Memantine in Alzheimer's Disease: Prolonging Time to Nursing-home Admission

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Recent evidence shows that the NMDA antagonist, memantine, significantly prolongs time to nursing-home admission when administered to patients with Alzheimer's disease (AD).[1] This finding, from an observational study conducted by Lopez et al in 2009,[1] has added important new information to the evidence base for memantine in moderate and severe AD. This review presents the design and results of this study, and examines the question of how memantine may have exerted such a dramatic influence on time to nursing-home admission. First, however, is a brief discussion of the impact of nursing-home placement on AD patients, their families and the healthcare system.

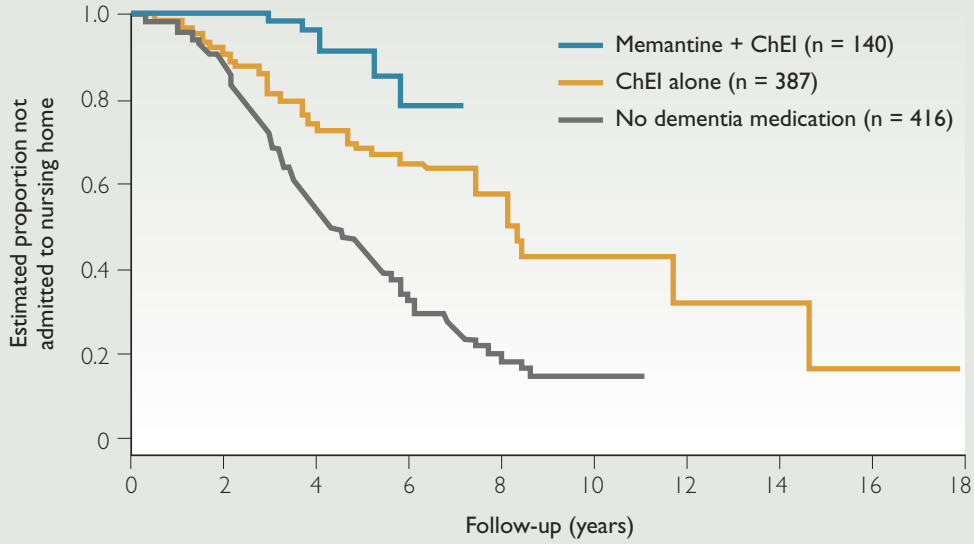
Impact of Nursing-home Placement

AD is a progressively degenerative condition; patients will ultimately succumb to the disease and most who survive into the disease's more severe stages will require nursing-home placement. Nursing-home placement is expected for approximately 75% of surviving AD patients by the age of 80 years.[2] The decision to place a person with AD into a long-term care (LTC) facility is a difficult one for caregivers (most often the patient's spouse or child). For the patient, moving to a nursing home can be a difficult transition, which can exacerbate behavioural and functional difficulties as he or she leaves a familiar location and has to adjust to new surroundings.

There is often also a significant financial aspect to institutionalization. Most nursing-home stays are subsidized by provincial health ministries. In addition to the burden on public healthcare budgets, residents (or their families) are also financially impacted by institutionalization. In Ontario, for example, residents are required to contribute a co-payment, with daily fees ranging from $53 to $71 (approximately $20,000 to $25,000 per year).[3] In Quebec, the annual fees range from approximately $12,000 to $20,000.[4]

Delaying time to institutionalization not only allows patients to reside in a more familiar, comfortable environment for a longer period of time, but also reduces financial and logistical burden on the healthcare system and reduces costs for the patient and his or her family. Furthermore, delaying time to institutionalization is in general beneficial to families, as it

FIGURE 1. **Time to Nursing-home Admission: Cholinesterase Inhibitors ± Memantine vs. No Dementia Medication (Cohort 1)**[1]



NB: Curve for memantine + ChEI ends abruptly based on maximum duration of follow-up following introduction of memantine.
Adapted from: Lopez OL, et al. J Neurosurg Psychiatry 2009; 80(6):600-7.

provides them with additional time to find a suitable nursing home for when institutionalization becomes necessary. For these reasons, prolonging time to nursing-home placement—until such placement is the most suitable option for patients and/or their family caregivers—is among the goals of treatment for patients with AD.

Effects of Memantine on Nursing-home Placement (Lopez et al, 2009)

Rationale for the study. There are two types of pharmacologic agents used for symptomatic treatment of AD: memantine and cholinesterase inhibitors (*i.e.*, donepezil, galantamine and rivastigmine). Previous research has shown that cholinesterase inhibition alone delays nursing-home placement. For example, a study published in 2003 found that long-term donepezil treatment (*i.e.*, therapy for at least nine to 12 months) was associated with an estimated prolongation to nursing-home placement of at least 17.5 months.[5] Also, in 2009, a follow-up analysis of patients who had participated in studies with galantamine found that, for each year of treatment with galantamine, the risk of being admitted to a nursing home within a given period was reduced by 31%.[6]

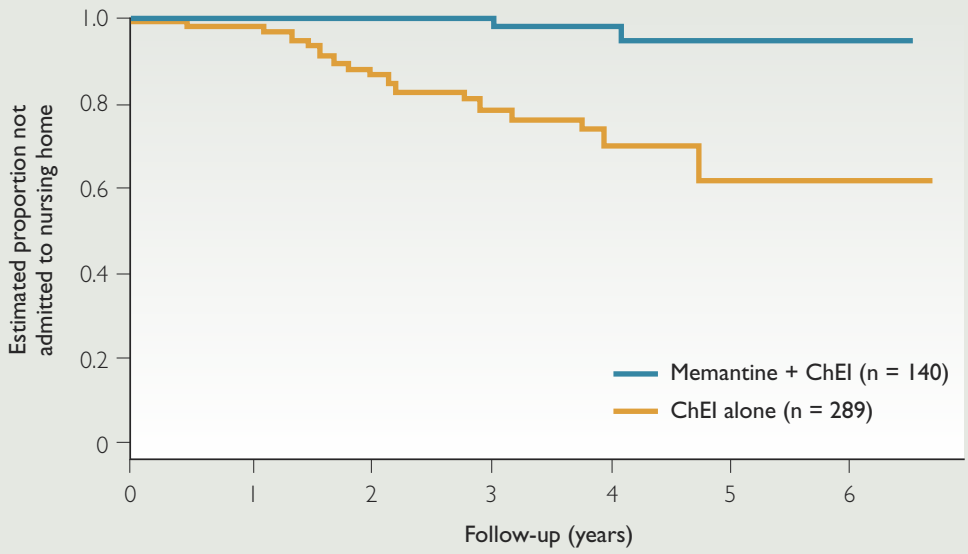
Prior to the Lopez study, however, there were no data conclusively showing a similar effect with memantine. There are data showing that memantine has a significant beneficial effect relative to placebo in terms of behaviour, overall function and cognition in AD.[10-13] The use of memantine has also been associated with a reduced use of psychotropic medications.[14] Based on the record of benefit in AD, particularly with respect to behavioural symptoms, these investigators therefore hypothesized that these benefits might translate into an increased time to nursing-home placement for patients taking memantine.

Design. This was a single-center, observational study examining data from patients examined at the Alzheimer Disease Research Center (ADRC) at the University of Pittsburgh from 1983 to 2006.

Patients were evaluated in two cohorts. Cohort 1 included all subjects with probable AD with at least a one-year follow-up evaluation (n = 943). Within this cohort, there were 140 patients (14.9% of the cohort) taking a cholinesterase inhibitor and memantine, 387 patients (45.0%) taking a cholinesterase inhibitor alone, and 416 patients (40.1%) who were not taking either type of AD pharmacotherapy (reference group).

Cohort 2 included all subjects taking medication who were enrolled after 1997 (the date of study enrolment for the first patient to take memantine). This

FIGURE 2. **Time to Nursing-home Admission: Cholinesterase inhibitors Alone vs. Cholinesterase Inhibitors + Memantine (Cohort 2)**[1]



Adapted from: Lopez OL, et al. J Neurosurg Psychiatry 2009; 80(6):600-7.

cohort included 429 patients, 140 (32.6%) of whom were taking a cholinesterase inhibitor and memantine. The remaining 289 patients (67.4%) were taking a cholinesterase inhibitor alone. For cohort 2, the cholinesterase-inhibitor-alone patients served as the reference group.

The primary study endpoints were time to nursing-home admission and death. The analysis was conducted with multivariable Cox proportional hazard models controlling for critical covariates.

The observational nature of this study conferred a significant advantage over typical short-term, randomized, controlled trials conducted with AD medications. The use of a longitudinal database allowed the investigators to examine much longer periods of time (up to 18 years in cohort 1 and up to seven years in cohort 2).

Results—Cohort 1. The investigators reported that, for Cohort 1, patients taking cholinesterase inhibitors alone had a relative hazard (RH) of nursing-home admission of 0.37 (95% CI 0.27-0.49) compared to untreated patients. For patients receiving a cholinesterase inhibitor and memantine, the risk was even lower (RH 0.29; 95% CI 0.11-0.72) (Figure 1). Based on these findings, the risk of nursing-home admission with a cholinesterase inhibitor and memantine was calculated to be reduced by a factor of 3.4 relative to the group taking only a cholinesterase inhibitor.

In this cohort, there was no impact of pharmacotherapy (monotherapy or combination) on overall time to death.

Results—Cohort 2. In the Cohort 2 analysis, patients using a cholinesterase inhibitor and memantine were significantly less likely to be admitted to a nursing home than those taking a cholinesterase inhibitor alone (RH 0.13, 95% CI 0.03-0.56) (Figure 2). This meant that patients taking both therapies were more than seven times less likely to be admitted to a nursing home compared to those taking a cholinesterase inhibitor alone.

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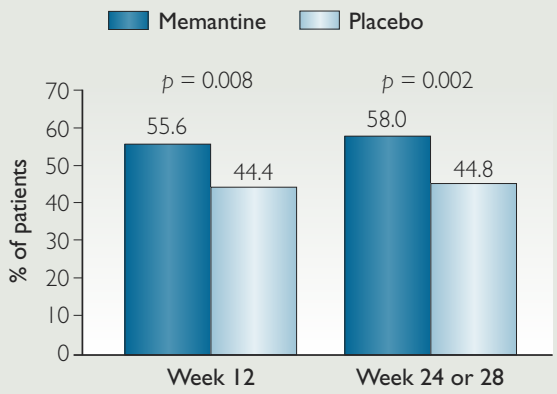
Although no association was found between pharmacotherapy and time to death in this cohort, nurs-

FIGURE 3. **Proportion of Patients Improving on the NPI Cluster of Agitation/Aggression and Psychosis (Pooled Analysis)[10]**



Adapted from: Wilcock GK, et al. J Clin Psychiatry 2008; 69(3):341-8.

ing-home admission was identified as a predictor of time to death (RH 1.94, 95% CI 1.17-3.24).

How Does Memantine Delay Nursing-home Placement?

The study by Lopez et al was not designed to answer the question of why memantine prolonged time to nursing-home placement. The authors did, however, put forth a hypothesis as to why memantine treatment had such a beneficial effect in this regard. They hypothesized that the use of memantine in dual-combination therapy enhances patients' communication skills and ability to perform basic activities of daily living (*i.e.*, getting dressed, bowel/bladder control).[1] Loss of these abilities may be an important motivator for families to seek nursing-home placement for their loved ones with AD.

This hypothesis is supported by many sources, including a study published in 2008, which found that patient loss of functional ability was a key determining factor in caregiver stress and rates of caregiver depression.[7] In the same study, the authors also identified problem behaviours associated with AD as predictors of caregiver stress and depression. A systematic review published in 2009 also identified dependencies for basic activities of daily living and behavioural symptoms as consistent patient-related predictors of nursing-home placement.[8]

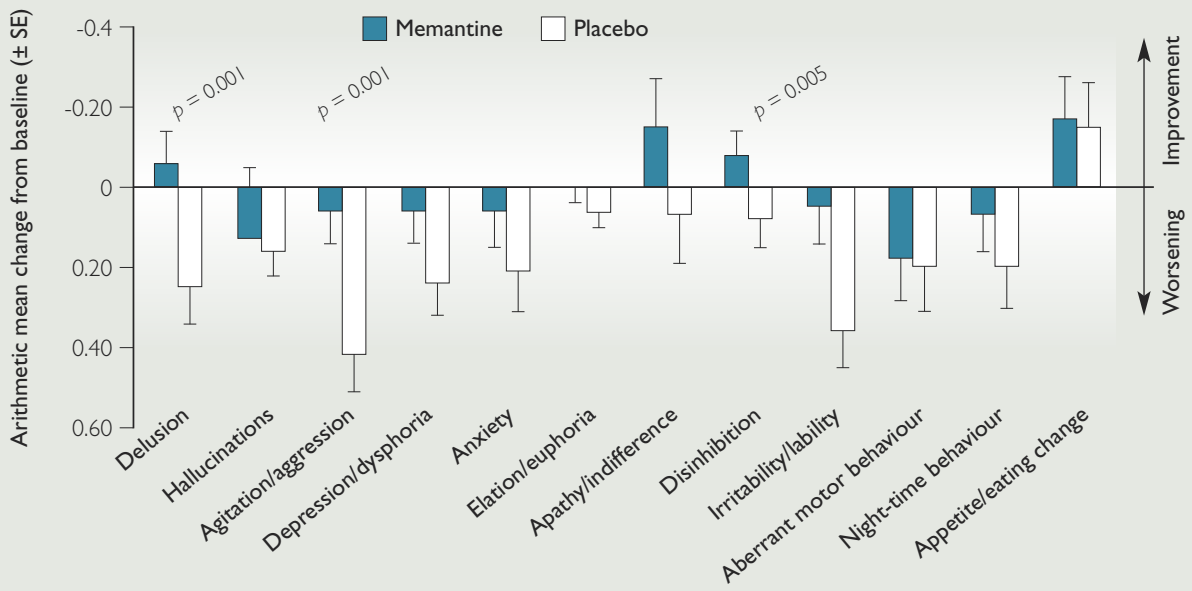
These findings are echoed elsewhere, including in the 2007 Canadian clinical practice guidelines for severe Alzheimer's disease, which state that behavioural and psychological symptoms of dementia are not only significant risk factors for nursing-home placement, but are also associated with more rapid cognitive and functional decline and increased mortality.[9] Indeed, studies have shown that AD patients with behavioural symptoms at baseline decline far more quickly on measures of cognition (*e.g.*, the Severe Impairment Battery [SIB]), global function (*e.g.*, the Clinician's Interview-based Impression of Change Plus Caregiver Input [CIBIC-Plus]), and functional ability (*e.g.*, the Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory [ADCS-ADL]). The rates of decline on the SIB, CIBIC-Plus and ADCS-ADL for patients with behavioural symptoms have been reported to be 87%, 66% and 48% faster, respectively, than for patients with no behavioural symptoms.[10]

Based on these observations of the link between behaviour and function and increased likelihood of nursing-home placement, it is perhaps not surprising that memantine has demonstrated a significant ability to delay the time to institutionalization. Research with memantine has demonstrated a significant beneficial impact on each of these domains of AD.

A recent pooled analysis of three memantine trials (up to 28 weeks' duration) evaluated the efficacy and safety of memantine among AD patients exhibiting common AD-related behavioural disturbances (agitation/aggression or psychosis) at baseline (n = 593 of the 983 total population of the three trials).[10] The investigators found that the proportion of patients showing improvement on the agitation/psychosis cluster (agitation/aggression, delusions and hallucinations) of the Neuropsychiatric Inventory (NPI) was significantly higher for memantine-treated patients compared to those receiving placebo (Figure 3). The mean changes in NPI cluster scores were -0.8 (improvement) for memantine vs. 0.5 (deterioration) for placebo at week 12, and -0.7 vs. 0.7 at week 24 or 28 (duration depending on the design of the individual studies).

Another pooled analysis of memantine studies included six individual trials involving a total of 2,311 patients.[11] The authors of this analysis examined the impact of memantine on overall NPI and on individual NPI items. On the overall NPI, memantine therapy was associated with significant benefit at week 12 and at week 24 or 28. It was also associated with statistically significant benefits relative to placebo on three individual NPI

FIGURE 4 **Changes in NPI Single Items at Week 24 or 28: Memantine vs. Placebo (Pooled Analysis)**[11]



Adapted from: Gauthier S, et al. Int J Geriatr Psychiatry 2008; 23(5):537-45.

items at week 24 or 28: delusions, agitation/aggression and irritability/lability (Figure 4). The findings for each of the other NPI items numerically favored memantine but did not reach statistical significance in these short-term studies. In the same analysis, the investigators also analyzed the subset of patients who were asymptomatic for the individual NPI items at baseline. They found memantine therapy had a preventive effect, with significantly fewer memantine-treated patients developing behavioural symptoms compared to those receiving placebo (Figure 5).

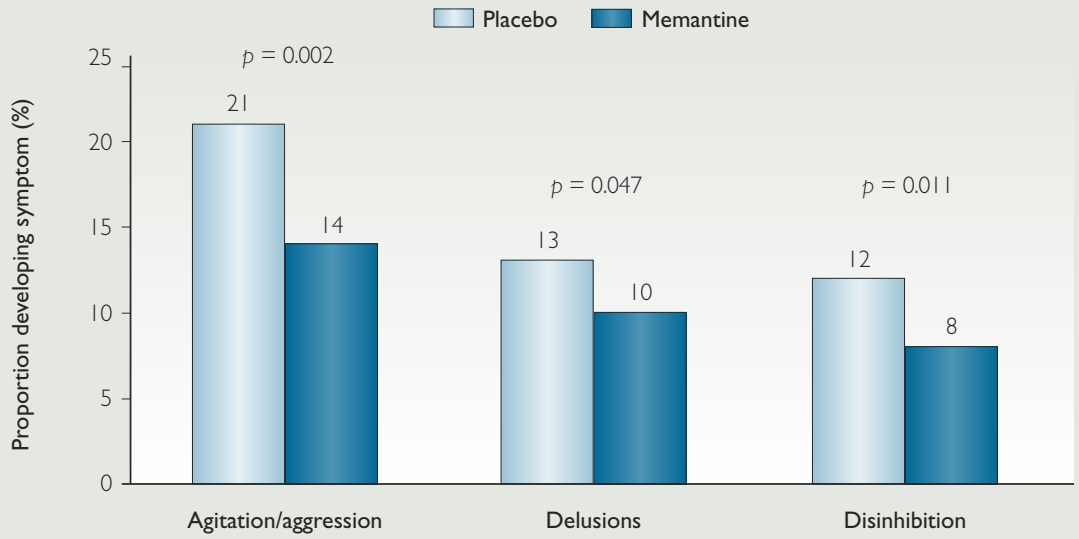
In addition to its significant beneficial impact on behavioural symptoms, memantine has demonstrated efficacy for other domains of AD that may predispose patients to institutionalization. In a randomized, controlled trial comparing memantine to placebo in 404 patients already receiving a cholinesterase inhibitor, memantine was associated with a statistically significant attenuation of decline on the ADCS-ADL.[12] Because memantine is a medication that exerts its benefits for AD patients through positive impacts on behavioural symptoms, functional abilities and cognition—all of which are important as factors in nursing-home placement and as separate aspects of the disease itself—its role should be considered in the treatment of all patients at some stages of this disease.

Conclusions

Delaying nursing-home placement is an important achievement to target in the care of a patient with AD. Delaying institutionalization may increase the amount of quality time the patient is able to spend with family and friends, and improve the overall quality of life of the patient and his or her caregiver. In our current healthcare environment, where physical and monetary resources are in high demand, minimizing the time for which a patient with AD requires nursing-home care is also an important goal for provincial governments. Many governmental agencies have recognized the potential cost saving and are investigating ways to maximize AD patients' time in the community.

Pharmacologic treatment of AD with cholinesterase inhibitors and memantine has been shown to result in a significant prolongation of time to nursing-home placement. The study by Lopez et al has shown that the difference between cholinesterase-inhibitor monotherapy and dual therapy including memantine is significant, combination therapy being associated with a seven-fold

FIGURE 5. **Proportion of Patients Developing Behavioural Symptoms Over 12 Weeks: Memantine vs. Placebo**[11]



Adapted from: Gauthier S, et al. Int J Geriatr Psychiatry 2008; 23(5):537-45.

reduction in the probability of nursing-home placement compared to treatment with a cholinesterase inhibitor alone.

Improvements in behaviour, functional abilities and cognition have all been previously demonstrated with memantine therapy relative to placebo in randomized, controlled trials. It is reasonable to hypothesize that these improvements decrease the burden of providing care for patients with AD and allow memantine-treated patients to continue living in the community for longer periods than those who do not receive such treatment.

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