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Is memantine a safe and effective treatment for Alzheimer's disease in patients over the age of 50?

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ABSTRACT

OBJECTIVE

The objective of this selective EBM review is to determine whether or not memantine is a safe and effective treatment for Alzheimer's disease in patients over the age of 50.

STUDY DESIGN

Systematic review of two randomized controlled trials published in 2006 and 2013 and one randomized controlled trial pooled analysis published in 2014.

DATA SOURCES

Two randomized controlled trials and one pooled analysis were obtained using PubMed.

OUTCOMES MEASURED

Efficacy of memantine as compared to control groups based on cognition, behavior, and adverse events. These were measured using Severe Impairment Battery (SIB), Neuropsychiatric Inventory (NPI), and Behavioral Pathology in AD Rating Scale (BEHAVE-AD).

RESULTS

Herrmann et al. (2013) and Peskind et al. (2006) failed to show superiority of memantine over a placebo. Nakamura et al. (2014) showed that memantine produced statistically better outcomes compared to the placebo in terms of behavior and cognitive function. In all three studies, the overall incidence of adverse events was similar between the memantine and placebo groups.

CONCLUSION

The trials analyzed in this selective EBM review showed conflicting evidence regarding the efficacy of memantine in the treatment of Alzheimer's disease. Further investigation is warranted to definitively evaluate the efficacy of memantine at improving cognition and behavior.

KEY WORDS
Memantine and Alzheimer's disease

INTRODUCTION

Alzheimer's disease is a progressive and degenerative neurological disorder characterized by a decline in cognition, function, behavior, and ability to perform activities of daily living.[1] It affects an estimated 5.5 million Americans, and approximately one in 10 people over the age of 65 has Alzheimer's disease.[2] In 2017, Alzheimer's cost the nation $259 billion.[2] An exact number of healthcare visits each year has not been identified; however, a person with dementia in 2012 had an annual average of 22.5 inpatient days.[2] The exact etiology of Alzheimer's disease is unknown, but the structural manifestations of the disease have been identified. These include extracellular amyloid plaques, intraneuronal neurofibrillary tangles, synaptic loss, neuronal death, and changes in the glutamatergic and cholinergic pathways.[1] The exact role of plaques and tangles is unknown, but most experts believe they play a critical role in blocking communication among nerve cells and disrupting cell survival processes.[3]

These structural manifestations contribute to the cardinal symptoms of Alzheimer's disease including memory impairment, executive function impairment, and neuropsychiatric symptoms.[4] The standard medical treatment for Alzheimer's includes cholinesterase inhibitors and partial N -methyl-D-aspartate antagonists.[5] Symptomatic therapies are available but they do not act on the evolution of the disease. Secondary symptoms such as depression, agitation, aggression, hallucinations, delusions, sleep disorders are treated with the following: antidepressants, anxiolytics, antiparkinsonian agents, beta-blockers, antiepileptic drugs, and neuroleptics.[5] Currently, there is no cure for Alzheimer's disease; however, the medications listed above have seemed to improve symptoms in patients.[5]

OBJECTIVE

The objective of this selective EBM review is to determine whether or not memantine is a safe and effective treatment for Alzheimer's disease in patients over the age of 50.

METHODS

This systematic review consists of two double-blind, randomized, controlled trials and one pooled analysis of two randomized, double-blind, placebo-controlled trials comparing the safety and efficacy of memantine as a treatment of Alzheimer's disease. The study population of the trials and pooled analysis consists of men and women over the age of 50 with Alzheimer's disease. The populations excluded from these studies are patients under the age of 50, those with an unstable medical condition, those with other psychiatric or neurological disorders, and those with a Hachinski Ischemia score > 4. Keywords used in the research for these studies include memantine and Alzheimer's disease. All articles used in this research are peer-reviewed journals published in English and were found via PubMed. Articles were selected based on their relevance to my clinical question and if they included patient oriented outcomes. They must have been published in 2006 or later. Exclusion criteria included articles published prior to the year 2006, articles that were not primary research in nature, or if they focused on disease oriented outcomes. Statistics used in the articles include RRI, ARI, NNH, mean change from baseline, p-value, and 95% CI. Table 1 below displays the demographics and characteristics of the studies that were reviewed.

Table 1: Demographics & characteristics of included studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Intervention
Herrmann[6] (2013)	RCT	369	≥ 50	-MMSE 8-18, ongoing ChEI therapy, knowledgeable and reliable caregiver, residence in the community, stable medical condition, NPI total ≥13 and NPI agitation/ aggression score ≥1	-unstable medical condition, other psychiatric or neurological disorder, vascular dementia, modified Hachinski Ischemia score > 4	63	Memantine 20 mg
Peskind[1] (2006)	RCT	403	≥ 50	-MMSE 10-22, CT or MRI consistent w/ Alzheimer's, knowledgeable and reliable caregiver, MADRS score <22, ambulatory, medically stable	-unstable medical condition, other psychiatric or neurological disorder, Hachinski Ischemia score > 4, delusions or delirium, cancer, substance abuse	71	Memantine 20 mg
Nakamura[7] (2014)	RCT pooled analysis	640	≥ 50	-MMSE 5-14, CT or MRI consistent w/ Alzheimer's, moderate to severe Alzheimer's, consistent caregiver	-serious neurological psychiatric disorder, history of treatment with memantine, planning to move to nursing home	7	Memantine 20 mg

OUTCOMES MEASURED

Cognition was measured using the Severe Impairment Battery (SIB), which is a validated scale used to assess cognitive function in patients with moderate-to-severe dementia.[6] Behavior was measured using the Neuropsychiatric Inventory (NPI) and the Behavioral Pathology in AD Rating Scale (BEHAVE-AD). The NPI is a 12-item scale that assesses frequency and severity of behavioral symptoms in patients with dementia.[1] The BEHAVE-AD evaluates behavioral and psychological symptoms of dementia using the following seven subdomains: paranoid and delusional ideation, hallucinations, activity disturbances, aggressiveness, diurnal rhythm disturbances, affective disturbance, and anxieties and phobias.[7]

Adverse events measured in the studies include the following: nausea, vomiting, diarrhea, decreased weight, fall, dizziness, depression, contusion, inflicted injury, insomnia, upper respiratory infections, agitation, and somnolence.[1,6,7] In the Herrmann study, the NPI was assessed at screening, baseline, week 4, week 8, week 12, week 18, and week 24. The SIB was assessed at baseline, week 12, and week 24. In the Peskind study, the NPI was assessed at baseline, week 12, week 24, and at the endpoint using a last observation carried over approach (LOCF). In the Nakamura study, both the SIB-J (Japanese equivalent of SIB) and BEHAVE-AD were assessed at baseline, week 4, week 12, week 24, and at the endpoint using a LOCF approach. In all of the studies, adverse events were recorded at baseline and each subsequent visit. This selective EBM review will focus on the results at week 24 and total adverse events for each study.

RESULTS

In both randomized controlled trials and the pooled analysis, the efficacy and safety of memantine is compared to a placebo. In the Herrmann study, a total of 369 patients entered the study and 306 patients completed the study. The exclusion parameters for this study included patients with an unstable medical condition, other psychiatric or neurological disorder, vascular dementia, or a modified Hachinski Ischemia score > 4. The patients were all males and females ≥ 50 years of age with Alzheimer's severity at baseline ranging from moderate to severe. The mean age of patients was 75 years. Of the 369 patients who entered the study, 187 were randomized to placebo and 182 were randomized to memantine in accordance with a randomization list generated by the sponsor following a standard routine. Patients receiving memantine were titrated in 5 mg weekly increments from a starting dose of 5 mg/day to 20 mg day administered once daily at the beginning of week 4. Active drug and placebo tablets were visually identical and all patients received four tablets of study medication daily. The mean change from baseline for NPI was -3.90±1.24 for the memantine group and 5.13±1.23 for the placebo group. The mean change from baseline for SIB was -2.34±0.76 for the memantine group and -1.86±0.75 for the placebo group. The mean change from baseline, CI, and p-values are reported in Tables 2-3.

Table 2. Statistical results of the Severe Impairment Battery (SIB) to assess cognitive function[6,7]

Study	95% CI	P-value	Mean change from baseline at week 24: memantine	Mean change from baseline at week 24: placebo
Herrmann	-2.3 to 1.34	0.60	-2.34±0.76	-1.86±0.75
Nakamura	Not reported	<0.0001	-0.25	-4.38

Table 3. Statistical results of the Neuropsychiatric Inventory (NPI) and the Behavioral Pathology in AD Rating Scale to assess behavior[1,6,7]

Study	95% CI	P-value	Mean change from baseline at week 24	Mean change from baseline at week 24: placebo
Herrmann	-1.75 to 4.21	0.42	-3.90±1.24	-5.13±1.23
Peskind	-4.9 to 0.7	0.14	-1.2	0.9
Nakamura	Not reported	0.0040	-0.52	0.52

The values for mean change from baseline in the Herrmann study are small given the nature of this study, so there is not a big difference in the patient's behavior, cognition, and function after taking memantine. The p-value is 0.42 for the NPI and 0.60 for the SIB. Since these values are greater than 0.05, the results were not statistically significant. The 95% CI is -2.3 to 1.34 for SIB and -1.75 to 4.21 for NPI. Adverse events reported during the study are included below in Table 4.

Table 4. Adverse events in the Herrmann study with an incidence ≥5% in either treatment group (all-patients-treated set)[6]

Adverse event	Memantine (N=182) N (%)	Placebo (N=187) N (%)
Fall	20 (11.0)	8 (4.3)
Agitation	15 (8.2)	7 (3.7)
Weight decreased	11 (6.0)	5 (2.7)
Somnolence	10 (5.5)	5 (2.7)
Nausea	4 (2.2)	11 (5.9)
Total adverse events	138 (75.8)	136 (72.7)

The incidence of adverse events considered related to the study drug was 30% in the placebo group and 36% in the memantine group, so the number of adverse events were similar between the two groups. The calculations for harm include relative risk increase (RRI), absolute risk increase (ARI), and numbers needed to harm (NNH). These calculations are reported in Table 5.

Table 5. Comparison and statistical significance of outcomes measured of included studies[1,6,7]

Study	RRI	ARI	NNH
Herrmann	66.7%	4%	25 patients
Peskind	90%	4.5%	23 patients
Nakamura	2.2%	1.7%	59 patients

In the Herrmann study, memantine increases a patient's risk of having an adverse event by 66.7%, and for every 25 patients, 1 additional patient would also experience an adverse event.

In the Peskind study, 403 patients were recruited from 42 U.S. sites, 332 patients completed the study, and 394 patients were included in the primary analysis. The exclusion parameters for this study included unstable medical condition, other psychiatric or neurological disorder, Hachinski Ischemia score > 4, delusions or delirium, cancer, or substance abuse. The patients were all males and females ≥ 50 years of age with Alzheimer's severity at baseline ranging from mild to moderate. The mean age was 77 for the placebo group and 78 for the memantine group. Patients were randomized to memantine or placebo groups in permuted blocks of four in accordance with the randomization list generated and retained by Forest Research Institute Department of Statistical Programming. All participants assigned to the memantine group received an initial dose of 5 mg per day; the dose was titrated in 5-mg weekly increments to a final dose of 20 mg/day (administered as two 5-mg tablets twice a day) on day 22. The placebo and memantine tablets were visually identical, and all participants received four tablets of study medication daily. The mean change from baseline, CI, and p-values are reported above in Tables 2-3. The mean change from baseline using the last observation carried forward (LOCF) approach at week 24 for NPI is -1.2 for memantine and 0.9 for the placebo.

Although the analysis favored memantine over the placebo, the results were not statistically significant. The p-value is 0.14 for the NPI, which indicates the estimate of treatment effect is not precise. The 95% CI is -4.9 to 0.7 for NPI. The adverse events reported during the trial are listed below in Table 6.

Table 6. Adverse events in the Peskind study with an incidence of ≥5.0% in either treatment group[1]

Adverse event	Placebo (N=202) N (%)	Memantine (N=201)	P Value
Fall	15 (7.4)	15 (7.5)	1.00
Agitation	12 (5.9)	15 (7.5)	0.56
Influenza-like symptoms	13 (6.4%)	14 (7.0)	0.85
Somnolence	2 (1.0)	14 (7.0)	0.002
Headache	9 (4.5)	13 (6.5)	0.39
Inflicted injury	11 (5.4)	12 (6.0)	0.83
Confusion	7 (3.5)	10 (5.0)	0.47
Dizziness	9 (4.5)	10 (5.0)	0.82
Hypertension	11 (5.4)	9 (4.5)	0.82
Depression	10 (5.0)	4 (2.0)	0.17
Upper respiratory infection	12 (5.9)	4 (2.0)	0.07

Adverse events occurred in 74% of the placebo group and 71% of the memantine group, so the number of adverse events were similar between the two groups. The calculations for harm are reported above in Table 5. In the Peskind study, memantine increases a patient's risk of having an adverse event by 90% and for every 23 patients, 1 additional patient would also experience an adverse event.

In the Nakamura pooled analysis, 640 patients were analyzed from various Japanese institutions. Of those 640 patients, 321 were treated with memantine and 319 were treated with the placebo. The final analysis comprised 633 patients with 318 receiving memantine and 315

receiving placebo. Seven patients were excluded from the pooled analysis due to a lack of post-baseline efficacy measurements. The exclusion parameters for this study included serious neurological psychiatric disorder, history of treatment with memantine, or planning to move to a nursing home. The patients were all males and females ≥ 50 years of age with Alzheimer's severity at baseline ranging from moderate to severe. The mean age was 74.5 for the placebo group and 74 for the memantine group. Patients were randomized to memantine or placebo groups. All participants assigned to the memantine group received an initial dose of 5 mg per day; the dose was titrated in 5-mg weekly increments to a final dose of 20 mg/day. The placebo and memantine tablets were visually identical. The mean change from baseline, CI, and p-values are reported above in Tables 2-3. The mean change from baseline using the last observation carried forward (LOCF) approach for BEHAVE-AD was -0.52 for the memantine group and 0.52 for the placebo group. The mean change from baseline for SIB was -0.25 for the memantine group and -4.38 for the placebo group. Memantine produced statistically better outcomes compared to the placebo in both behavior and cognitive function. The p-value is <0.0001 for the SIB and 0.0067 for the BEHAVE-AD, so the estimate of treatment effect is precise. The adverse events reported during the trials are listed below in Table 7.

Table 7. Adverse events in the Nakamura study with an incidence of ≥ 5% in either treatment group[7]

Adverse events	Memantine (N=321) N (%)	Placebo (N=319) N (%)
Constipation	37 (11.5)	33 (10.3)
Diarrhea	14 (4.4)	18 (5.6)
Vomiting	10 (3.1)	12 (5.3)
Nasopharyngitis	46 (14.3)	54 (16.9)
Fall	31 (9.7)	33 (10.3)
Contusion	18 (5.6)	20 (6.3)
Insomnia	18 (5.6)	16 (5.0)
Total adverse events	252 (78.5)	245 (76.8)

Adverse events occurred in 78.5% of the memantine group and 76.8% of the placebo group, so the number of adverse events were similar between the two groups. The calculations for harm are reported above in Table 5. In the Nakamura study memantine increases a patient's risk of having an adverse event by 2.2% and for every 59 patients, 1 additional patient would also experience an adverse event.

DISCUSSION

This systematic review assessed the efficacy and safety of memantine compared to a placebo as a treatment for Alzheimer's disease in terms of cognition, behavior, and adverse events. The two randomized controlled trials failed to show superiority of memantine over a placebo; however, the pooled analysis showed that memantine produced statistically better outcomes compared to the placebo in terms of behavior and cognitive function. In all three studies, the overall incidence of adverse events was similar between the memantine and placebo groups.

There were several limitations noted with each study. In the Herrmann study, there was under-recruitment which resulted in a decreased statistical power to show the superiority of memantine over placebo.[6] This study was amended a total of seven times with implications on the patient population selected.[6] There were higher agitation scores in the memantine group and lower exposure to antipsychotics and antidepressants in the placebo group, so several baseline differences existed.[6] Patients were already severely behaviorally impaired, so worsening was less likely. This reduced the opportunity to demonstrate a drug–placebo benefit.[6] In the Peskind study, patients in the placebo group who worsened left the trial before they could be measured at

the end point which influenced the results.[1] In the Nakamura study, a potential limitation relates to the information obtained from the caregivers on the status of the patient.[7] For those patients in the study who used long-term care services, information from only one caregiver might have been insufficient to reflect actual changes in clinical symptoms.[7]

Memantine is used in over 80 countries worldwide and has been used to treat patients with Alzheimer's for over 10 years.[7] It is approved by the U.S. Food and Drug Administration and the EMEA for the treatment of moderate to severe Alzheimer's.[1] Memantine is widely available in the United States, so insurance and access to the study drug were non-issues and did not affect the results of the studies.

CONCLUSION

The trials analyzed in this selective EBM review showed conflicting evidence regarding the efficacy of memantine in the treatment of Alzheimer's disease. The Nakamura study demonstrated the most convincing data that memantine improves cognition and behavior and was also the largest study analyzing this topic. The Peskind study favored memantine over the placebo, but the results were not statistically significant. The Herrmann study failed to show superiority of memantine over the placebo. In all three studies, the incidence of adverse events was similar between memantine and the placebo. Future investigation is warranted to definitively evaluate the efficacy of memantine at improving cognition and behavior. It would be beneficial to have a larger study group with more similar baselines among participants.

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