National PBM Drug Monograph
Memantine (Namenda®)

VHA Pharmacy Benefits Management Strategic Healthcare Group, Alzheimer's Disease Workgroup and Medical Advisory Panel

The following recommendations are based on current medical evidence and expert opinion from clinicians. The content of the document is dynamic and will be revised as new clinical data becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. The clinician should utilize this guidance and interpret it in the clinical context of the individual patient situation.

Introduction[1]

Dementia is a significant cause of morbidity in the elderly population. Three common etiologies include dementia associated with Alzheimer's disease (AD), vascular changes and mixed dementia. Several hypotheses are being investigated for the causative agent in dementia of the Alzheimer's type. One pathway involves neuronal death that may be accelerated with excess glutamate release. Blockade of the major glutamate receptor, N-methyl-D-aspartate (NMDA receptor) would block this pathway and preserve neurons. Memantine is a NMDA receptor antagonist that has been investigated in a variety of disease states and recently gained approval in the treatment of moderate to severe AD.

Pharmacology/Pharmacokinetics [2-6]

Memantine is a specific, moderate affinity, noncompetitive NMDA receptor antagonist. Other agents proposed to work at the NMDA receptor include amantadine, rimantadine, and ketamine. Since memantine is not a high affinity NMDA receptor antagonist, it is unlikely to interfere with the physiologic activity of the receptor. It displays rapid association and disassociation with the receptor. It does not interact with other receptors, transporters or enzyme systems.

Memantine displays linear, dose proportional pharmacokinetics. It demonstrates 100% oral bioavailability and rapidly crosses the blood-brain barrier. Food does not appear to alter the bioavailability of the agent. Memantine has minimal protein binding, an elimination half-life of 60-80 hours, is renally excreted as the parent compound and has limited hepatic metabolism. It has been shown to have no effect in CYP1A2, 2A6, 2C9, 2D6, 2E1 or 3A in vitro.

FDA Approved Indication(s) and Off-label Uses [7-12]

Memantine is indicated for the treatment of patients with moderately severe to severe Alzheimer's disease. Several other uses for this agent are currently being investigated and their place in therapy remains to be determined. These uses include combination therapy with cholinesterase inhibitors (CI) in patients with moderate to severe Alzheimer's disease, use in vascular dementia (VaD), treatment of phantom limb pain as well as other pain syndromes[7], neurogenic bladder dysfunction,[8] Parkinson's disease[11,12], and as a vigilance enhancer in comatose patients[9,10].

Current VA National Formulary Status

Currently the VA National Formulary includes donepezil, galantamine, and various vitamin supplements as therapies for AD.

Dosage and Administration[2]

Memantine is given twice daily for a total dose of 20 mg/day. Currently, a titration schedule of 5 mg/day for one week, 5 mg BID for one week, 5 mg in am and 10 mg in pm followed by 10 mg BID is advocated in the package insert. In patients with a creatinine clearance of 40-60ml/min/1.73m^2 the recommended dose is 10 mg per day.

Adverse Effects (Safety Data)[5,6,13]

In the clinical trials of memantine the incidence rates for adverse events did not differ significantly from those patients who received placebo. The most frequently reported adverse effects of memantine are dizziness, headache, hallucination, insomnia, confusion and constipation. These events were most often rated as mild to moderate in severity.

Precautions/Contraindications [2,14]

Memantine is a weak base that is largely renally excreted. Alteration of urine pH to an alkaline state may lead to significant retention of the parent compound. In patients with a creatinine clearance of 40-60ml/min/1.73m^2 the recommended dose is 10 mg per day[14]. The agent should be avoided in patients with chronic renal failure or those receiving dialysis.

Theoretically, agents that utilize the same cationic transport mechanism in the renal tubule as amantadine may also inhibit memantine secretion. Possible agents implicated in this mechanism include cimetidine, ranitidine, hydrochlorothiazide, quinidine and triamterene. Careful monitoring should be employed if these agents are used concurrently.

Concomitant use of amantadine, ketamine and dextromethorphan should be avoided due to a theoretical additive effect at NMDA receptors.

Drug Interactions [15,16]

There are no documented in vivo interactions with memantine. Since this agent has little effect on the hepatic enzyme systems and is excreted unchanged renally, it is unlikely that an interaction will occur. Memantine has been given with a tubular excreted agent (hydrochlorothiazide/triamterene) with no change in memantine area under the curve as well as minimal change to the co-administered agent; however this was a limited trial in normal volunteers.

Clinical Trials

Efficacy Measures[17-21]

1. Alzheimer's Disease Assessment Scale (ADAS-Cog) – The ADAS-Cog is the cognitive portion of the Alzheimer's Disease Assessment Scale (ADAS). The ADAS has demonstrated validity and reliability in overall dysfunction and the cognitive and non-cognitive subscale of the test. It is an 11-item scale with scores ranging from 0 (no impairment) to 70 (very severe impairment). The average score of patients with mild to moderately severe AD is 15-25. On average, untreated patients with moderate AD decline 7 to 11 points per year while mild or severe patients may only decline 0 to 5 points per year. This difference in scale sensitivity to stage of disease is important to recognize when comparing different treatments in different populations. An improvement of 4 or more points is considered to be clinically meaningful.
2. Mini-Mental State Examination (MMSE) – The MMSE is a short test that quantifies cognitive impairment. Scores range from 0 to 30 with 0 implying severe impairment and 30 being the best possible score.
3. AD Cooperative Study-Activities of Daily Living Inventory (ADCS/ADL)- Is a rating scale which involves a 23 item assessment of ADL that is scored from 0(greatest impairment) to 52(no impairment). The ADCS/ADL-Sev version is adapted for nursing home use and in patients with severe impairment (MMSE< 10). This scale is scored form 0 to 78.
4. Global Deterioration Scale (GDS) -a 7-point global status rating scale used to stage patients based on magnitude of impairment based on cognitive and functional capacity. A score of 1-2

is considered normal with dementia severity worsening with increasing score. It may be more sensitive to mild and severe impairment.

5. Clinical Dementia Rating (CDR) - a global status rating used to assign a performance impairment rating based on six cognitive function categories including memory, orientation, judgment, problem solving, community affairs, home and hobbies, and self-care. It distinguishes mild (CDR 1.0), moderate (CDR 2.0) and severe (CDR 3.0) dementia. The term can also be seen described as CDR-SB ("sum of boxes" used to calculate score). The CDR has utility in describing the middle stages of AD. The scale is appropriate for assessing long-term clinical outcomes and has demonstrated validity. Reliability has been demonstrated with the CDR.
6. Sever Impairment Battery (SIB)-This is a 40 item test developed to assess cognitive function in severe dementia. The primary subscale assesses memory, orientation, language, attention, construction and visual-spatial ability. The scores range from 0(total impairment) to 100(no impairment). For untreated patients with a MMSE of 5-9 decline is approximately 3 per month and for untreated patients with a MMSE of 10-15 decline is roughly 2 per month.
7. Clinician's Interview Based Assessment of Change-Plus (CIBIC-Plus) – CIBIC-Plus is a global change rating scale. It is more appropriate for measuring clinical outcomes associated with treatment of 6 months or less duration than a global status rating. The patient and caregiver are interviewed separately. A seven-point scale is used for scoring the clinician's impression of change from baseline at each visit. One (1) represents marked improvement, 2=moderate improvement, 3= mild improvement, 4 = no change, 5=mild worsening, 6=moderate worsening and 7 is marked worsening.
8. Neuropsychiatric Inventory (NPI) - This scale is used to assess 12 aspects of behavior change including delusions, hallucinations, mood, agitation/aggression, euphoria, disinhibition, irritability/lability, apathy, anxiety, aberrant motor activity, nighttime behavior, and appetite and eating behavior. It is based on a clinician interview of the caregiver. Scores are derived by multiplying the frequency by the severity for each of the 10 items and range from 10 to 120 with 120 implying most frequent, severe behaviors. There is a nursing home version of the scale (NPI-NH).

There have been several controlled clinical trials of memantine in dementia patients.[24-27,32] However, these trials have several limitations, which may make their extrapolation to clinical use more difficult. The groups tested in the various trials have different and non-comparable histories and stages of dementia. Disease progression is dependendent on severity; if this factor is not well characterized there is difficulty in interpretation of benefit. Additionally, the trials have been conducted over short periods; the longest follow-up to date is 28 weeks. These limitations should be kept in mind as the results of the clinical trials for memantine in dementia are discussed.

The results of memantine therapy on patients with moderate to severe AD are summarized in **Table 1**. In addition to the significant changes in the primary outcomes of CIBIC plus and ADCS-ADLsev there was less agitation in the memantine treatment group.

Two trials have investigated the use of memantine in VaD. The results of these trials are summarized in **Table 2**. In regard to secondary outcomes of these trials, there was a significant improvement in MMSE from baseline to endpoint but the clinical benefit of this was not seen in the caregiver, provider or observational scales used. In addition, a post hoc analysis of these trials concluded that benefits of memantine might be more pronounced in certain subpopulations.[28]

In a trial that enrolled both patients with AD and those with vascular dementia who were institutionalized, Winblad and colleagues[27] demonstrated the effects of memantine in a population with baseline MMSE <10. At the 12-week endpoint, using Intention to treat analysis, memantine improved care dependence versus placebo as measured by Behavioral Rating Scale for Demented patients (BGP) and the CGI as rated by the

physician. There was no rating scale such as ADAS cog available at the time of the study so effects on cognition are more difficult to ascertain from the trial.

Tariot and colleagues recently published the results of combination therapy with memantine and a CI.[29,30] Patients included in this trial were community dwelling with an MMSE of 5-14. The effects of combination therapy versus therapy with a CI and placebo provided significant improvement on the scales measuring cognition, daily functioning, clinical global status and behavior. Refer to **Table 3**. Patients treated with CI/placebo demonstrated a progressive decline in these measures from baseline. It should be noted that no to minimal change was seen in 72% of the memantine/donepezil treatment group and in 62% of the placebo/donepezil treated group. This trial is the first to document an improvement in cognition from baseline and raises the possibility of combination therapy being able to stabilize or delay further declines in cognitive function.

A pharmacoeconomics evaluation of the Reisberg study has been conducted. [31] This trial was a prospective portion of the clinical outcomes study. Results were assessed via a baseline and follow up questionnaire. After controlling for baseline differences in the groups, the Resource Utilization in Dementia (RUD) scale was employed to measure the primary efficacy outcomes for patient and caregiver resource utilization. There was a significant difference between memantine and placebo in regards to caregiver time assessed over a two month period (difference 51.5 hr. per month, p=0.02), total caregiver cost (difference $823.77 per month p=0.03), direct non-medical costs (difference of $430.84 per month p=0.07), direct medical costs (placebo less than memantine p<0.01) and time to institutionalization at week 28 showed a trend to significance (p=0.052) by log rank testing. It should be noted that the cost data was positively skewed and that the standard deviations were large, indicating a large variability in the data.

Table 1. Memantine in moderate to severe Alzheimer's Disease

	Study design	N	Duration	Demographics	Inclusion	Primary Efficacy parameters	Tolerability	Outcomes At 28 weeks
Reisberg 2003[24]	DB, R, PC, PG	181	28 weeks	Mean age 76 yrs. Mean MMSE 7.9 Community dwelling	Moderate-severe AD by DSM-IV and NINDS-ADRDA criteria	CIBIC Plus, ADCS-ADLsev,	Frequency/severity of AE were similar in the two groups	Statistically significant difference in favor of memantine on CIBIC Plus (mean difference 0.3,p=0.06) and ADCS (mean difference –3.4, p= 0.003)

DB- double blind, R- randomized, PC, Placebo controlled, PG- parallel group
NINDS-ADRDA- National Institute of Neurological diseases and Stroke- Alzheimers Disease and Related Disorders Association.
DSM- Diagnostic and Disease Statistical Manual (of the American Psychiatric Association)
ADCS-ADL sev- adapted for severe dementia
AE- adverse event

Table 2. Memantine in vascular dementia

	Study design	N	Duration	Demographics	Inclusion	Primary Efficacy parameters	Tolerability	Outcomes at 28 weeks
Orgozo, 2002[25]	DB, R, PC, PG	388	28 weeks	Mean age 76.6 years MMSE 16.9 ADAS-Cog 20.6 Outpatient	Mild-moderate VaD (DSM III-R and NINDS ADRDA criteria)	ADAS-Cog CIBIC-Plus	Frequency and severity of AE were similar in the two groups	Difference in ADAS cog favored M. Other outcomes NS. Improvement in MMSE favored M (mean increase of 1.75 points vs 0.52 points for placebo
Wilcock, 2002[26]	DB, R, PC, PG	548	28 weeks	Mean age 77.2 years MMSE 17.5 ADAS-Cog 26.2 Outpatient	Mild-moderate VaD (DSM III-R and NINDS AIDRDA criteria)	ADAS-Cog CGI	Frequency and severity of AE were similar in the two groups	Difference in ADAS cog at week 28 significantly favored M. Other outcomes NS

DB- double blind, R- randomized, PC, Placebo controlled, PG- parallel group
NINDS-ADRDA- National Institute of Neurological diseases and Stroke- Alzheimers Disease and Related Disorders Association.
DSM- Diagnostic and Disease Statistical Manual (of the American Psychiatric Association)
ADCS-ADL sev- adapted for severe dementia
AE- adverse event
NS-non-significant
M-memantine

Table 3. Memantine in combination with donepezil

	Study design	N	Duration	Demographics	Inclusion	Primary Efficacy parameters	Tolerability	Outcomes At 24 weeks
Tariot, 2004[30]	DB, R, PC, PG	404	24 weeks	Mean age 75 yrs. Mean MMSE 10.1 Community dwelling	Moderate-severe AD by DSM-IV and NINDS-ADRDA criteria	SIB ADCS_ADL	Frequency/severity of AE were similar in the two groups	Statistically significant difference in favor of memantine on SIB, -2.4 vs 1.0 p<0.001 and ADCS-ADL, -3.3 vs –1.7 p=0.02 for placebo vs memantine respectively.

DB- double blind, R- randomized, PC, Placebo controlled, PG- parallel group
NINDS-ADRDA- National Institute of Neurological diseases and Stroke- Alzheimers Disease and Related Disorders Association.
DSM- Diagnostic and Disease Statistical Manual(of the American Psychiatric Association)
SIB- Severe Impairment Battery
ADCS-ADL- AD Cooperative Study-Activities of Daily Living Inventory
AE- adverse event

Acquisition Costs

There is currently no FSS pricing available for this agent. Memantine is not expected to be available until late January 2004. The projected average wholesale price for the agent is $139.50 for 60 tablets.

Conclusions

Memantine offers a unique approach to therapy from those agents currently available. In patients with moderate to severe AD, memantine demonstrated less functional and cognitive deterioration as measured by various scales. However, this difference was not apparent in the clinical impression of these changes. The data to date are from relatively short trials, 28 weeks in duration. Given the chronic and progressive

nature of the disease, longer trials will be needed to define the outcomes and benefits of this agent. In the treatment of patients with VaD, memantine therapy produced a significant change in cognition scales; however measures of activities of daily living, global scales and clinical impression scales were not significantly changed. The initial reports of combination therapy with a CI are positive but the true benefit of this approach remains to be determined.

The safety and tolerability profile of memantine would be of benefit in the AD population. Considering the prolonged half-life of this agent, development of a daily dosing schedule may be undertaken and proven efficacious. The lack of drug interactions with this agent may be of benefit in a population with co-morbid disease states requiring pharmacotherapy.

Recommendations

Memantine offers characteristics that are beneficial in a population being treated for AD. The data received thus far are interesting but need to be more complete. The published trials are too short to provide documentation of benefit and safety in a chronic disease group. There have been no comparative trials to date with the CIs , the accepted standard for AD therapy. Additionally, given the lack of efficacy in other disease groups (pain for example) the possible off label inappropriate use exists. The lack of agreement between rating scales and clinical impressions is of concern. While memantine may provide significant change on a number scale (i.e. MMSE) the relation of that scale to clinical benefit remains to be defined.

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