Received: 21 December 2024 | Revised: 10 February 2025 | Accepted: 18 February 2025

DOI: 10.1002/trc2.70071

Alzheimer's & Dementia
Translational Research & Clinical Interventions

RESEARCH ARTICLE

Effect of long-term treatment with memantine on mortality in patients with major cognitive disorders: A systematic review and meta-analysis

Victoria Zolnowski-Kolp[1] | **Bruno Oquendo**[1] | **Charlotte Havreng-Théry**[2,3] | **Carmelo Lafuente-Lafuente**[1,4] | **Joël Belmin**[1,2]

[1]Service de Gériatrie, Hôpital Charles Foix, Assistance Publique-Hôpitaux de Paris, Ivry-sur-Seine, France

[2]Laboratoire LIMICS, Sorbonne Université, Paris, France

[3]Présage Care, PariSanté Campus, Paris, France, Paris, France

[4]Clinical Epidemiology and Aging (CEpiA) team, Univ Paris Est Creteil, INSERM, IMRB, FHU Senec, Creteil, France

Correspondence
Joël Belmin, Service de Gériatrie, Hôpital Charles Foix, 7 avenue de la République, 94200 Ivry-sur-Seine, France.
Email: j.belmin@aphp.fr

Abstract

BACKGROUND: Dementia is responsible for a reduction in life expectancy, and the effect of memantine on mortality is still poorly understood. Our aim was to evaluate the effect of long-term treatment with memantine on all-cause mortality.

METHODS: In this systematic review and meta-analysis, we searched five databases from their creation to June 2024.

RESULTS: We found 12 randomized trials (n = 4266) and 7 observational studies (n = 20,216). Treatment with memantine was associated with a reduction in all-cause mortality (risk ratios [RRs] 0.81, 95% CI: 0.72–0.92, p = 0.001). In the sensitivity analysis, the pooled RR was similar for randomized controlled trials (RCT) (RR 0.86) and non-randomized studies (RR 0.81) but pooled results from RCTs did not reach statistical significance (95% confidence interval [CI]: 0.59–1.26, p = 0.45), while they did for observational studies (95% CI: 0.70–0.95, p = 0.008), so we consider the overall evidence as of low certainty.

CONCLUSION: Our results suggest that the use of memantine in patients with dementia may be associated with a reduction in all-cause mortality.

KEYWORDS
dementia, memantine, meta-analysis, mortality, systematic review

Highlights

- Dementia reduces patients' survival and the effect of long-term use of memantine on all-cause mortality is not well known.
- This systematic review and metanalysis included 19 studies including more than 24000 patients.
- We found that memantine in patients with dementia may be associated with a reduction in all-cause mortality.

1 | INTRODUCTION

Major neurocognitive disorders (MNDs) or dementia are chronic progressive diseases that lead to a decline in cognitive function, dependence, disability, and possibly behavioral disorders. MNDs affect the quality of life of patients and their families and are a frequent cause of admission to long-term care facilities. It also reduces life expectancy and increases all-cause mortality by a factor of 5.9 compared with people without dementia.[1] These diseases are recognized as the 7th leading cause of death in the world, making them a major public health problem of our time.[2] The best known and most widespread of these is Alzheimer's disease, which is the leading cause of dementia (60%–70% of cases).[3] Its worldwide prevalence is set to rise sharply over the coming decades, from around 46 million sufferers in 2015 to an estimated 131 million in 2050.[4]

Memantine is one of the existing anti-dementia treatments, prescribed mainly for moderate to severe forms of Alzheimer's disease. This drug was discovered in 1968 and initially developed as a treatment for diabetes. It was approved for the treatment of Alzheimer's disease in 2002 by the European Agency for the Evaluation of Medicinal Products (EMEA) and in 2003 by the Food and Drug Administration (FDA) in the United States.[5] Memantine belongs to the group of drugs known as N-methyl-D-aspartate (NMDA) receptor antagonists and has the potential to improve the transmission of nerve signals. This drug also helps to protect neurons against the excitotoxic effects of glutamate, by inhibiting overactivation of the NMDA receptor and countering the undesirable effect of increased glutamate levels in the brain. In addition, memantine has the ability to enhance the long-term potentiation (LTP) of neurons, which is a biochemical mechanism that generates a durable strengthening of synapses between two simultaneously activated neurons.[6,7] In randomized control studies conducted in Alzheimer's disease, memantine significantly reduced the decline in cognitive abilities and functional independence as compared to placebo-treated patients and was very well tolerated.[8,9] Nevertheless, the value of this drug, like that of other dementia treatments, is controversial due to the limited extent of its clinical effects and its inability to halt the progression of neurodegenerative diseases.[10,11]

A less studied effect of this drug than that on the cognitive aspects of the disease is its association with mortality. Overall, there is relatively little data on this association, and some randomized studies present rather divergent results.[12,13] The randomized trials were of relatively short duration and were not designed to assess a potential effect on mortality. Some observational studies suggest that memantine may reduce mortality.[14–16] However, we believe that it would be useful to understand the impact of this drug, with its antioxidant and anti-inflammatory properties, on mortality in a population whose life expectancy is already reduced by MNDs. In this context, and in order to better understand the effect of memantine, we undertook a systematic review of randomized and observational studies that have measured these aspects. Our aim was to assess the effect of long-term treatment with memantine on all-cause mortality in patients with dementia.

RESEARCH IN CONTEXT

1. **Systematic reviews**: MND reduces patients' life expectancy. Acetylcholinesterase inhibitors reduce mortality, but the effect of memantine is not well known. An initial PubMed search identified several studies providing information on mortality in major neurocognitive disorders (MND) patients treated or not treated with memantine, but there were no randomized controlled trials (RCTs) or meta-analyses designed to investigate this question. So, we undertook a systematic review/meta-analysis for this purpose. We found seven observational studies that addressed memantine and mortality, and 12 RCTs that presented mortality as a safety outcome.
2. **Interpretation**: Among the 24,482 MND patients, those treated by memantine had significantly lower mortality than untreated patients. The reduction in mortality observed in RCTs was similar to that observed in observational studies but did not reach significance.
3. **Future directions**: These findings suggest that memantine might reduce mortality in MND patients. However, a large RCT is required to obtain a higher level of certainty.

2 | METHODS

2.1 | Search strategy and selection criteria

We carried out a systematic review and meta-analysis of randomized and non-randomized parallel controlled trials, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[17]

Five databases were used to carry out our research, namely PubMed, Embase, Cochrane Database of Controlled Clinical Trials (CENTRAL), ClinicalTrials.gov, and World Health Organization (WHO) International Clinical Trials Registry. We searched for data published from the creation of the databases to June 30th, 2024 using the following keywords: (« memantine » OR « antidementia ») AND (« Alzheimer » OR « dementia » OR « Lewy » OR « neurocognitive disorder ») AND (« clinical trial » OR « randomized controlled trial » OR « cohort study » OR « case-control study » OR « placebo » OR « control group »). An overview of the search strategies is given in Table S1 of the supplementary material.

Only publications in English were taken into account. The articles included had to compare the use of memantine in patients with any type of dementia with a parallel control group taking placebo or with no exposure to the drug. They also had to be followed up for at least 6 months (which seemed to us to be the minimum period for identifying a possible effect on mortality) and report all-cause mortality. We included randomized clinical trials (RCTs) as well as prospective and retrospective observational studies and post hoc analyses from RCTs.

As regards the selection of studies, three authors (J.B., B.O., V.Z.K.) were involved in carrying out these tasks. The initial screening of all references retrieved on the basis of title and abstract was assessed by two authors. This step was essential to identify potential studies for inclusion. Two authors then carefully assessed the candidate studies independently to determine which could be included. For each study included, the authors assessed the risk of bias and extracted the data using predefined forms. To describe the studies, we used the PICO model (patient, intervention, comparison, outcome). If any discrepancies were identified, they were discussed by these three authors and resolved by consensus to converge on the same result. In the case of several articles containing data of interest to our project but for which data for memantine alone did not appear, we contacted their authors.[16]

2.2 | Data analysis

Data extraction was carried out by one author (V.Z.K.) and checked by another (J.B.). Information extracted included the study design, setting, total number of participants, age of participants, number of deaths, type of dementia, treatment, and comparator, and Mini-Mental State Examinataion (MMSE) test results were collected.

The primary outcome was all-cause mortality, so we looked for and listed the number of deaths in each study and the total number of patients who received memantine and the comparator.

To measure the risk of bias of the selected studies, we used Cochrane RoB2 for randomized studies and ROBINS-I for non-randomized studies. Rob2 takes five areas into account to measure the risk of bias. These are assessment of the randomization process, deviations from intended interventions, missing outcome data, measurement of outcomes, and selection of reported results. Like ROb2, ROBINS-I assesses deviations from intended interventions, missing outcome data, measurement of outcomes, and selection of reported results, as well as three additional areas specific to non-randomized studies, namely confounding factors, selection of participants, and classification of interventions.

A global assessment of certainty level for main outcome was estimated using the GRADE framework.[18]

Data on mortality was pooled and risk ratios (RRs) calculated for death rate using the Mantel–Haenszel method. When studies reported multivariate adjusted risks of death, hazard ratios (HRs) were also estimated using an inverse variance method, as HR has different mathematical properties than RRs, and Mantel–Haenszel cannot be employed to pool them.[19] A random effect model was employed in all cases and heterogeneity between studies was assessed by calculating I^2.[20] Roughly, an I^2 of 30%–60% represents moderate heterogeneity, 50%–75% substantial heterogeneity, and 75%–100% considerable heterogeneity. If significant heterogeneity occurred, an attempt to explain it was done by exploring the specific characteristics of the studies responsible. The RR for individual studies and pooled RR were plotted as forest plots. A sensitivity analysis was carried by: (a) selectively pooling studies including more than 500 patients, (b) selectively pooling those studies with low risk of bias in all domains assessed in RoB2 and ROBINS-I. All analyses were carried out using Review Manager (version 5.4, Cochrane Collaboration).

The protocol of systematic review was registered in the PROSPERO international prospective registry of systematic reviews under the number CRD42023438430 and is available with the Prisma checklist from the following link: https://doi.org/10.17605/OSF.IO/Z9BGW.

2.3 | Changes from the initial protocol

There were some minor modifications: (1) we included one study that compared the outcome in patients exposed to memantine soon after the diagnosis of dementia to patients not exposed to antidementia drugs or exposed to memantine late after the diagnosis; (2) the secondary outcome on cardiovascular mortality was not analyzed as the causes of mortality were not available in the studies.

The study protocol is available at https://doi.org/10.17605/OSF.IO/Z9BGW.

2.4 | Role of the funding source

There was no funding source for this study.

3 | RESULTS

3.1 | Study selection

Figure 1 shows a PRISMA flowchart detailing the selection process of the studies included. Searches of the various databases yielded a total of 2008 results. Based on the predefined eligibility criteria, we finally selected 115 articles for full-text evaluation. In the end, after excluding 96 articles for various reasons explained in Figure 1 and detailed and available at the following link: https://doi.org/10.17605/OSF.IO/Z9BGW, 19 articles were retained. Of these studies, 12 were randomised[12,13,21–30] and 7 were observational.[14–16,31–34]

3.2 | Study characteristics

The selected studies date from 2002 to 2024. The randomized studies were conducted in the United States ($n = 4$), Germany ($n = 2$), Canada ($n = 1$), UK ($n = 1$), France ($n = 1$), and three were multinational. The observational studies were conducted in France ($n = 2$), UK ($n = 2$), Finland ($n = 1$), United States ($n = 1$) and one was multinational. A total of 4266 patients were included in the randomized studies and 20,216 in the observational studies. The mean age of participants in the randomized studies was 74.9 ± 7.6, with a mean MMSE of 15.1 ± 3.3. In the observational studies, the mean age of participants was 80.6 ± 6.4 and the mean MMSE was 16.8 ± 5.5. Tables 1 and 2 provide more detailed information on the characteristics of included studies, designs, types of patients.

TABLE 1 Characteristics of included RCTs.

Author, year, country	Design	Patients (E/NE) (*n*)	Setting	Age (years)	Dementia type	Baseline MMSE score	Treatment	Comparator	Follow-up (months)
Bakchine 2008, Multi.[21]	RCT DB	470 (318/152)	Community	73.7 ± 7.2	AD	18.8 ± 3.3	Memantine	Placebo	6
Emre 2010, Multi.[22]	RCT DB	195 (96/99)	Community	73.5 ± 6.4	PD or DLB	20.7 ± 3.0	Memantine	Placebo	6
Grossberg 2013, Multi.[23]	RCT DB	676 (341/335)	Community	76.5 ± 8.1	AD	10.8 ± 2.9	Memantine	Placebo	6
Hermann 2013, Canada[24]	RCT DB	369 (182/187)	Community	74.9 ± 7.4	AD	11.9 ± 3.0	Memantine	Placebo	6
Howard 2012, UK[25]	RCT DB	295 (149/146)	Community	77.1 ± 8.4	AD	9.1 ± 2.6	Memantine	Placebo	13
Peskind 2006, US[26]	RCT DB	403 (201/202)	Community	77.5 ± 7.8	AD	17.3 ± 3.6	Memantine	Placebo	6
Peters, 2015, Germany[27]	RCT DB	226 (112/114)	Community	72.4 ± 8.2	AD	22.2 ± 3.2	Memantine	Placebo	13
Porsteinsson 2008, US[28]	RCT DB	433 (217/216)	Community	75.5 ± 8.0	AD	16.9 ± 3.7	Memantine	Placebo	6
Reisberg 2003, US[13]	RCT DB	252 (126/126)	Community	76.1 ± 8.1	AD	7.9 ± 3.6	Memantine	Placebo	7
Van Dyck 2007, US[29]	RCT DB	350 (172/178)	Community	78.2 ± 7.9	AD	10.2 ± 3.0	Memantine	Placebo	6
Vercelletto 2011, France[12]	RCT DB	49 (23/26)	Community	65.6 ± 7.4	FTD	24.8 ± 3.2	Memantine	Placebo	12
Wilcock 2002, Germany[30]	RCT DB	548 (277/271)	Community	77.4 ± 7.0	VD	17.6 ± 2.3	Memantine	Placebo	7

Abbreviations: AD, Alzheimer's disease; DLB, dementia with Lewy's bodies; E/NE, exposed/not exposed; FTD, fronto-temporal disease; MMSE, Mini-Mental State Examination; PD, Parkinson's disease; RCT DB, randomized controlled trial double-blind; VD, vascular dementia.

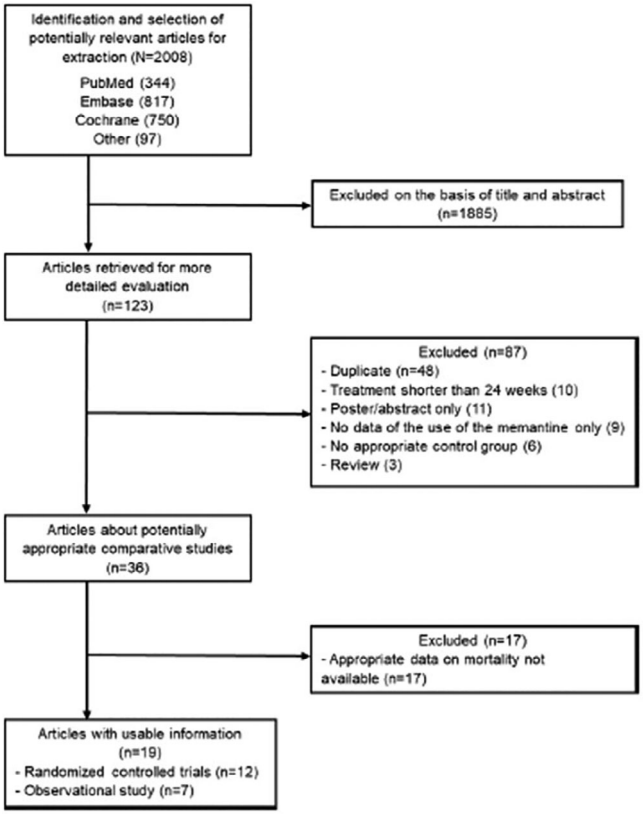

FIGURE 1 Flowchart of studies selection.

3.3 | Interventions and comparisons

Follow-up in RCTs was comprised between 6 months (7 studies) and 12–13 months (3 studies), with an average duration of 7.8 months. Conversely, follow-up time in observational studies was highly variable, ranging from 6 to 32 months, with an average duration of 19.2 months. MNDs was related to Alzheimer's disease alone in 12 studies,[13,16,21,23–29,32,34] of unspecified origin in 2 studies,[14,15] related to dementia with Lewy bodies associated or not with cognitive disorders of Parkinson's disease in 2 studies,[22,31] Alzheimer's disease associated or not with vascular cognitive disorders,[33] vascular dementia alone[30] and frontotemporal dementia.[12]

All randomized trials compared memantine with a placebo group with a double-blind design. In four RCTs (Grossberg,[23] Hermann,[24] Peters,[27] Porsteinsson[28]), all patients in both groups received cholinesterase inhibitor (ChEI). In the Howard RCT,[25] 73/149 patients in the group exposed to memantine and 73/146 in the group unexposed to memantine were receiving donepezil. In the other RCTs, patients in the memantine and control groups did not receive a ChEI during the trial. All Mortality was not considered a primary outcome in any of the RCTs but was reported in each trial as a safety outcome.

Most observational studies compared populations exposed to memantine to patients not exposed to any dementia treatment. Two studies, however, employed a different design: Linna's study compared patients with Alzheimer's disease, some of whom had been exposed to memantine shortly after diagnosis "early users", with a comparator group of patients who had not received any antidementia drug after diagnosis or who had received it later "late users"[16]; in Chen's study, all the patients treated with memantine received also ChEIs and we took as a comparator the patients receiving ChEI alone.[31] We decided to include these studies after discussion between the authors, as we believe that they can provide informative data on the specific effect of memantine. In all included observational studies, mortality was a primary outcome. Only four studies provided multivariate adjusted HR for mortality. Tables 1 and 2 provide information on the nature and duration of the interventions and observations.

TABLE 2 Characteristics of included observational studies.

Author, year, country	Design	Patients (E/NE) (*n*)	Setting/data source	Age (years)	Dementia type	Baseline MMSE score	Treatment	Comparator	Mean follow-up (months)
Chen 2022, UK[31]	Retrospective cohort	373 (273/100)	Health service registry	81.4 ± 7.5	DLB	NA	Memantine[a]	Not exposed[a]	32
Farlow 2010, US[32]	Post hoc analysis (RCT)	261 (135/126)	Community	77.2 ± 8.0	AD	18.4 ± 3.9	Memantine	Not exposed	6
Hager 2016, Multi.[33]	Post hoc analysis (RCT)	1021 (245/776)	Community	73.4 ± 8.8	AD or MD	18.7 ± 4.1	Memantine	Not exposed	24
Hapca 2019, UK[14]	Retrospective cohort	5830 (798/5032)	Emergency hospitalisation	84.2 ± 0.5	Undefined	NA	Memantine	Not exposed	12
Havreng-Théry 2024, France[15]	Retrospective cohort	4401 (1600/2801)	Nursing homes	85.4 ± 6.8	Undefined	16.2 ± 8.5	Memantine	Not exposed	19
Linna 2019, Finland[16]	Retrospective cohort	2635 (1274/1361)	National registry	83.0 ± 5.6	AD	NA	Memantine[b]	Not exposed[c]	22
Vidal 2008, France[34]	Retrospective historical control	5695 (5283/412)	Health service registry	79.6 ± 7.6	AD	14.1 ± 5.5	Memantine	Not exposed	20

Abbreviations: AD, Alzheimer's disease; DLB, dementia with Lewy's bodies; E/NE, exposed/not exposed; MD, mixed dementia; MMSE, Mini-Mental State Examination; NA, not available; RCT, randomized controlled trials.

[a]All the patients of treatment and comparator groups were receiving cholinesterase inhibitors.

[b]Treatment group "early-users" patients treated with memantine soon after diagnosis.

[c]Control group "late users" patients without drug or with antidementia drug started late after diagnosis.

3.4 | Risk of bias

Among the 12 RCTs, 11 studies[12,13,21,22–28,30] had a low risk of bias assessed using RoB2. Only one RCT had a moderate risk of bias due the randomization process, deviations from planned interventions, and the measurement of outcomes.[29] Details of the determination of the risk of bias for each study according to the different categories assessed are presented in the supplementary material and all items could be assessed for all studies (Figure S1).

Among the seven observational studies, three had a low risk of bias assessed by the ROBIN I tool,[15,32,33] two had a moderate risk,[16,31] and two were considered at serious risk of bias.[14,34] Details of the nature of the risks estimated according to the seven ROBIN I assessment categories are presented in the supplementary material (Figure S2).

3.5 | Mortality

Overall, all studies combined, long-term treatment with memantine was associated with lower all-cause mortality (RR 0.81, 95% CI: 0.72–0.92, $p = 0.001$) (Figure 2). Pooled RR were very similar both for randomized studies (RR 0.86) and for observational studies (RR 0.81). However, results from randomized studies were statistically non-significant (95% CI: 0.59–1.26, $p = 0.45$) while they were significant for observational studies (95% CI: 0.70–0.95, $p < 0.001$).

Four observational studies provided results on all-cause mortality after adjusting for multiple variables.[33,14–16] Treatment with memantine was still associated with a reduction in all-cause mortality, when combining multivariate adjusted HR from these four studies (HR 0.78, 95% CI: 0.67–0.90, $p = 0.001$) (Figure 3). We estimated that results on all-cause mortality are of low certainty as the main contributors were observational studies.

There was no important heterogeneity regarding RCTs (I2% = 0%) or all studies combined (I2% = 52%) but significant heterogeneity was observed between observational studies (I2% = 82%, $p < 0.001$). This heterogeneity is largely explained by the Linna et al. study,[16] which stands out from the others. In this study, the treatment group consisted of patients in whom memantine had been introduced shortly after diagnosis. The comparator group included patients for whom no antidementia drug had been introduced or later after diagnosis. Excluding this study from the analysis greatly reduced the heterogeneity of observational studies (I2% = 55%, $p = 0.05$) but did not change the results (pooled RR for observational studies 0.86, 95% CI: 0.77–0.96; pooled RR for all studies 0.83, 95% CI: 0.78–0.88) (Figure S3).

In further sensitivity analysis, pooling only best quality studies (those with low risk of bias in all domains assessed) or selectively pooling studies including 500 patients or more, did not change the main results (Figures S4 and S5).

In subgroup analysis, grouping studies by mean age of included patients practically replicated the results of the main analysis, as all RCTs had a mean age < 80 years and all studies having a mean age > 80 years at inclusion were non-randomized. There were too many studies with a mean age near 75 as to make this figure a reliable cut-off for analysis There was no significant difference between age groups, anyway (test for subgroup differences: $p = 0.34$, Figure S6). There was no significant difference neither on the effect in all-cause mortality between studies including patients with more severe dementia and those with mild or moderate dementia (test for subgroup differences: $p = 0.69$, Figure S7).

4 | DISCUSSION

This meta-analysis highlights that the long-term use of memantine is associated with a significant reduction in all-cause mortality of patients with dementia. This phenomenon is particularly visible in observational studies, where patients are followed over longer periods, than in randomized trials.

To our knowledge, few studies have looked specifically at the mortality risk associated with memantine, and no meta-analysis has been carried out, so this study sheds new light on the issue. Several meta-analyses had already targeted the impact of memantine in people with MNDs based on randomized trials but on parameters other than mortality. In fact, studies have sought to determine: the benefit of adding memantine to people already being treated with ChEIs[35]; the impact of memantine monotherapy on cognition, behavior, and functional independence[10]; the efficacy and safety of memantine monotherapy or in combination with ChEIs[36]; and an assessment of the efficacy and safety of ChEIs and memantine in vascular dementia.[37] Two further meta-analyses were carried out to examine the associations between treatment with ChEIs and mortality. Both found that this treatment reduced mortality in Alzheimer's disease[38] and MND[39] and shed new light on conventional drug treatment of dementia. These results led us to formulate our hypothesis and conduct the present study.

The results of our study are interesting insofar as a similar effect on mortality was observed both in randomized and observational studies. Observational studies were conducted on a larger number of patients with more varied characteristics and closer to real-life conditions than the highly selected patients enrolled in randomized controlled trials. Nevertheless, in randomized studies, the pooled RR was similar to that in observational studies (RR 0.86 and 0.81, respectively) but did not reach the level of statistical significance. Due to its mechanisms of action, the effects of memantine are generally observed over the long term. Thus, its effect on mortality might be less prominent in short-term studies. In addition, due to selection bias, RCTs include patients in better health status with a better prognosis. In our study mortality in groups not exposed to memantine was much lower in RCTs than in observational studies. Finally, the number of patients included in the RCTs was much smaller than in observational studies. These two points might have resulted in a lower statistical power in the RCTs. These may explain why the reduction of mortality is not significant in RCTs considered separately from observational studies.

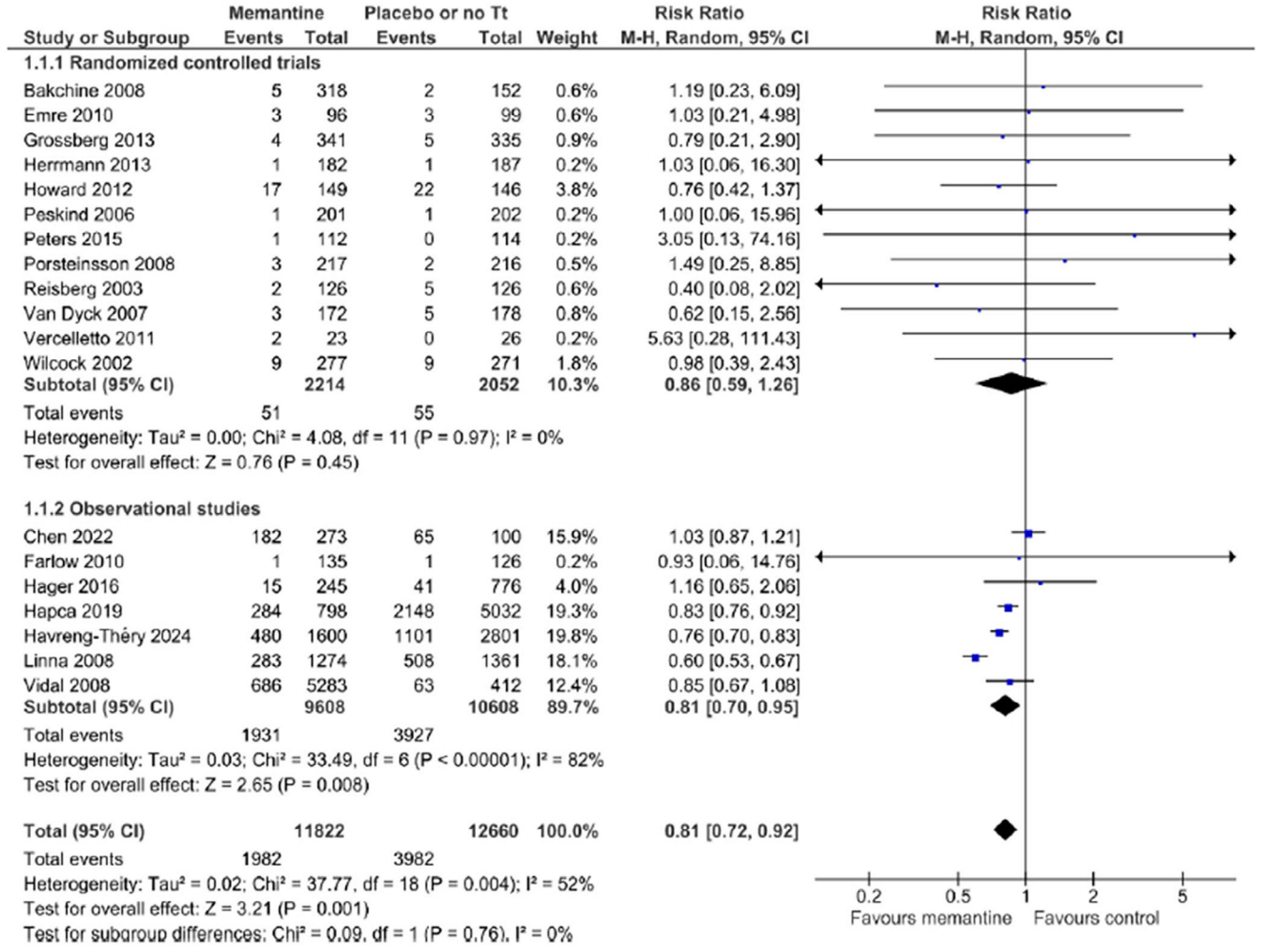

FIGURE 2 Forest plot of all-cause mortality, all studies.

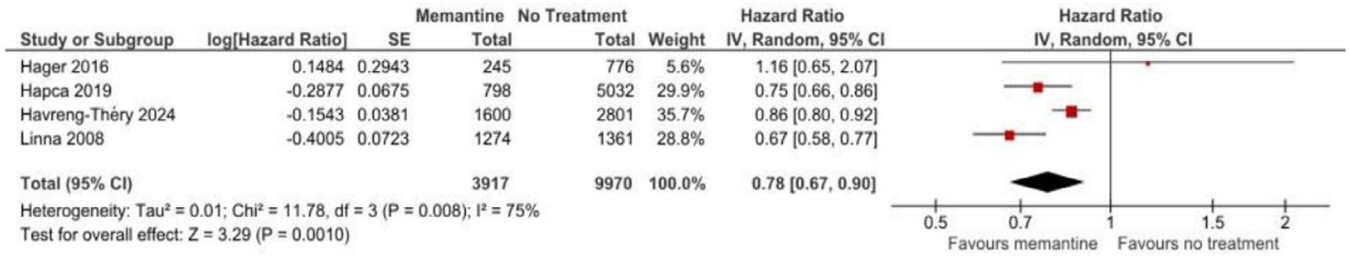

FIGURE 3 Forest plot of all-cause mortality, multivariate adjusted HR. HR, hazard ratios.

4.1 | Strengths and limitations

The main limitation of our study relies on the fact that non-randomized studies are a major contributor to the overall results. Even if they are good-quality parallel cohorts, non-randomized studies can always include unknown selection bias. Also, a significant heterogeneity was observed among observational studies. This may be due to the variable nature of these studies (retrospective, post hoc analysis of an RCT, retrospective historical control), to fairly variable durations of 6–32 months, but also to a diversified context (ambulatory, secondary care, emergency hospitalization, nursing home, healthcare database). Furthermore, heterogeneity remains significant after removing the study with the greatest impact on this characteristic. The combination of multivariate-adjusted HRs could only be performed with data

from four studies, limiting the conclusions on the other data. We also included two studies that differed from the others because they combined galantamine and ChEIs with memantine, which may have an influence on the reduction in mortality which is difficult to measure. However, we conducted several sensitivity analyses that did not alter our findings.

In conclusion, our systematic review suggests that long-term treatment with memantine is probably associated with reduced all-cause mortality in patients with dementia. These results, together with its known effects on cognitive decline are arguments for a more wide use of this drug in patients with dementia. This is an important point, given that a large proportion of patients receive no drug treatment for these diseases.[40–42] Lecanemab[43] and aducanumab,[44] two anti-amyloid monoclonal antibodies approved in the United States for the treatment of Alzheimer's disease have recently raised new hopes. They reduce amyloid markers, particularly in the early stages of the disease, and help reduce cognitive decline. These new drugs will not be used in all patients because of their adverse effects and high cost, and the use of inexpensive, well-tolerated conventional drugs such as memantine remains relevant.

AUTHOR CONTRIBUTIONS

Study concept and design: Victoria Zolnowski-Kolp, Carmelo Lafuente-Lafuente, Joël Belmin; data acquisition: Victoria Zolnowski-Kolp, Bruno Oquendo; data analysis and interpretation: Victoria Zolnowski-Kolp, Joël Belmin, Carmelo Lafuente-Lafuente, Bruno Oquendo, Charlotte Havreng-Théry; drafting of the manuscript: Victoria Zolnowski-Kolp, Joël Belmin, Carmelo Lafuente-Lafuente; critical revision of the manuscript for important intellectual content: all authors

ACKNOWLEDGMENTS

The authors have nothing to report.

CONFLICT OF INTEREST STATEMENT

The author declares no conflicts of interest. Author disclosures are available in the Supporting Information.

FUNDING INFORMATION

There was no funding source for this study.

DATA AVAILABILITY STATEMENT

All data are presented either in the manuscript, in the supplementary material, or available from the following link: https://doi.org/10.17605/OSF.IO/Z9BGW

CONSENT STATEMENT

This systematic review and meta-analysis mobilize previously published data. In addition, we did not collect new data directly from human participants, so informed consent was not applicable.

ORCID

Victoria Zolnowski-Kolp https://orcid.org/0000-0002-9736-1253

REFERENCES

1. Liang CS, Li DJ, Yang FC, Tseng PT, et al. Mortality rates in Alzheimer's disease and non-Alzheimer's dementias: a systematic review and meta-analysis. *Lancet Healthy Longev*. 2021;2(8):e479-e488. doi:10.1016/S2666-7568(21)00140-9
2. World Health Organization. *Dementia*. 2023. Accessed June 10, 2024. https://www.who.int/news-room/fact-sheets/detail/dementia
3. Alzheimer's Association. Alzheimer's Association Report. 2019 Alzheimer's disease facts and figures. *Alzheimers Dement*. 2020;15(3):321-387.
4. M. Prince, Wimo A, Guerchet M, Ali GC, Wu YT, Prina M. *World Alzheimer Report 2015: The Global Impact of Dementia: An Analysis of Prevalence, Incidence, Cost and Trends*. Alzheimer's Disease International; 2015. Accessed June 13, 2024. https://www.alzint.org/resource/world-alzheimer-report-2015
5. Tang BC, Wang YT, Ren J. Basic information about memantine and its treatment of Alzheimer's disease and other clinical applications. *Ibrain*. 2023;9(3):340-348. doi:10.1002/ibra.12098
6. Frankiewicz T, Parsons CG. Memantine restores long term potentiation impaired by tonic N-methyl-D-aspartate (NMDA) receptor activation following reduction of Mg2+ in hippocampal slices. *Neuropharmacology*. 1999;38(9):1253-1259. doi:10.1016/s0028-3908(99)00060-x
7. Karimi Tari P, Parsons CG, Collingridge GL, Rammes G. Memantine: Updating a rare success story in pro-cognitive therapeutics. *Neuropharmacology*. 2024;244:109737. doi:10.1016/j.neuropharm.2023.109737
8. McShane R, Areosa Sastre A, Minakaran N. Memantine for dementia. *Cochrane Database Syst Rev*. 2006;2006(2):CD003154. doi:10.1002/14651858.CD003154.pub5
9. Matsunaga S, Kishi T, Iwata N. Memantine monotherapy for Alzheimer's disease: a systematic review and meta-analysis. *PLoS One*. 2015;10(4):e0123289. doi:10.1371/journal.pone.0123289
10. Benninghoff J; Perneczky R. Anti-dementia medications and anti-Alzheimer's disease drugs: side effects, contraindications, and interactions. In: Riederer P, Laux G, Nagatsu T, Le W, Riederer C, eds. *NeuroPsychopharmacotherapy*. Springer International Publishing; 2022:2779-2788.
11. Fink HA, Linskens EJ, MacDonald R, et al. Benefits and harms of prescription drugs and supplements for treatment of clinical Alzheimer-type dementia. *Ann Intern Med*. 2020;172(10):656-668. doi:10.7326/M19-3887
12. Vercelletto M, Boutoleau-Bretonnière C, Volteau C, et al. Memantine in behavioral variant frontotemporal dementia: negative results. *J Alzheimers Dis*. 2011;23(4):749-759. doi:10.3233/JAD-2010-101632
13. Reisberg B, Doody R, Stöffler A, et al. Memantine in moderate-to-severe Alzheimer's disease. *N Engl J Med*. 2003;348(14):1333-1341. doi:10.1056/NEJMoa013128
14. Hapca S, Burton JK, Cvoro V, Reynish E, Donnan PT. Are antidementia drugs associated with reduced mortality after a hospital emergency admission in the population with dementia aged 65 years and older?. *Alzheimers Dement*. 2019;5:431-440. doi:10.1016/j.trci.2019.07.011
15. Havreng-Théry C, Oquendo B, Zolnowski-Kolp V, et al. Cholinesterase inhibitors and memantine are associated with a reduced mortality in nursing home residents with dementia: a longitudinal observational study. *Alzheimers Res Ther*. 2024;16(1):117. doi:10.1186/s13195-024-01481-0
16. Linna M, Vuoti S, Silander K, et al. Impact of anti-dementia medication on the risk of death and causes of death in Alzheimer's disease. *J Alzheimers Dis*. 2019;71(4):1297-1308.doi:10.3233/JAD-190288
17. Page MJ, Mckenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. doi:10.1136/bmj.n71

18. Balshem H, Helfand M, Schünemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol*. 2011;64(4):401-406. doi:10.1016/j.jclinepi.2010.07.015
19. Deeks JJ, Higgins JPT, Altman DG, et al. Chapter 10: Analysing data and undertaking meta-analyses [last updated November 2024]. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, eds. *Cochrane Handbook for Systematic Reviews of Interventions version 6.5*. Cochrane. 2024. Accessed February 3, 2025.
20. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21(11):1539-58. doi:10.1002/sim.1186
21. Bakchine S, Loft H. Memantine treatment in patients with mild to moderate Alzheimer's disease : Results of a randomised, double-blind, placebo-controlled 6-month study. *J Alzheimers Dis*. 2008;13(1):97-107. doi:10.3233/jad-2008-13110
22. Emre M, Tsolaki M, Bonuccelli U, et al. Memantine for patients with Parkinson's disease dementia or dementia with Lewy bodies: a randomised, double-blind, placebo-controlled trial. *Lancet Neurol*. 2010;9(10):969-977. doi:10.1016/S1474-4422(10)70194-0
23. Grossberg GT, Manes F, Allegri RF, et al. The safety, tolerability, and efficacy of once-daily memantine (28 mg): a multinational, randomized, double-blind, placebo-controlled trial in patients with moderate-to-severe Alzheimer's disease taking cholinesterase inhibitors. *CNS Drugs*. 2013;27(6):469-478. doi:10.1007/s40263-013-0077-7
24. Herrmann N, Gauthier S, Boneva N, Lemming OM; 10158 Investigators. A randomized, double-blind, placebo-controlled trial of memantine in a behaviorally enriched sample of patients with moderate-to-severe Alzheimer's disease. *Int Psychogeriatr*. 2013;25(6):919-927. doi:10.1017/S1041610213000239
25. Howard R, McShane R, Lindesay J, et al. Donepezil and memantine for moderate-to-severe Alzheimer's disease. *N Engl J Med*. 2012;366(10):893-903. doi:10.1056/NEJMoa1106668
26. Peskind ER, Potkin SG, Pomara N, et al. Memantine treatment in mild to moderate Alzheimer disease: a 24-week randomized, controlled trial. *Am J Geriatr Psychiatry*. 2006;14(8):704-715. doi:10.1097/01.JGP.0000224350.82719.83
27. Peters O, Fuentes M, Joachim LK, et al. Combined treatment with memantine and galantamine-CR compared with galantamine-CR only in antidementia drug naïve patients with mild-to-moderate Alzheimer's disease. *Alzheimers Dement*. 2015;1(3):198-204. doi:10.1016/j.trci.2015.10.001
28. Porsteinsson AP, Grossberg GT, Mintzer J, Olin JT; Memantine MEM-MD-12 Study Group. Memantine treatment in patients with mild to moderate Alzheimer's disease already receiving a cholinesterase inhibitor: a randomized, double-blind, placebo-controlled trial. *Curr Alzheimer Res*. 2008;5(1):83-89. doi:10.2174/156720508783884576
29. van Dyck CH, Tariot PN, Meyers B, Malca Resnick E; Memantine MEM-MD-01 Study Group. A 24-week randomized, controlled trial of memantine in patients with moderate-to-severe Alzheimer disease. *Alzheimer Dis Assoc Disord*. 2007;21(2):136-143. doi:10.1097/WAD.0b013e318065c495
30. Wilcock G, Möbius HJ, Stöffler A; MMM 500 group. A double-blind, placebo-controlled multicentre study of memantine in mild to moderate vascular dementia (MMM500). *Int Clin Psychopharmacol*. 2002;17(6):297-305. doi:10.1097/00004850-200211000-00005
31. Chen S, Price AC, Cardinal RN, et al. Association between antidementia medication use and mortality in people diagnosed with dementia with Lewy bodies in the UK: a retrospective cohort study. *PLoS Med*. 2022;19(12):e1004124. doi:10.1371/journal.pmed.1004124
32. Farlow MR, Alva G, Meng X, Olin JT. A 25-week, open-label trial investigating rivastigmine transdermal patches with concomitant memantine in mild-to-moderate Alzheimer's disease: a post hoc analysis. *Curr Med Res Opin*. 2010;26(2):263-269. doi:10.1185/03007990903434914
33. Hager K, Baseman AS, Nye JS, et al. Effect of concomitant use of memantine on mortality and efficacy outcomes of galantamine-treated patients with Alzheimer's disease: post-hoc analysis of a randomized placebo-controlled study. *Alzheimers Res Ther*. 2016;8(1):47. doi:10.1186/s13195-016-0214-x
34. Vidal JS, Lacombe JM, Dartigues JF, et al. Memantine therapy for Alzheimer disease in real-world practice: an observational study in a large representative sample of French patients. *Alzheimer Dis Assoc Disord*. 2008;22(2):125-130. doi:10.1097/WAD.0b013e31815a9e10
35. McShane R, Westby MJ, Roberts E et al. Memantine for dementia. *Cochrane Database Syst Rev*. 2019;3(3):CD003154. doi:10.1002/14651858.CD003154.pub6
36. Kishi T, Matsunaga S, Oya K, Nomura I, Ikuta T, Iwata N. Memantine for Alzheimer's disease: an updated systematic review and meta-analysis. *J Alzheimers Dis*. 2017;60(2):401-425. doi:10.3233/JAD-170424
37. Kavirajan H, Schneider LS. Efficacy and adverse effects of cholinesterase inhibitors and memantine in vascular dementia: a meta-analysis of randomised controlled trials. *Lancet Neurol*. 2007;6(9):782-792.doi:10.1016/S1474-4422(07)70195-3
38. Blanco-Silvente L, Castells X, Saez M, et al. Discontinuation, efficacy, and safety of cholinesterase inhibitors for Alzheimer's disease: a meta-analysis and meta-regression of 43 randomized clinical trials enrolling 16 106 patients. *Int J Neuropsychopharmacol*. 2017;20(7):519-528. doi:10.1093/ijnp/pyx012
39. Truong C, Recto C, Lafont C, Canoui-Poitrine F, Belmin J, Lafuente-Lafuente C. Effect of cholinesterase inhibitors on mortality in patients with dementia: a systematic review of randomized and nonrandomized trials. *Neurology*. 2022;99(20):e2313-e2325. doi:10.1212/WNL.0000000000201161
40. Olazarán J, Carnero-Pardo C, Fortea J, et al. Prevalence of treated patients with Alzheimer's disease: current trends and COVID-19 impact. *Alzheimers Res Ther*. 2023;15(1):130. doi:10.1186/s13195-023-01271-0
41. Ippoliti I, Ancidoni A, Da Cas R, Pierantozzi A, Vanacore N, Trotta F. Anti-dementia drugs: a descriptive study of the prescription pattern in Italy. *Neurol Sci*. 2023;44(5):1587-1595. doi:10.1007/s10072-022-06586-8
42. Reyes C, Newby D, Raventós B, et al. Trends of use and characterisation of anti-dementia drugs users: a large multinational-network population-based study. *Age Ageing*. 2024;53(5):afae106. doi:10.1093/ageing/afae106
43. van Dyck CH, Swanson CJ, Aisen P, et al. Lecanemab in early Alzheimer's disease. *N Engl J Med*. 2023;388(1):9-21. doi:10.1056/NEJMoa2212948
44. Salloway S, Chalkias S, Barkhof F, et al. Amyloid-related imaging abnormalities in 2 phase 3 studies evaluating aducanumab in patients with early Alzheimer disease. *JAMA Neurol*. 2022;79(1):13-21. doi:10.1001/jamaneurol.2021.4161

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Zolnowski-Kolp V, Oquendo B, Havreng-Théry C, Lafuente-Lafuente C, Belmin J. Effect of long-term treatment with memantine on mortality in patients with major cognitive disorders: A systematic review and meta-analysis. *Alzheimer's Dement*. 2025;11:e70071. https://doi.org/10.1002/trc2.70071