

Memantine: efficacy and safety in mild-to-severe Alzheimer's disease

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Abstract: Alzheimer's disease (AD) is the most common cause of dementia, accounting for 25 million cases worldwide. Until recently, the pharmacotherapy of AD was limited to the use of cholinesterase inhibitors (ChEIs) that are approved only for the mild to moderate stages of the illness. Memantine, an NMDA receptor antagonist has been found to be effective, both as monotherapy and in combination with donepezil, in the treatment of patients with moderate to severe stage AD. More recent studies have examined the role of memantine in the treatment of the mild to moderate stages of the disease, although the collective results of these studies remain inconclusive. Available pharmacoeconomic data indicate that treatment with memantine is cost-effective when compared with no treatment in patients with moderate to severe AD. Memantine treatment is predicted to be associated with lower costs of care, longer time to dependence and institutionalization, and gains in quality-adjusted life-years. In this article, we review the evidence for the use of memantine in patients with AD, ranging from the mild to severe stages of disease.

Keywords: Alzheimer's disease, memantine, NMDA antagonist, cholinesterase inhibitors

Introduction

Alzheimer's disease (AD) is the most common etiology of dementia, accounting for approximately 25 million cases worldwide (Wimo et al 2003). About 6.1% of the world's population over the age of 65 years is estimated to develop dementia (about 0.5% of the worldwide population). The number of new cases of dementia in 2000 was approximated at 4.6 million. In the United States population alone, there were about 4.5 million persons with AD (Hebert et al 2003). The cost of the disease to the individual and to society is immense. In the United States alone, the total cost of caring for patients with AD was calculated in 2000 to be over US\$100 billion annually (Johnson et al 2000). Age remains the number one risk factor for the development of AD, as evidenced by the sharp prevalence increase from 6.1% of the population ≥ 65 years of age to 40% of the population ≥ 85 years of age (Jorm 1991; Wimo et al 2003). As the world population ages, the number of people suffering from this disease is predicted to increase significantly. Forecasts indicate that the number of demented elderly will increase from the present number of 25 million to 63 million by 2030 (41 million in less developed regions) and to 114 million in 2050 (84 million in less developed regions) (Wimo et al 2003).

Recent reports have emphasized that AD often goes unrecognized and undiagnosed until later in the illness (Small et al 1997; Hebert et al 2003). Early diagnosis and treatment can reduce the disability due to the disease and prepare patients and their families for future challenges with the disease (Grossberg and Desau 2003). Until recently, the pharmacological options for the treatment of cognitive deficits in AD were limited to the use of the cholinesterase inhibitors (ChEIs) tacrine, donepezil, rivastigmine, and galantamine, which were all approved for mild to moderate stage AD (Cummings 2003). Data concerning the benefits of these drugs in the more advanced stages of the disease are limited. Moreover, the side-effect profile of the

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ChEIs – including gastrointestinal disturbances like nausea, vomiting, diarrhea and anorexia – restrict their use. Several other potential agents, including antioxidants, ginkgo biloba, non-steroidal anti-inflammatory agents (NSAIDs), lipid-lowering agents, hormones, chelating agents, growth factors, and anti-amyloid strategies, have not yet demonstrated efficacy for AD (Doraiswamy 2002). In this article, we review the evidence for the use of memantine hydrochloride, an NMDA receptor antagonist, in the treatment of AD.

Mechanisms of action and pharmacokinetics

During normal synaptic transmission the NMDA receptor is activated by the binding of glutamate, the major excitatory neurotransmitter in the central nervous system (CNS) (Lipton 2004). Depolarization of the postsynaptic neuron leads to removal of the magnesium ion blockade from the NMDA channel, allowing the influx of monovalent and divalent cations (Lipton 2004). The entry of calcium is critical for learning and memory formation by induction of long-term potentiation (LTP) (Danysz and Parsons 2003). However, excessive influx of calcium ions may result in excitotoxic cell damage. Excitotoxicity is defined as the excessive exposure of neurons to glutamate or overstimulation of its membrane receptors, leading to neuronal injury or death (Lipton 2004).

Memantine (1-amino-3, 5-dimethyladamantanate) is an adamantane derivative that blocks the NMDA receptor-associated ion channel similar to magnesium by binding to or near the magnesium-binding site (Lipton 2004). Memantine is an uncompetitive, low-affinity, open-channel blocker that enters the receptor channel preferentially when it is excessively open (Lipton 2004).

Equally important is the “off-rate” of memantine, which is relatively fast, resulting in low accumulation in the channel and minimal interference with normal synaptic transmission (Chen et al 1992; Danysz and Parsons 2003; Lipton 2004). Memantine is classified as an uncompetitive antagonist, as it needs prior activation of the NMDA receptor by glutamate before it can access the binding sites on the receptor. It also has lower affinity for the receptors than some other potent NMDA receptor channel blockers like phencyclidine (PCP), ketamine, and MK-801 (Rogawski and Wenk 2003). These factors may allow memantine to block channel activity induced by low, tonic levels of glutamate – an action that might contribute to symptomatic improvement and protect against weak excitotoxicity – while sparing synaptic

responses required for normal cognitive functioning and enhancing tolerability (Rogawski and Wenk 2003).

The putative neuroprotective effects of memantine have been studied in several rodent models. In a rat model of transient forebrain ischemia, memantine reduced cerebral infarct size and hippocampal cell loss in a dose-dependent manner (Seif el Nasr et al 1990). In a rat model of progressive functional neurodegeneration (bilateral clamping of the carotid arteries) memantine pre-treatment prevented neuronal necrosis and protected against NMDA-specific learning and memory deficiencies in the Morris water maze (Heim and Sontag 1995). Finally, chronic administration of memantine prevented the decline in cortical choline acetyltransferase activity associated with injection of NMDA into the nucleus basalis magnocellularis and attenuated reference memory deficits in the radial maze produced by entorhinal cortex lesions (Wenk et al 1997).

Memantine is well absorbed from the gastrointestinal tract after oral administration, and its absorption is unaffected by food (Forest Laboratories 2003). It reaches a maximum plasma concentration (C_{max}) after a single dose in 3–7 hours, and it has a plasma half-life of about 60–80 hours. The dose–plasma concentration relationship is linear in the therapeutic dose range of 10–40 mg daily (Forest Laboratories 2003). It is 45% protein bound and is partly metabolized by the liver. About 48% of the drug is excreted unchanged in the urine. The remainder of the drug is metabolized by the liver into three polar compounds that possess minimal NMDA receptor antagonist activity, ie, N-glucuronide conjugate, 6-hydroxy memantine, and 1-nitroso-deaminated memantine. A total of 74% of the administered dose is excreted as the sum of the parent drug and the N-glucuronide conjugate. Memantine is mainly excreted via the kidneys (74%) after undergoing active tubular secretion moderated by pH dependant tubular reabsorption. In elderly volunteers with reduced renal function, a significant correlation has been observed between creatinine clearance and total renal clearance of memantine, indicating that patients with severe renal disease may require lower dosages (see Dosing Schedule).

Memantine does not induce the cytochrome P450 isozymes CYP1A2, CYP2C9, CYP2E1, and CYP3A4/5 (Forest Laboratories 2003). Studies have shown that memantine produces minimal inhibition of CYP450 enzymes CYP1A2, CYP2A6, CYP2C9, CYP2D6, CYP2E1, and CYP3A4, indicating that no pharmacokinetic interactions with drugs metabolized by these enzymes are expected. The clearance of memantine is reduced by about

80% under alkaline urine conditions at pH 8, and hence alterations of urine pH towards the alkaline state may lead to an accumulation of the drug with a possible increase in adverse effects. Drugs that alkalize urine like carbonic anhydrase inhibitors and sodium bicarbonate may reduce renal elimination of memantine (Forest Laboratories 2003). The mean cerebrospinal fluid to plasma concentration for memantine is about 50% (Kornhuber and Quack 1995). No drug–drug interactions between memantine and ChEIs have been observed, and hence they can be used together safely without dose adjustment (Periclou et al 2004).

Memantine for moderate to severe AD

Memantine has been evaluated in moderate to severe AD patients in four major studies: 3 involving memantine monotherapy and 1 involving combination therapy with donepezil. The first was a trial conducted in 166 patients admitted to 6 nursing homes and a psychiatric hospital in

Latvia (Winblad and Poritis 1999). The three other trials were conducted in community dwelling subjects and involved samples of 252 subjects (Reisberg et al 2003), 350 subjects (van Dyck et al 2007), and 404 subjects (Tariot et al 2004). The efficacy results of these studies are summarized in Table 1 and the various rating scales utilized are detailed in Table 2.

Monotherapy studies

Winblad and Poritis study

This was a 12-week, placebo-controlled trial of memantine 10 mg daily, conducted in nursing home residents and psychiatric hospital patients. Men and women (N=166) between the ages of 60 and 80 years were included if they met DSM-III-R criteria for dementia (APA 1987). Further inclusion criteria were severity stages 5-7 of the Global Deterioration Scale (GDS) (Reisberg et al 1982), Mini-Mental State Examination (MMSE) (Folstein et al 1975) score of <10 points, duration of dementia >12 months, and

Table 1 Mean change on outcome measures in clinical trials of memantine

Study	Treatment arm	Subject sample	Outcome measures					
			CIBIC-Plus	CGIC	ADAS-Cog	SIB	ADCS-ADL	BGPcare
Moderate to severe AD								
Monotherapy studies								
Winblad and Poritis 1999	Memantine	82		3.21 ^c				-3.1 ^a
	Placebo	84		3.64				-1.1
Reisberg et al 2003	Memantine	126	4.5 ^a			-4.0 ^c	-3.1 ^b	
	Placebo	126	4.8			-10.1	-5.2	
van Dyck et al 2007	Memantine	178	4.3			-2.0	-2.0	0.5
	Placebo	172	4.6			-2.5	-2.7	1.4
Combination therapy studies								
Tariot et al 2004	Memantine	203	4.41 ^a			0.9 ^c	-2.0 ^b	0.8 ^c
	Placebo	201	4.66			-2.5	-3.4	2.3
Mild to moderate AD								
Monotherapy studies								
Peskind et al 2006	Memantine	201	4.2 ^b		-0.8 ^a			-2.9
	Placebo	201	4.5		1.1			-3.0
Combination therapy studies								
MEM-MD-12	Memantine	214	4.4		0.4			-2.9
	Placebo	213	4.4		1.1			-2.9

Notes: All values are from intent to treat, last observation carried forward analyses. Backchine et al (2005) study is omitted from this table, as mean change data are unavailable.

Differs from placebo group: ^ap<0.05, ^bp<0.01, ^cp<0.001

Abbreviations: CIBIC-Plus, Clinicians Interview Based Impression of Change with Caregiver Input (higher score indicates greater deterioration); CGIC, Clinical Global Impression of Change (higher score indicates greater deterioration); ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale (positive score indicates deterioration); SIB, Severe Impairment Battery (positive score indicates improvement); ADCS-ADL, Alzheimer's Disease Cooperative Study-Activities for Daily Living Inventory (positive score indicates improvement); BGPcare, Behavioral Rating Scale for Geriatric Patients care dependence subscore (positive score indicates deterioration).

Table 2 Common rating scales used in dementia studies

Scale	Reference	Assesses	Score range		Higher score indicates	Interviewee
			Low	High		
ADCS-ADL	Galasko et al 2005	Activities of daily living	0	78	Better ADL performance	Caregiver
ADAS-Cog	Rosen et al 1980	Cognition	0	70	Worse cognition	Patient
BGP	van der Kam and Hoeksma 1989	Cognition, function, and behavior	0	70	Worse functioning	Patient
CGI-C	Schneider et al 1997	Global change	1	7	Global worsening	Patient, Caregiver ^a
CIBIC-Plus	Schneider et al 1997	Global change	1	7	Global worsening	Patient, Caregiver
FAST	Sclan and Reisberg 1992	Global functioning	1	7	Poorer functioning	Patient, Caregiver
GDS	Reisberg et al 1982	Global functioning	1	7	Poorer functioning	Patient, Caregiver
MMSE	Folstein et al 1975	Cognition	0	30	Better cognition	Patient
NPI	Cummings et al 1994	Neuropsychiatric symptoms	0	144	Greater disturbance	Caregiver
SIB	Schmitt et al 1997	Cognition	0	100	Better cognition	Patient

^aCaregiver interview is not required for CGI-C

Abbreviations: ADCS-ADL, Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory; ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive subscale; BGP, Behavioral Rating Scale for Geriatric Patients; CGI-C, Clinicians Global Impression of Change; CIBIC-Plus, Clinician's Interview Based Impression of Change, with Caregiver input; FAST, Functional Assessment Staging Scale; GDS, Global Deterioration Scale; MMSE, Mini Mental State Examination; NPI, Neuropsychiatric Inventory; SIB, Severe Impairment Battery.

the absence of CNS-active drug use within 14 days prior to the start of the trial. Primary endpoints were the Clinical Global Impression of Change (CGI-C) (Schneider et al 1997) rated by the study physician, and the Behavioral Rating Scale for Geriatric Patients (BGP), subscore "care dependence", rated by the nursing staff (van der Kam and Hoeksma 1989). Secondary endpoints included the modified D-Scale (Arnold/Ferm) (Ferm 1974).

The intent to treat (ITT) sample comprised 166 patients of which 151 completed the protocol. At 12-week ITT endpoint analysis, 82 subjects had received memantine, 10 mg daily, and 84 had received placebo. Dementia classification was 49% of the Alzheimer type and 51% of the vascular type, based on CT scan and Hachinski ischemia score (Rosen et al 1980). A positive response (ie, improvement) in the CGI-C was seen in 73% of memantine-treated vs 45% of placebo-treated patients (stratified Wilcoxon $p < 0.001$), independent of the etiology of dementia. Twenty-one per cent of the patients were rated as much improved in the memantine group compared with 11% in the placebo group, again independent of dementia etiology. As shown in Table 1, the mean CGI-C score was significantly better for memantine-treated (3.21) than for placebo-treated (3.64) patients ($p < 0.001$). The results in the

BGP subscore "care dependence" were 3.1 points improvement under memantine and 1.1 points under placebo ($p = 0.016$). Responder analyses showed that for the CGI-C, 76% of memantine-treated patients were classified as responders (ie, showing any improvement) compared with 44.7% in the placebo group. On the BGP "care dependence" subscore, by contrast, 65.3% of patients were classified as responders compared with 39.5% in the placebo group. Coincident response in the two primary outcome measures was observed in 61.3% (memantine) vs 31.6% (placebo). Secondary endpoint analysis of the D-Scale assessing basic activities of daily living (ADL) functions indicated that for every item, response rates were greater for memantine than placebo, reaching statistical significance ($p < 0.05$) in 8 of 16 items.

Reisberg et al study

The first pivotal trial of memantine in the United States was a 28-week, placebo-controlled outpatient trial of memantine 10 mg twice daily. It enrolled subjects with moderate to severe AD who were aged 50 years or more, living in the community, and had a diagnosis of probable AD based on US National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related

Disorders Association (NINCDS-ADRDA) criteria (McKhann et al 1984) and Diagnostic and Statistical Manual of Mental Disorders (DSM) 4th edition (APA 1994). All subjects also had a MMSE (Folstein et al 1975) score between 3 and 14 at baseline. Efficacy assessments were performed at baseline, 4 weeks, 12 weeks, and at 28 weeks (or earlier termination). Primary outcome measures included the Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC-Plus) (Schneider et al 1997), and the modified 19-item Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory (ADCS-ADL₁₉) (Galasko et al 2005) at 28 weeks compared with baseline.

The CIBIC-Plus (Schneider et al 1997) assessment was completed by experienced clinicians who did not know the results of any of the other assessments and were unaware of any adverse events (AEs) reported by the participants. Although memantine lacked a statistically significant effect on the CIBIC-Plus in the Last Observation Carried Forward (LOCF) analysis (4.5 vs 4.8, $p=0.06$, Table 1), a significant benefit was observed in the analysis of patients who completed the 28-week study (4.4 vs 4.7, $p=0.03$). Scores on the ADCS-ADL₁₉ were similar in both groups at baseline, but at 28 weeks, patients in the memantine group had significantly better outcome than patients in the placebo group in both the LOCF (-3.1 vs -5.2 , $p=0.02$, Table 1) and completers (-2.5 vs -5.9 , $p=0.003$) analyses. Beneficial effects of memantine were also reported for three of the other outcome measures using LOCF analysis: the Severe Impairment Battery (SIB) (Schmitt et al 1997) (-4.0 vs -10.1 , $p<0.001$, Table 1); the Functional Assessment Staging (FAST) scale (Sclan and Reisberg 1992) (0.2 vs 0.6 , $p=0.02$); and the Resource Utilisation in Dementia (RUD) instrument (which assesses caregiver burden and economic data). Response rate (predefined as improvement or no deterioration in the CIBIC-Plus and either the ADCS-ADL₁₉ or SIB) was higher in the memantine group (29%) than in the placebo group (10%; $p<0.001$). The changes in the MMSE (-0.5 vs -1.2 , $p=0.18$) and GDS (0.1 vs 0.2 , $p=0.11$) did not differ significantly between the treatment groups. In this trial, no significant differences were observed between memantine and placebo in neuropsychiatric symptoms, as assessed by the Neuropsychiatric Inventory (NPI) (Cummings et al 1994) total change score (0.5 vs 3.8 , $p=0.33$).

Following the initial report of Reisberg et al (2003) secondary analyses have appeared that have shed additional light on this study. A post hoc analysis of ADCS-ADL₁₉ data by Rive et al (2004) showed that memantine-treated

patients were 3 times more likely (odds ratio [OR] = 3.03; 95% confidence intervals [CI] = [1.38, 6.66], $p=0.006$) to remain autonomous after 28 weeks, even after controlling for autonomy and severity at baseline. This finding was confirmed by LOCF (OR = 2.31; 95% CI = [1.12, 4.76], $p=0.023$) and completers (OR = 2.88; 95% CI = [1.15, 7.32], $p=0.024$) analyses. Dependent patients had significantly longer disease duration, poorer cognition, more behavioral alterations, and higher total societal costs compared with autonomous patients. By contrast, Livingston and Katona (2004) employed a number needed to treat (NNT, the number of subjects who need to be treated for one subject to achieve a particular outcome) analysis of several outcome measures from this study. They showed that memantine (NNT 6-8) compared favorably with ChEIs (NNT 4-13) for favorable response on the CIBIC-Plus, SIB, or ADCS-ADL₁₉ (Livingston and Katona 2004).

van Dyck et al study

A more recent study of memantine monotherapy in subjects with moderate to severe AD (MEM-MD-01; website summary available at www.forestclinicaltrials.com) (van Dyck et al 2007) failed to demonstrate a statistically significant benefit of memantine treatment compared with placebo. This was a 24-week, randomized, double-blind, placebo-controlled trial of memantine 10mg twice daily conducted in 350 outpatients with moderate to severe AD recruited from 37 US centers. Inclusion criteria were: age of 50 years or older, diagnosis of probable AD according to NINCDS-ADRDA criteria (McKhann et al 1984), and MMSE (Folstein et al 1975) score between 5 and 14. Primary efficacy variables were the SIB (Schmitt et al 1997) and the ADCS-ADL₁₉ (Galasko et al 2005). Secondary efficacy variables included the CIBIC-Plus (Schneider et al 1997), NPI (Cummings et al 1994), FAST (Sclan and Reisberg 1992), BGP (van der Kam and Hoeksma 1989), and BGP care dependence subscale. The central efficacy analyses were conducted using the LOCF approach and compared change from baseline between memantine and placebo groups for the SIB, BGP, ADCS-ADL₁₉, FAST, and NPI using a 2-way analysis of covariance (ANCOVA), with treatment group and center as main effects, and baseline as covariate (least squares means; note that unadjusted within-group mean changes are reported on the website summary (www.forestclinicaltrials.com)). For the CIBIC-Plus, the Cochran-Mantel-Haenszel (CMH) test using modified Ridit scores (Van Elteren test) controlling for study center was used to compare distributions between groups.

Prospectively defined analyses failed to demonstrate a statistically significant benefit of memantine treatment compared with placebo on the SIB at Week 24 end point (-2.0 vs -2.5 , $p=0.62$), although a significant advantage was observed for memantine at Weeks 12 and 18. The ADCS-ADL₁₉ did not differ significantly between groups at Week 24 endpoint (-2.0 vs -2.7 , $p=0.28$) or in any other analysis. CIBIC-Plus scores did not significantly favor memantine at Week 24 (4.3 vs 4.6 , $p=0.18$) despite a significant advantage for memantine at Weeks 12 and 18. Other secondary outcome measures showed no significant treatment differences. Due to violations of normality assumptions for the SIB and ADCS-ADL₁₉, post hoc non-parametric analyses were performed; statistically significant benefit of memantine over placebo was demonstrated for the SIB at Week 24, but not for the ADCS-ADL₁₉ (van Dyck et al 2007).

The discrepant results in the study of van Dyck et al (2003) compared with those of Reisberg et al (2003) may be attributable to methodological or subject differences; however, variations in protocol design were minimal. The study of van Dyck et al (2007) was of slightly shorter duration than the trial by Reisberg et al (2003) (24 weeks vs 28 weeks), but was otherwise of similar design. The subject population of van Dyck et al (2007) compared with that of Reisberg et al (2003) was somewhat older (78.2 years vs 76.1 years) and contained a higher percentage of women (71.4% vs 67.5%) and a lower percentage of white participants (80.9% vs 90.1%). In addition, 62.6% of patients in van Dyck et al (2007) had previously been treated with ChEIs, compared with 31.3% in the Reisberg et al (2003) study. However, in the study of van Dyck et al (2007), post hoc analyses of potentially confounding covariates (age, prior ChEI use) did not substantially alter the results.

Combination therapy studies

The established efficacy of ChEIs in AD (Cummings 2003) naturally raised the question of whether memantine would also provide clinical benefit for moderate to severe stage patients already treated with one of these drugs. In vitro studies have demonstrated that memantine does not diminish the cholinesterase inhibition of ChEIs suggesting the possibility of using them in conjunction (Hartmann and Mobius 2003; Periclou et al; 2004, Yao et al 2005). A "combination therapy" study of memantine and the ChEI donepezil has also recently been conducted.

Tariot et al study

This study involved 404 subjects with probable AD who had received stable doses of donepezil for at least 3 months who were randomized to receive memantine 10 mg twice daily or placebo. This 24-week study included subjects over the age of 50 years and with MMSE (Folstein et al 1975) scores between 5 and 14 and was conducted at 37 US sites. Subjects who were randomized to memantine treatment were titrated in 5 mg weekly increments from a starting dose of 5 mg daily to 10 mg twice daily. Cognitive, functional, and global outcome measures were obtained at baseline and at the end of weeks 4, 8, 12, 18, and 24. The primary efficacy measures were the change from baseline on the SIB (Schmitt et al 1997) and the ADCS-ADL₁₉ (Galasko et al 2005). Secondary outcome measures included the CIBIC-Plus (Schneider et al 1997), the NPI (Cummings et al 1994), and the BGP (van der Kam and Hoeksma 1989).

Analyses were conducted using the LOCF approach. Subjects treated with memantine had statistically significant benefits on the SIB (0.9 vs -2.5 , $p<0.001$) and ADCS-ADL₁₉ (-2.0 vs -3.4 , $p=0.03$) compared with placebo (Table 1). Post hoc analyses of subjects completing the protocol also showed that patients treated with memantine had statistically significant benefits on the SIB (1.0 vs -2.4 , $p<0.001$) and ADCS-ADL₁₉ (-1.7 vs -3.3 , $p=0.02$). On secondary measures, the CIBIC-Plus score was significantly better in the memantine group (4.41 vs 4.66 , $p=0.03$, Table 1) compared with placebo. Overall, 55% of the subjects in the memantine group were rated as unchanged or improved on the CIBIC-Plus compared to 45% in the placebo group. The total NPI change score was also lower in the memantine group in both the LOCF (-0.1 vs 3.7 , $p=0.002$) and completers (-0.5 vs 2.9 , $p=0.01$) analyses. On the BGP care dependency subscale statistically significant improvement was seen in the memantine group in the LOCF (0.8 vs 2.3 , $p=0.001$, Table 1) and completers (0.6 vs 2.2 , $p=0.001$) analyses.

A recent post hoc analysis of the effects of memantine on the NPI data in the studies conducted by Reisberg et al (2003) and Tariot et al (2004) showed that the change in NPI total scores at endpoint was consistently in favor of memantine treatment, reaching statistical significance in the Tariot et al combination study ($p=0.002$) (Gauthier et al 2005). Memantine treatment showed a significant beneficial effect in comparison to placebo in the NPI agitation/aggression subscale in both studies ($p=0.008$; $p=0.001$). A dichotomized analysis of the Reisberg et al (2003) monotherapy study showed that there was significantly less

agitation/aggression emerging in the memantine-treated group compared to placebo ($p=0.003$). Factor analysis demonstrated that hyperactivity accounted for 27% of the data variance.

Memantine for mild to moderate AD

Memantine has been evaluated in mild to moderate AD patients in 3 major studies: 2 involving memantine monotherapy, and 1 involving combination therapy with ChEIs. All of these trials were conducted in community-dwelling subjects and included samples of 403 subjects (Peskind et al 2006), 318 subjects (Bakchine et al 2005), and 433 subjects (Mem-MD-12; www.forestclinicaltrials.com). The efficacy results of these studies (except Bakchine et al (2005), for which mean change data are unavailable) are summarized in Table 1 and the various rating scales utilized are detailed in Table 2.

Monotherapy studies

Peskind et al study

A study of memantine monotherapy in subjects with mild to moderate AD has recently been reported by Peskind et al (2006). This was a randomized, double-blind, placebo-controlled trial of memantine 10 mg twice daily, in which 403 community-dwelling subjects were followed for 24 weeks. This trial included male and female patients 50 years or older, who had the diagnosis of probable AD by the NINCDS-ADRDA criteria (McKhann et al 1984), and MMSE (Folstein et al 1975) scores between 10 and 22 (inclusive). Primary outcome measures were the CIBIC-Plus (Schneider et al 1997) and Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog) (Rosen et al 1984). Changes from baseline on the primary end points of CIBIC-Plus (4.2 vs 4.5, $p<0.004$), ADAS-Cog (-0.8 vs 1.1 , $p<0.003$) and NPI (-1.4 vs 2.1 , $p=0.01$) using the LOCF method favored memantine compared with placebo (see Table 1). Scores on the ADCS-ADL₂₃ (a version of the ADCS-ADL validated for mild to moderate stage AD patients), did not favor memantine compared to the placebo group (-2.9 vs -3.0 , $p=0.89$).

Bakchine et al study

A second study of memantine monotherapy in mild to moderate AD patients has been conducted in Europe and presented in abstract form (Bakchine et al 2005). Subjects were included in the study, if they were 50 years or older, had a diagnosis of probable AD according to NINCDS-

ADRDA (McKhann et al 1984) and DSM-IV-TR criteria, a MMSE (Folstein et al 1975) score between 11 and 23, and a Modified Hachinski Ischemia Score (Rosen et al 1980) of ≤ 4 . Subjects in this study were randomized to receive either memantine 20 mg daily or placebo in a 2:1 ratio. Of the 318 patients randomized to and treated with memantine, 85% completed the study, compared with 91% of the 152 patients randomized to the placebo group. In this 24-week study, on the ADAS-Cog (Rosen et al 1984) memantine-treated patients showed statistically significant improvement relative to placebo treated patients at weeks 12 ($p=0.01$) and 18 ($p=0.016$) but only nonsignificant numerical superiority at week 24 endpoint ($p=0.156$). On the CIBIC-Plus (Schneider et al 1997) memantine demonstrated statistically significant superiority over placebo at weeks 12 ($p=0.033$) and 18 ($p=0.012$) but only numerical superiority at week 24 endpoint ($p=0.523$).

Interestingly, the authors also pooled data from this study (Bakchine et al 2005) and the US study by Peskind et al (2006) and conducted a post hoc analysis of the datasets. When using the protocol specified LOCF analysis, they found that at week 24 there was a 1.9-point difference on the ADAS-Cog ($p=0.003$) and 0.31-point difference on the CIBIC-Plus ($p=0.004$). A statistically significant separation of memantine from placebo was observed on both scales from week 12 onwards. The authors concluded that based on the dual responder criteria, a numerically greater proportion of memantine-treated patients responded at every assessment with statistical significance being met at Weeks 12 ($p=0.001$), 18 ($p=0.001$), and 24 ($p=0.015$) (Bakchine et al 2005). Despite meeting statistical significance, these effect sizes are smaller than those reported for approved ChEIs in patients with mild to moderate AD, and their clinical significance remains to be established.

Combination therapy studies

MEM-MD-12 Study

One "combination therapy" study of memantine has thus far been conducted in mild to moderate stage AD patients already stabilized on ChEIs (Mem-MD-12; www.forestclinicaltrials.com). In a randomized, double-blind, placebo-controlled trial evaluating memantine in outpatients with AD, 216 subjects were randomized to memantine and 217 to placebo. Subjects were eligible for participation in the study, if they were 50 years of age or older, had a diagnosis of probable AD according to NINCDS-ADRDA criteria (McKhann et al 1984) and a MMSE (Folstein et al 1975) score between 10 and 22 inclusive. Eligible patients

must have received ongoing therapy with donepezil, rivastigmine, or galantamine for at least 6 months with a stable dose for 3 months prior to randomization. All patients had to continue to receive ChEI therapy at a stable dose for the duration of the study. The primary efficacy parameters were the change from baseline in the total ADAS-Cog (Rosen et al 1984) and CIBIC-Plus (Schneider et al 1997) rating at Week 24 using the LOCF approach. A 2-way ANCOVA model with treatment group and study center as factors and baseline score as covariate was used. 89.4% of the subjects in the memantine/ChEI group completed the study compared with 88.4% in the placebo/ChEI group. The change in ADAS-Cog at Week 24 compared with baseline was 0.4 ± 0.4 for the memantine/ChEI group compared with 1.1 ± 0.4 ($p=0.184$) in the placebo/ChEI group. On the CIBIC-Plus, the scores at Week 24 were identical in both groups at 4.4 ± 0.1 ($p=0.843$). There was no statistically significant difference between the two groups at Week 24 in any of the secondary efficacy parameters, including ADCS-ADL23 (-2.9 ± 0.5 vs -2.9 ± 0.6), MMSE (-0.3 ± 0.2 vs -0.7 ± 0.2) or change in NPI total score (1.1 ± 0.8 vs 0.6 ± 0.7) (www.forestclinicaltrials.com).

Limitations of memantine studies

A potential limitation common to all previous memantine studies contained in this review is the use of LOCF as a means of imputing missing data. Although a convenient and acceptable way of ensuring maximal use of trial data, the LOCF method may introduce biases, including favoring the treatment group with the higher drop out rate in a deteriorating illness. Several alternative statistical methods have emerged for dealing with missing data including, random regression, multiple imputation, and generalized estimating equations (GEE) (Zeger and Liang 1986). The Generalized Estimating Equations (GEE) approach, an adaptation of generalized linear modeling (Zeger and Liang 1986), is particularly promising, as it takes into account correlation between repeated observations on individual subjects that occurs when subjects are evaluated with the same outcome measures over time.

A recent post hoc responder analysis of the Tariot et al study (Tariot et al 2004) has been undertaken in which missing data were imputed using the GEE approach and treatment response was evaluated using three sets of responder criteria (van Dyck et al 2006). The results of this study showed that when treatment response required cognitive improvement relative to baseline, memantine yielded higher response rates than placebo. When treatment

response was alternatively defined as stabilization of individual outcomes, memantine resulted in significantly higher response rates than placebo for all outcomes. More conservative definitions of response that required simultaneous stabilization on multiple outcome measures again favored memantine treatment for 6 of 10 combinatorial definitions. These results suggest that when an alternative method (to LOCF) is used to impute missing data, memantine treatment is still associated with favorable treatment response (improvement and stabilization of symptoms, across multiple outcomes) (van Dyck et al 2006).

Another limitation pertains to the design of the available combination therapy studies. Combination studies of memantine with ChEIs have thus far compared a memantine/ChEI group with a placebo/ChEI group. The lack of placebo only and memantine only arms in these studies limits the interpretability of the results, as the efficacy of the individual drugs, their combination, and placebo cannot simultaneously be compared. In a recent commentary, Fox et al (2006) have concluded that the available data do not justify the use of combination therapy.

Safety and tolerability

In the trials detailed in this review, memantine has shown excellent safety and tolerability, with a frequency of adverse events (AEs) similar to placebo. In the Winblad and Poritis study in institutionalized patients (Winblad and Poritis 1999), 22% of the memantine-treated subjects had AEs compared with 21% of placebo-treated subjects. For the six outpatient trials of memantine reported in this review (Reisberg et al 2003; Tariot et al 2004; Bakchine et al 2005; Peskind et al 2006; van Dyck et al 2007) (and the MemMD-12; www.forestclinicaltrials.com) overall treatment-emergent AEs are summarized in Table 3. In the two published studies of moderate to severe stage AD by Reisberg et al, and Tariot et al, subjects in the memantine groups did not experience significantly more AEs than subjects taking placebo (84% vs 87%, and 78% vs 72%, respectively) (Reisberg et al 2003; Tariot et al 2004). Most AEs were rated as mild to moderate and unrelated to study medication. In the Reisberg et al trial, subjects on placebo had a higher incidence of agitation (32% vs 18%) and urinary tract infection (6% vs 2%) compared with the memantine-treated patients. In the Tariot et al study, AEs that occurred in >5% of the memantine group and with an incidence at least twice that of the placebo group were headache (6.4% vs 2.5%, $p=0.09$), and confusion (7.9% vs

Table 3 Treatment-emergent adverse events in outpatient trials of memantine

Adverse event	Moderate to severe AD											
	Reisberg et al 2003				van Dyck et al 2007				Tariot et al 2004			
	Memantine (n=126)		Placebo (n=126)		Memantine (n=178)		Placebo (n=172)		Memantine (n=202)		Placebo (n=201)	
	n	%	n	%	n	%	n	%	n	%	n	%
Agitation	23	18.3%	40	31.7%	16	9.0%	24	14.0%	19	9.4%	24	11.9%
Accidental injury					10	5.6%	13	7.6%	10	5.0%	16	8.0%
Fall					10	5.6%	17	9.9%	15	7.4%	14	7.0%
Dizziness					12	6.7%	11	6.4%	14	6.9%	16	8.0%
Influenza-like symptoms					10	5.6%	8	4.7%	15	7.4%	13	6.5%
Urinary tract infection	7	5.6%	17	13.5%	9	5.1%	9	5.2%	12	5.9%	10	5.0%
Headache					3	1.7%	11	6.4%	13	6.4%	5	2.5%
Diarrhea	12	9.5%	10	7.9%	10	5.6%	8	4.7%				
Confusion					9	5.1%	8	4.7%	16	7.9%	4	2.0%
Insomnia	13	10.3%	10	7.9%	4	2.2%	9	5.2%				
Urinary incontinence	14	11.1%	14	11.1%					11	5.4%	6	3.0%
Depression					9	5.1%	5	2.9%				
Upper respiratory infection									10	5.0%	13	6.5%
Peripheral edema					12	6.7%	8	4.7%	9	4.5%	17	8.5%
Hypertension					14	7.9%	4	2.3%				
Constipation					11	6.2%	8	4.7%				
Abnormal gait												
Anxiety					10	5.6%	6	3.5%				
Rhinitis												
Somnolence									4	2.0%	10	5.0%
Fecal incontinence												
Back pain												

Notes: Adverse events were reported, if they occurred in $\geq 10\%$ (Reisberg et al), $\geq 5\%$ (van Dyck et al, Peskind et al, Tariot et al, Mem-MD-12), or $\geq 4\%$ (Bakchine et al) of either treatment group.

Table 3 Continued

Adverse event	Mild to moderate AD											
	Peskind et al 2006				Bakchine et al 2005				Mem-MD-12			
	Memantine (n=201)		Placebo (n=202)		Memantine (n=318)		Placebo (n=152)		Memantine (n=217)		Placebo (n=216)	
	n	%	n	%	n	%	n	%	n	%	n	%
Agitation	15	7.5%	12	5.9%	5	1.6%	7	4.6%	17	7.8%	17	7.9%
Accidental injury	12	6.0%	11	5.4%	16	5.0%	8	5.3%	20	9.2%	16	7.4%
Fall	15	7.5%	15	7.4%	17	5.3%	6	3.9%	22	10.1%	15	6.9%
Dizziness	10	5.0%	9	4.5%	17	5.3%	6	3.9%	16	7.4%	16	7.4%
Influenza-like symptoms	14	7.0%	13	6.4%					15	6.9%	12	5.6%
Urinary tract infection	13	6.5%	9	4.5%	18	5.7%	3	2.0%	9	4.1%	9	4.2%
Headache									9	4.1%	9	4.2%
Diarrhea									12	5.5%	14	6.5%
Confusion	10	5.0%	7	3.5%					12	5.5%	9	4.2%
Insomnia									10	4.6%	10	4.6%
Urinary incontinence												
Depression	4	2.0%	10	5.0%					14	6.5%	15	6.9%
Upper respiratory infection	4	2.0%	12	5.9%					12	5.5%	6	2.8%
Peripheral edema												
Hypertension	9	4.5%	11	5.4%								
Constipation												
Abnormal gait												
Anxiety												
Rhinitis					14	4.4%	7	4.6%				
Somnolence	14	7.0%	2	1.0%								
Fecal incontinence												
Back pain									6	2.8%	9	4.2%

Notes: Adverse events were reported, if they occurred in $\geq 10\%$ (Reisberg et al), $\geq 5\%$ (van Dyck et al, Peskind et al, Tariot et al, Mem-MD-12), or $\geq 4\%$ (Bakchine et al) of either treatment group.

2%, $p=0.01$) (Tariot et al 2004). Conversely, diarrhea (8.5% vs 4.5%) and fecal incontinence (5% vs 2%) were more commonly seen in the placebo-treated group (Tariot et al 2004).

In both the Reisberg et al and Tariot et al studies, premature discontinuations from the study due to AEs were actually more common in the placebo groups (Reisberg et al: 17% vs 10%; Tariot et al: 12% vs 7%) than in the memantine groups. In the Reisberg et al study the AE most often associated with premature discontinuation was agitation, resulting in discontinuation in 7% of placebo-treated patients, compared with 5% of memantine-treated patients (Reisberg et al 2003). By contrast, in the Tariot et al study the AE most often associated with premature discontinuation was confusion, resulting in discontinuation in 1.5% of placebo-treated patients, compared to 2% of memantine treated patients (Tariot et al 2004).

In the study of van Dyck et al (MEM-MD-01) (2007), memantine was well tolerated with similar rates of treatment emergent AEs in the memantine (73.6%) and placebo (72.7%) groups. The only AE that occurred in 5% or more of the memantine group, and with an incidence at least twice that of the placebo group, was hypertension (7.9% vs 2.3%, respectively). AEs that occurred in 5% or more of the placebo group, and with an incidence at least twice that of the memantine group, were insomnia (5.2% vs 2.2%, respectively) and headache (6.4% vs 1.7, respectively). There was less agitation reported in the memantine group than the placebo group (9.0% vs 14.0%, respectively). A similar percentage of participants in both groups discontinued the study prematurely due to AEs (placebo, 13.4% vs memantine, 12.4%). The AE most often associated with discontinuation was agitation, which occurred in 3.5% of placebo-treated patients and 1.7% of memantine-treated patients.

In the study by Peskind et al (2006), AEs occurred in 71% and 74% of the memantine and placebo groups, respectively. The only AE that occurred in 5% or more of the memantine group, and with an incidence at least twice that of the placebo group, was somnolence (7.0% vs 1.0%) group, whereas subjects treated with placebo were more likely to develop depression (5.0% vs 2.0%) and upper respiratory tract infection (6.0% vs 2.0%) (Peskind et al 2006).

In the Bakchine et al study (2005), 56% of the memantine-treated patients had treatment emergent side-effects compared with 52.6% patients on placebo. The only AE that occurred in 5% or more of the memantine group,

and with an incidence at least twice that of the placebo group, was headache (5.7% vs 2.0%). Agitation (4.6% vs 1.6%) was slightly more common in the placebo group.

In the MEM-MD-12 study, 10.6% of the subjects withdrew in the memantine/ChEI group compared with 11.6% in the placebo/ChEI group. The reason for withdrawal in the two groups due to AEs was (6.0% vs 7.9%). Treatment-emergent AEs were seen in 79.7% of the memantine/ChEI group compared with the 77.8% of the placebo/ChEI group. No AEs occurred in 5% or more of the memantine/ChEI group, and with an incidence at least twice that of the placebo/ChEI group (www.forestclinicaltrials.com).

Serious adverse events (SAEs) have been very uncommon across all memantine studies. In the study by Winblad and Poritis (1999), 5% of the memantine subjects had SAEs compared with 6% in the placebo group. One patient died before randomization, whereas 4 patients died in each randomized treatment arm (memantine and placebo). For all SAEs, the causal relationship to study medication was rated as "unlikely" by the investigators. In the study by Reisberg et al (2003), SAEs were reported in 13% of subjects receiving memantine compared with 18% receiving placebo. There were 7 deaths, 2 of which occurred in the memantine group. Most SAEs, including all of the deaths, were considered to be unrelated to study medication. No clinically relevant changes in vital signs, laboratory data, or electrocardiography measurements were reported in any of the studies. In the study of van Dyck et al (MEM-MD-01) (2007), SAEs were less common in the memantine group (14.6% vs 16.9%) compared with placebo. Five subjects in the memantine group had fatal SAEs compared with 3 fatal SAEs in the placebo group. The investigators concluded that these SAEs were not related to the study drug (van Dyck et al 2007). In the study of Peskind et al (2006) SAEs occurred in 10% of the participants in each treatment group. Overall the type and incidence of SAEs were similar between groups. One participant death occurred in each group during the trial, neither considered treatment-related by the investigators (Peskind et al 2006). In the Mem-MD-12 study there were a total of 3 fatal SAEs in the memantine/ChEI group compared with 2 in the placebo/ChEI group, but they were determined to be unrelated to the trial drugs (www.forestclinicaltrials.com).

Dosing schedule

In adult and elderly patients the recommended maintenance dose of memantine is 20 mg daily, administered as 10 mg twice daily (Forest Laboratories 2003). The recommended

starting dose for memantine is 5 mg daily and the dosage titration is by 5 mg daily in weekly increments to 10 mg twice daily by Week 4. In subjects with impaired creatinine clearance (5–29 mL/min) a target dose of 5 mg BID is recommended (Forest Laboratories 2003). However, a new study conducted in patients with moderate to severe AD has shown that once-daily dosing of memantine at 20 mg was as well tolerated as the twice-daily dosing (Jones et al 2005).

Memantine in clinical practice

Memantine was first developed in Europe in the 1970s, but its action at NMDA receptors was not recognized until the late 1980s (Parsons et al 1999). It was subsequently registered in Germany in 1989 for the treatment of cerebral ischemia and AD. Since then, based on studies including those detailed in this review (Winblad and Poritis 1999; Reisberg et al 2003; Tariot et al 2004), it has been approved for use in the United States in patients with moderate to severe AD and in Europe for patients with moderately severe to severe AD. Moreover, based in part on the study of Peskind et al (2006), applications have been made to the regulatory authorities in Europe and in the United States to expand its use to mild to moderate AD (Forest Laboratories 2004; Lundbeck Pharmaceuticals 2004). Although the United States Food and Drug Administration (FDA) has issued a non-approvable letter for this expanded indication, the matter remains under discussion (Forest Laboratories 2005). Data supporting the use of ChEIs in more advanced stages of AD are limited. In these severe patients, the use of memantine may therefore become even more important.

Although memantine is approved only for AD, two double-blind studies have suggested possible beneficial effects of memantine in patients with vascular dementia (Orgogozo et al 2002; Wilcock et al 2002). A pooled analysis of these studies further suggested that memantine may be more effective in subjects with small-vessel disease (white matter lesions and or lacunae) (Mobius and Stoffler 2002). Given that 40%–50% of patients with AD have these vascular changes in the brain, these findings are encouraging.

Cost effectiveness

Despite the accumulated data on the beneficial effects of memantine in patients with AD, a preliminary evaluation by The National Institute for Clinical Excellence (NICE) in the United Kingdom (April 2006) has concluded that “on

the basis of current evidence on clinical effectiveness memantine could not reasonably be considered a cost-effective therapy for moderately severe to severe Alzheimer’s disease” (www.nice.org.uk/, last accessed 25 April 2006). This was in contrast to the NICE conclusion regarding ChEIs that “the resulting estimates of cost effectiveness could be considered sufficiently acceptable to allow the prescribing of AChE inhibitors for people with Alzheimer’s disease and moderate cognitive impairment (MMSE scores between 10 and 20)” (www.nice.org.uk/, last accessed 25 April 2006).”

However, a recent review of multinational pharmaco-economic data concluded that the limited available data suggest the cost-effectiveness of memantine treatment when compared with no treatment in patients with moderate to severe AD (Plosker and Lyseng-Williamson 2005). This conclusion was further supported by a Swedish study showing that, compared with no treatment, memantine treatment was predicted to be associated with lower costs of care, longer time to dependence and institutionalization, and gains in quality-adjusted life-years (Jonsson 2005). The author concluded that from a public payer’s perspective, the observed effect of memantine on cognitive and physical function is predicted to translate into economic benefits that offset the added treatment cost.

Conclusion

In conclusion, well-designed studies have demonstrated that memantine is safe and effective in modifying the progression of cognitive, functional and global outcomes in patients with moderate to severe AD, either as monotherapy or in combination with the ChEI donepezil. Although there is still debate on the efficacy of this medication in the treatment of earlier stages of this disease, emerging data suggest its potential benefits in patients with mild to moderate AD. Despite recent NICE recommendations indicating that memantine is not cost effective and that it should be prescribed only as part of clinical studies, preliminary pharmaco-economic data analyses support the use of memantine as a cost-effective treatment in the AD patient population.

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