, among the recruited participants 72 had RRMS, 13 SPMS and one had been diagnosed with the clinically isolated syndrome (CIS). Table 2 summarizes the characteristic of the population among the included studies.

Interventions Employed in the Included Studies

All of the studies compared AChEIs with placebo. Three trials[27–29] used donepezil as the treatment intervention. Shahpouri *et al*. used a daily dose of donepezil 10 mg/tablet for a duration of 12 weeks. The other two trials used an initial dose of 5 mg then increased to 10 mg/tablet daily at week 4 for a duration of 24 weeks. Two trials[25,26] employed rivastigmine as the treatment intervention. Shaygannejad *et al*. used a dose of 1.5 mg once daily increment over 4 weeks to 3 mg twice daily.[25] In the other trial, participants received rivastigmine patch of 5 cm^2 (4.6 mg/day) for four weeks increasing to 10 cm^2 (9.5 mg/day). Both trials gave rivastigmine for 12 weeks.[26]

Outcome Measures

Change in Serial Reminding Test Score (SRT): The SRT is a neuropsychological test used to measure verbal learning and memory. It distinguishes short-term from long-term memory. A positive change means improvement.[30,31]

Change in The Paced Auditory Serial Addition Test (PASAT): PASAT is a test to measure sustained attention and information processing speed. It is scored from 0-60 and a positive change means improvement in the cognitive domains measured.[32]

Multiple Sclerosis Quality of Life questionnaire: MSQOL is a 54-item questionnaire that measures 12 domains of physical and mental health. The total score ranges from 0 to 100 with a higher

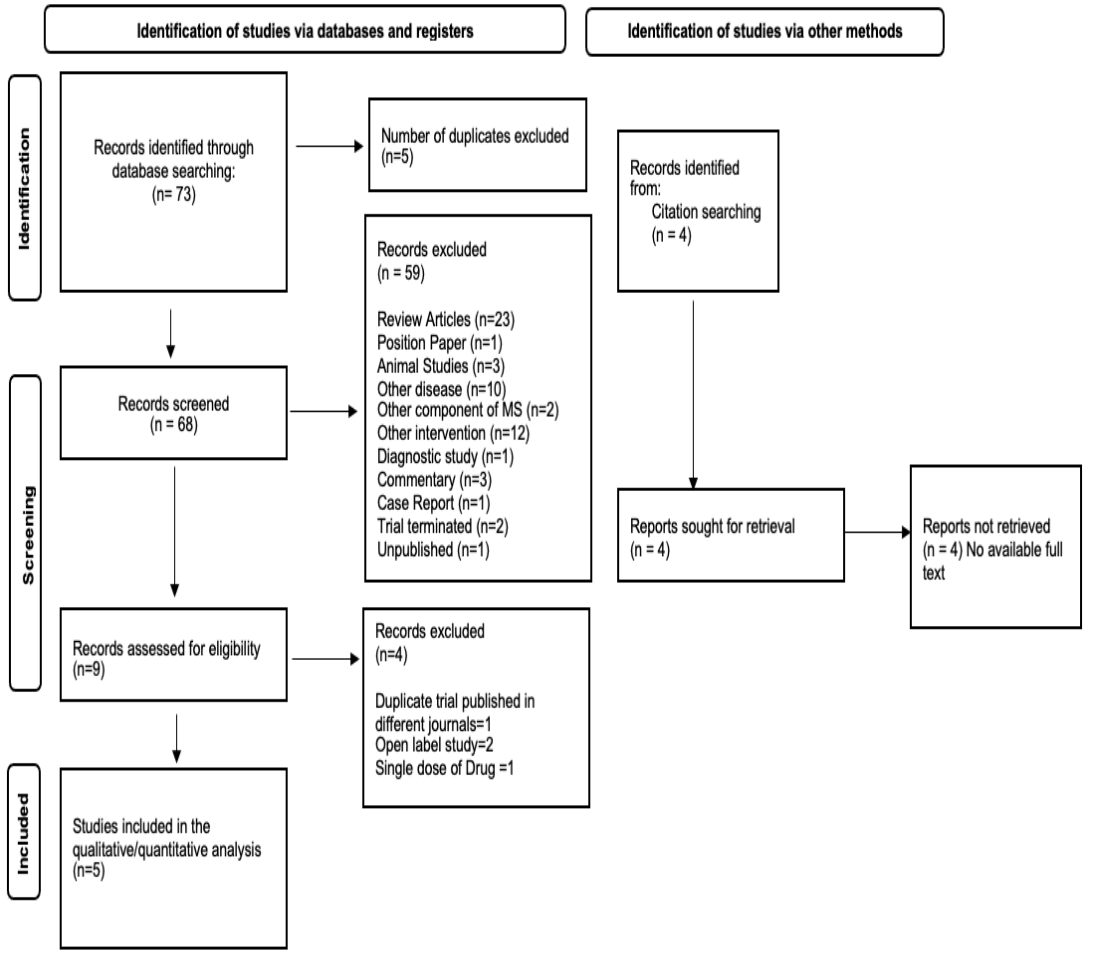

Figure 1. PRISMA Flow Diagram

score indicating improved quality of life.[33]

Everyday Memory Questionnaire: EMQ is a 28-item subjective measure of memory failure in everyday life. Higher scores represent worse cognitive function.[34]

Weschler Memory Scale (WMS): WMS is a clinical test that measures sustained attention, information processing, memory retrieval, working memory, and dual processing.[25]

Digit Span Test (DST): DST is one of the components of the WMS. Subjects are asked to repeat a series of numbers ranging from 2 to 9 either forward or backward. The forward digit span is a measure of attention and short-term verbal memory while the backward digit span measures working memory.

Prospective and retrospective memory questionnaire (PRMQ): PRMQ is a 16-item subjective questionnaire that is designed to assess different types of memory failures. The scale also includes an assessment of the level of "frustration" (in the informant) caused by these failures.[35]

Assessment of risk of bias

Figure 2 summarizes the risk of bias assessment done on the five trials included in the study. Four trials had a low risk of selection, performance, attrition, detection, and reporting bias. Two trials[26,29] provided outcomes for nearly all of the randomized participants. The trial of Maurer *et al*[26] had an attrition rate of 4.4 % and 7.3% for the treatment and placebo groups, respectively. It did not analyze all participants in the group that they were randomized hence the study was deemed to have an unclear risk of attrition bias. The study of Shahpouri *et al*[29] was deemed to have an unclear risk for reporting bias due to the

Table 1: Study characteristics of the included studies

Study	Intervention	Sample Size	Duration (in weeks)	Mean age ± SD	Education (# of years) ± SD	EDSS Score ± SD	Primary Outcomes	Other Relevant Outcomes
Krupp *et al*, 2004[25]	Donepezil	35	24 weeks	42.49 ± 9.27	14.40 ± 2.37	4.25 ± 1.62	SRT	AE, PASAT
	Placebo	34		45.85 ± 7.65	14.82 ± 2.32	3.14 ± 1.78		
Krupp *et al*, 2011[26]	Donepezil	61	24 weeks	46.2 ± 7.5	14.0 ± 2.2	3.96 ± 1.78	SRT	AE, PASAT
	Placebo	59		47.3 ± 8.9	13.2 ± 2.0	3.74 ± 1.98		
Shahpouri *et al*, 2020[27]	Donepezil	50	12 weeks	31.9 ± 5.89	NR	2.71	EMQ, AMT, PRMQ, and "digit span test"	AE, MSQOL, BDI
	Placebo	50		30.65 ± 5.43	NR	2.58		
Shaygannejad *et al*, 2008[25]	Rivastigmine	30	12 weeks	33.4 ± 9.6	NR	4.0 ± 1.2	WMT	
	Placebo	30		31.6 ± 7.6	NR	3.0 ± 1.1		
Maurer *et al*, 2012[26]	Rivastigmine	43	16 weeks	44.6 ± 9.4	NR	NR	SRT	MADRS, PASAT, AE
	Placebo	38		44.0 ±7.3	NR	NR		

AE (Adverse Events), NR (Not reported), Selective Reminding Test(SRT), Multiple Sclerosis Neuropsychological Questionnaire (MSNQ), Everyday Memory Questionnaire (EMQ), Abbreviated Memory Test (AMT), Prospective and Retrospective Memory Questionnaire (PRMQ), Multiple Sclerosis Quality of Life Scale (MSQOL), Beck's Depression Inventory (BDI,) Montgomery-Asberg Depression Rating Scale (MADRS)

unavailability of the results of the Abbreviated Mental Test (AMT) in the published article.

Effect of acetylcholinesterase inhibitors on cognitive impairment in multiple sclerosis patients

Two studies were used to determine the effect of donepezil on the cognitive function of MS patients when compared to placebo using the SRT score. There was no significant difference in terms of the mean difference of SRT score between patients given donepezil and placebo [MD (95% CI)= 1.68(-2.21,5.58), p= 0.40, I^2=67%] see Figure 3. Three trials were also merged to determine the effect of acetylcholinesterase inhibitors (rivastigmine and donepezil) using the PASAT score. There was also no significant difference in the mean difference of PASAT score between the AChEIs and placebo groups [MD (95%CI)= 1.91(-0.35,4.17), p= 0.10, I^2=0% see Figure 4]. One study[29] utilized different outcome measures: the Everyday Memory Questionnaire (EMQ), Prospective and Retrospective Memory Questionnaire (PRMQ), and the Digit Span Test (DST). There was significant difference between pre- and post-intervention mean scores in the donepezil group (p<0.001) on all outcome measures. Another trial[25] used the Weschler Memory Scale (WMS) as an outcome measure, the average general memory score for this test did not change significantly between the rivastigmine and placebo group (mean difference, 0.4; 95% CI, -2.0, 2.8,). AChEIs did not show significant improvement in objective cognitive measures of cognition(e.g. PASAT, SRT and WMS). However, using self-report scales such as EMQ and PRMQ, patients noted significant improvement in their memory performance in daily life.

Effect on quality of life

Only the trial of Shahpouri[29] showed the effect of donepezil on the quality of life of MS patients. The physical and mental health scores of the Multiple Sclerosis Quality of Life questionnaires (MSQOL) significantly improved after giving donepezil (p<0.001). Analysis of Co-Variance showed the independent role of Donepezil on this improvement (p<0.001).

Safety of acetylcholinesterase inhibitors in patients with MS

In the five trials, the rate of adverse events among patients receiving any acetylcholinesterase inhibitors ranged from 0 to 34.4%. Some common

Table 2: Population characteristics in the included studies (N=433)

Characteristics	Acetylcholinesterase inhibitors (%)	Placebo (%)
Sample (n=433)	221 (51)	212 (49)
Age, years (mean)	39.72	39.88
Sex		
Female	140 (63)	147 (69)
Male	81 (37)	65 (31)
MS Subtype (n=433)		
RR	115	103
PP	15	10
SP	46	60
Not Reported	84*	

**Shahpouri et al.[27] did not include 3 subjects in the final analysis while Maurer et al[26] did not provide specific types of MS per intervention*

adverse effects included abnormal/unusual dreams, headache, gastrointestinal, and fatigue. The study of Krupp *et al*.[27] showed no significant difference among the rates of the common adverse events. In another trial[28], it was reported that diarrhea was more common among patients receiving donepezil when compared to placebo ($p<0.05$). Pooled data from four trials showed a significantly higher number of patients receiving AChEIs experienced or reported gastrointestinal adverse events compared to patients who received placebo [MD (95% CI) = 1.60(1.21,2.12),

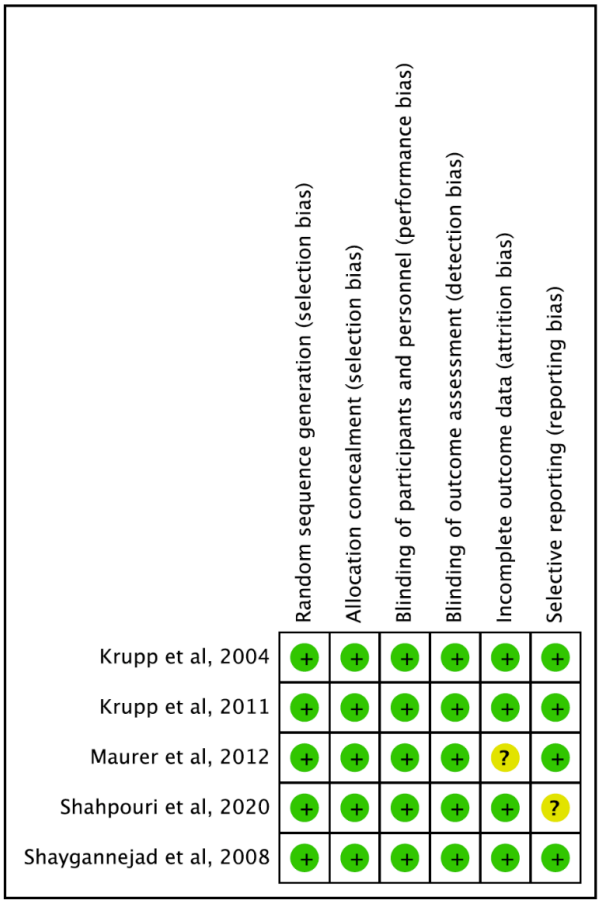

Figure 2. Risk of bias summary of the studies[25–29] included in the analysis.

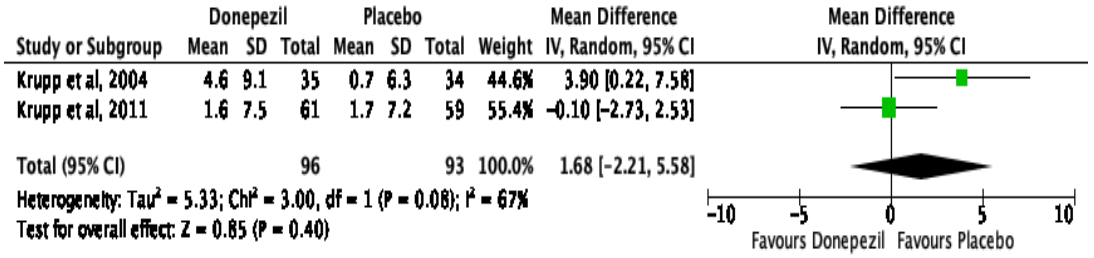

Figure 3. Forest plot of mean difference in Total SRT scores for studies[27,28] comparing Donepezil and placebo.

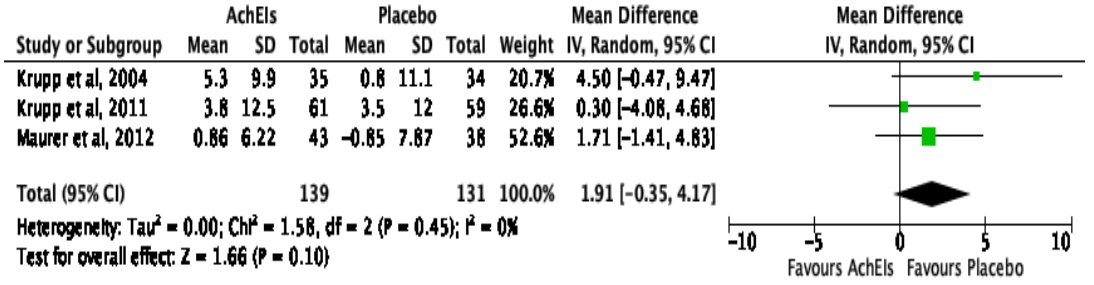

Figure 4. Forest plot of mean difference in PASAT scores for studies[26–28] comparing AchEIs and placebo.

p= 0.001, I^2=30%] as shown in Figure 5. There were no serious adverse events reported by patients receiving AChEIs in all trials. These adverse effects could be secondary to overstimulation of peripheral cholinergic activity or muscarinic receptor activation.[36,37] These effects however did not result in the discontinuation or premature termination of the trials. These adverse reactions were lessened by the proper administration and titration of the drug.

DISCUSSION

This review provided evidence derived from five randomized controlled trials on the efficacy of AChEIs in MS patients with CI. Furthermore, this review showed the value of these drugs in patients' quality of life, and their safety profile.

AChEIs were used as treatments for a variety of dementing diseases such as AD, VaD and DLB.[16–19] The use of these drugs in MS is still not currently recommended despite their benefits in other diseases.[13,38,39] Pooled evidence from our study did not show significant cognitive improvement in these patients based on the mean difference in the SRT and PASAT scores. The study by Shahpouri et al showed a significant difference in the outcome measures EMQ and PRMQ. Based on the current review, there are conflicting data that support the use of AChEIs in MS patients with CI. The discrepancy in the results could be due to the different mechanisms that cause CI in MS patients, aside from the role of acetylcholine. Despite evidence of decreased cholinergic activity in MS, increasing acetylcholine through the use of AChEis alone may not be enough to improve cognitive impairment.[12,40,41]

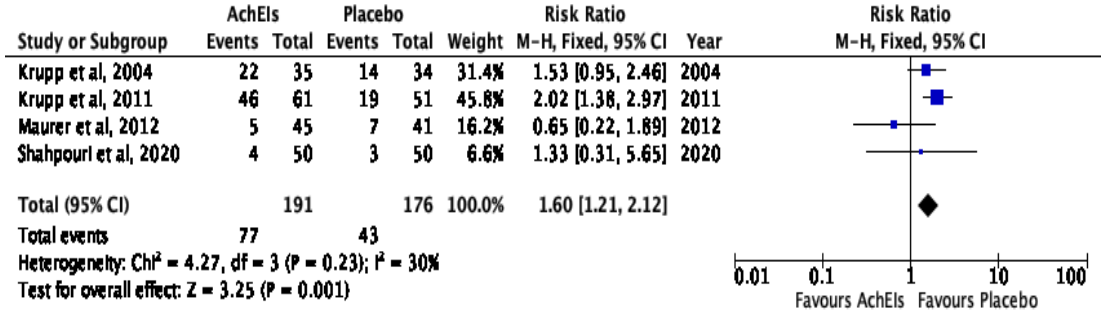

Figure 5. Number of gastrointestinal adverse events in the studies[26–29] that reported.

Other drugs especially the disease-modifying therapy (ocrelizumab, interferon B-1b, and natalizumab)[42–44] demonstrated positive effects on the cognition of MS patients. The included studies did not perform subgroup analysis for these patients.

The severity of CI is different in patients with MS as they may present with mild to moderate impairment in contrast to patients with Alzheimer's dementia who usually present with mild to severe impairment.[6] The outcome measures (PASAT and SRT scores) used in the trials may not be sensitive to detect subtle changes in cognition among patients with MS. The PASAT score has a sensitivity of 74% in detecting CI in MS patients[45], whereas. The Montreal Cognitive Assessment (MoCA) Scale is adapted for detecting mild cognitive impairment. Some studies showed the value of MoCA in detecting subtle changes in cognition among patients with MS.[46,47] Another test, The Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS), was first introduced in 2010 by a group of experts to facilitate the assessment of cognition in MS patients.[48] It mainly measures information processing speed, verbal memory, and visual memory.[49,50] Future research may utilize these tools as they are widely available and are designed for patients with MS.

Another possible explanation for the conflicting effects of AchEIs was the duration of treatment. Several studies showed that the effects of AchEIs for different diseases were evident as early as 12 weeks of treatment.[16–18] This may not apply to MS patients since the decline in cognitive function was dependent on the number or location of the plaques, and the frequency of relapses or attacks. The 12 to 24 weeks period may not be enough to determine the effect of AchEIs on these patients.

Only one study[29] determined the effect of cholinesterase inhibitors on the QOL of MS patients with CI. Physical and Mental scores were significantly improved in those receiving donepezil compared to placebo. This effect was also seen in Alzheimer's disease patients.[51]

Strengths and Limitations of the Study

For this study, we included only double-blind, randomized, placebo-controlled trials. These are considered the most thorough among the different study designs used for medical research, limiting the impact of potential confounders on the treatment outcomes.

The study combined drugs that have similar mechanisms of action. However, it is important to note that despite belonging to the same class of drugs, drugs have variations in their pharmacodynamic and pharmacokinetic properties, which may affect their effectiveness. Future studies may analyze specific drugs once more data becomes available.

The authors suggest that future studies focus on the possible effect of AChEIs considering the MS subtypes and the different disease-modifying therapy used. A longer duration of administration among these studies is warranted. Trials should also increase the number of samples included. Lastly, the authors suggest that succeeding trials use a more sensitive outcome measure that may detect early changes in cognition among MS patients such as the BICAMS.

In conclusion, based on the pooled data from this study, the use of AChEIs (donepezil 10 mg/day or rivastigmine 10 mg/day for 12 to 14 weeks) among MS patients provided no significant benefit in improving objective measures of cognition but has positive impact on subjective scales of cognition (EMQ and PRMQ). AChEIs were shown to improve patients' quality of life. Despite the presence of non-serious adverse effects, the use of AChEIs was safe and well tolerated among MS patients.

DISCLOSURE

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Conflict of interest: None

REFERENCES

1. Walton C, King R, Rechtman L, *et al*. Rising prevalence of multiple sclerosis worldwide: Insights from the Atlas of MS, third edition. *Mult Scler J* 2020;26(14):1816-21. doi:10.1177/1352458520970841
2. Lovera J, Kovner B. Cognitive impairment in multiple sclerosis. *Curr Neurol Neurosci Rep* 2012;12(5):618-27. doi:10.1007/s11910-012-0294-3
3. Guimarães J, Sá MJ. Cognitive dysfunction in multiple sclerosis. *Front Neurol* 2012; 3:74. doi:10.3389/fneur.2012.00074
4. Amato MP, Ponziani G, Siracusa G, Sorbi S. Cognitive dysfunction in early-onset multiple sclerosis A reappraisal after 10 years. *Arch Neurol* 2001; 58(10):1602-6. doi: 10.1001/archneur.58.10.1602.
5. Chiaravalloti ND, DeLuca J. Cognitive impairment in multiple sclerosis. *Lancet Neurol* 2008;7(12):1139-51. doi:10.1016/S1474-4422(08)70259-X
6. Langdon DW. Cognition in multiple sclerosis. *Curr Opin Neurol* 2011;24(3):244-9. doi:10.1097/WCO.0b013e328346a43b
7. DeLuca GC, Yates RL, Beale H, Morrow SA. Cognitive impairment in multiple sclerosis: Clinical, radiologic and pathologic insights. *Brain Patho* 2015;25(1):79-98. doi:10.1111/bpa.12220

8. Rocca MA, Amato MP, de Stefano N, *et al*. Clinical and imaging assessment of cognitive dysfunction in multiple sclerosis. *Lancet Neurol* 2015;14(3):302-17. doi:10.1016/S1474-4422(14)70250-9
9. Grzegorski T, Losy J. Cognitive impairment in multiple sclerosis - A review of current knowledge and recent research. *Rev Neurosci* 2017;28(8):845-60. doi:10.1515/revneuro-2017-0011
10. Brochet B, Ruet A. Cognitive impairment in multiple sclerosis with regards to disease duration and clinical phenotypes. *Front Neurol* 2019;10:261. doi:10.3389/fneur.2019.00261
11. Bagert B, Camplair P, Bourdette D. Cognitive dysfunction in multiple sclerosis. *CNS Drugs* 2002;16(7):445-55. doi:10.2165/00023210-200216070-00002
12. Comi G, Martinelli, Martinelli V. Pathophysiology of cognitive impairment in multiple sclerosis. *Italian J Neurol Sci* 1998;199:S443-S447.
13. Calabrese P, Penner IK. Cognitive dysfunctions in multiple sclerosis - A "multiple disconnection syndrome"? *J Neurol* 2007;254(2 Suppl):1118-21. doi:10.1007/s00415-007-2006-5
14. Gatta V, Mengod G, Reale M, Tata AM. Possible correlation between cholinergic system alterations and neuro/inflammation in multiple sclerosis. *Biomedicines* 2020;8(6):153. doi:10.3390/BIOMEDICINES8060153
15. Kooi EJ, Prins M, Bajic N, *et al*. Cholinergic imbalance in the multiple sclerosis hippocampus. *Acta Neuropathol* 2011;122(3):313-22. doi:10.1007/s00401-011-0849-4
16. Birks J. Cholinesterase inhibitors for Alzheimer's disease. *Cochrane Database Syst Rev* 2006;(1):CD005593. doi:10.1002/14651858.CD005593
17. Birks J, Mcguinness B, Craig D. Rivastigmine for vascular cognitive impairment. *Cochrane Database Syst Rev* 2013; 2013(5):CD004744. doi:10.1002/14651858.CD004744.pub3
18. Malouf R, Birks J. Donepezil for vascular cognitive impairment. *Cochrane Database of Syst Rev* 2004;2010(1):CD004395. doi:10.1002/14651858.CD004395.pub2
19. Stinton C, McKeith I, Taylor JP, *et al*. Pharmacological management of lewy body dementia: A systematic review and meta-analysis. *Am J Psychiatry* 2015;172(8):731-42. doi:10.1176/appi.ajp.2015.14121582
20. Page MJ, McKenzie JE, Bossuyt PM, *et al*. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ* 2021;372. doi:10.1136/bmj.n71
21. McDonald WI, Compston A, Edan G, *et al*. Recommended diagnostic criteria for multiple sclerosis: Guidelines from the International Panel on the Diagnosis of Multiple Sclerosis. *Ann Neurol* 2001;50(1):121-7. doi:10.1002/ana.1032
22. Carroll WM. 2017 McDonald MS diagnostic criteria: Evidence-based revisions. *Mult Scler* 2018;24(2):92-5. doi:10.1177/1352458517751861
23. Thompson AJ, Banwell BL, Barkhof F, *et al*. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol* 2018;17(2):162-73. doi:10.1016/S1474-4422(17)30470-2
24. Higgins JPT, Altman DG, Gøtzsche PC, *et al*. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d4928. doi:10.1136/bmj.d5928
25. Shaygannejad V, Janghorbani M, Ashtari F, Zanjani HA, Zakizade N. Effects of rivastigmine on memory and cognition in multiple sclerosis. *Can J Neurol Sci* 2008;35(4):476-81. doi:10.1017/S0317167100009148
26. Mäurer M, Ortler S, Baier M, *et al*. Randomised multicentre trial on safety and efficacy of rivastigmine in cognitively impaired multiple sclerosis patients. *Mult Scler J* 2013;19(5):631-8. doi:10.1177/1352458512463481
27. Krupp LB, Christodoulou C, Melville P, Scherl WF, MacAllister WS, Elkins LE. Donepezil improved memory in multiple sclerosis in a randomized clinical trial. *Neurology* 2004;63(9):1579-85. doi:10.1212/01.WNL.0000142989.09633.5A
28. Krupp LB, Christodoulou C, Melville P, *et al*. Multicenter randomized clinical trial of donepezil for memory impairment in multiple sclerosis. *Neurology* 2011;76(17):1500-7. doi:10.1212/WNL.0b013e318218107a
29. Shahpouri M, Barekatain M, Tavakoli M, Badihian S, Shaygannejad V. Effect of donepezil on cognitive impairment, quality of life, and depression in multiple sclerosis patients: A randomized clinical trial. *Int J Prev Med* 2020;11(1):69. doi:10.4103/ijpvm.IJPVM_154_19
30. Rao SM, Leo GJ, Bernardin L, Unverzagt F. Cognitive dysfunction in multiple sclerosis.: I. Frequency, patterns, and prediction. *Neurology* 1991;41(5):685-91. doi:10.1212/WNL.41.5.685
31. Buschke H. Selective reminding for analysis of memory and learning 1. Vol 12. Tulving & Colotla; 1973.
32. Boringa JB, Lazeron RH, Reuling IE, *et al*. The brief repeatable battery of neuropsychological tests: normative values allow application in multiple sclerosis clinical practice. *Mult Scler J* 2001;7(4):263-67. doi:10.1177/135245850100700409
33. Vickrey BG, Hays RD, Harooni R, Myers LW, Ellison GW. A health-related quality of life measure for multiple sclerosis. *Qual Life Res* 1995;4(3):187-206. doi: 10.1007/BF02260859.
34. Royle J, Lincoln NB. The Everyday Memory Questionnaire - revised: Development of a 13-item scale. *Disabil Rehabil* 2008;30(2):114-21. doi:10.1080/09638280701223876
35. Smith G, Della Sala S, Logie RH, Maylor EA. Prospective and retrospective memory in normal ageing and dementia: A questionnaire study. *Memory* 2000;8(5):311-21. doi:10.1080/09658210050117735
36. Pariente A, Sanctussy DJR, Miremont-Salamé G, Moore N, Haramburu F, Fourrier-Réglat A. Factors associated with serious adverse reactions to cholinesterase inhibitors. *CNS Drugs* 2010;24(1):55-63. doi:10.2165/11530300-000000000-00000
37. Ali TB, Schleret TR, Reilly BM, Chen WY, Abagyan R. Adverse effects of cholinesterase inhibitors

in dementia, according to the pharmacovigilance databases of the United-States and Canada. *PLoS One* 2015;10(12):e0144337. doi:10.1371/journal.pone.0144337
38. Huolman S, Hämäläinen P, Vorobyev V, *et al*. The effects of rivastigmine on processing speed and brain activation in patients with multiple sclerosis and subjective cognitive fatigue. *Mult Scler J* 2011;17(11):1351-61. doi:10.1177/1352458511412061
39. Sumowski JF, Benedict R, Enzinger C, *et al*. Cognition in multiple sclerosis: State of the field and priorities for the future. *Neurology* 2018;90(6):278-88. doi:10.1212/WNL.0000000000004977
40. Halder N, Lal G. Cholinergic system and its therapeutic importance in inflammation and autoimmunity. *Front Immunol* 2021; 12:660342. doi:10.3389/fimmu.2021.660342
41. Reale M, de Angelis F, di Nicola M, *et al*. Relation between pro-inflammatory cytokines and acetylcholine levels in relapsing-remitting multiple sclerosis patients. *Int J Mol Sci* 2012;13(10):12656-64. doi:10.3390/ijms131012656
42. O'Connor P, Goodman A, Kappos L, *et al*. Long-term safety and effectiveness of natalizumab redosing and treatment in the STRATA MS Study. *Neurology* 2014;83(1):78-86. doi:10.1212/WNL.0000000000000541
43. Kappos L, Freedman MS, Polman CH, *et al*. Long-term effect of early treatment with interferon beta-1b after a first clinical event suggestive of multiple sclerosis: 5-year active treatment extension of the phase 3 BENEFIT trial. *Lancet Neurol* 2009;8(11):987-97. doi: 10.1016/S1474-4422(09)70237-6.
44. Hauser SL, Bar-Or A, Comi G, *et al*. Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis. *N Engl J Med* 2017;376(3):221-34. doi:10.1056/nejmoa1601277
45. Rosti E, Hämäläinen P, Koivisto K, Hokkanen L. The PASAT performance among patients with multiple sclerosis: analyses of responding patterns using different scoring methods. *Mult Scler J* 2006;12(5):586-93. doi:10.1177/1352458506070624
46. Al-Falaki TA, Hamdan FB, Sheaheed NM. Assessment of cognitive functions in patients with multiple sclerosis. *Egyptian J Neurol Psychiatr Neurosurg* 2021;57(1):127. doi:10.1186/s41983-021-00383-4
47. Charest K, Tremblay A, Langlois R, Roger É, Duquette P, Rouleau I. Detecting subtle cognitive impairment in multiple sclerosis with the Montreal Cognitive Assessment. *Can J Neurol Sci* 2020;47(5):620-6. doi:10.1017/cjn.2020.97
48. Langdon DW, Amato MP, Boringa J, *et al*. Recommendations for a brief international cognitive assessment for multiple sclerosis (BICAMS). *Mult Scler J* 2012;18(6):891-8. doi:10.1177/1352458511431076
49. Corfield F, Langdon D. A systematic review and meta-analysis of the Brief Cognitive Assessment for Multiple Sclerosis (BICAMS). *Neurol Ther* 2018;7(2):287-306. doi:10.6084/m9.figshare.6490256
50. Benedict RHB, Amato MP, Boringa J, *et al*. Brief International Cognitive Assessment for MS (BICAMS): international standards for validation. *BMC Neurol* 2012;12:55. doi:10.1186/1471-2377-12-55
51. Li Q, He S, Chen Y, Feng F, Qu W, Sun H. Donepezil-based multi-functional cholinesterase inhibitors for treatment of Alzheimer's disease. *Eur J Med Chem* 2018;158:463-77. doi:10.1016/j.ejmech.2018.09.031