INTERNATIONAL JOURNAL OF GERIATRIC PSYCHIATRY
Int J Geriatr Psychiatry 2004; **19**: 919–925.
Published online in Wiley InterScience (www.interscience.wiley.com). **DOI**: 10.1002/gps.1166

The place of memantine in the treatment of Alzheimer's disease: a number needed to treat analysis

Gill Livingston[1]* and Cornelius Katona[2]

[1]*Department of Mental Health Sciences/Camden and Islington Mental Health and Social Care Trust, University College London, London, UK*
[2]*Kent Institute of Medicine and Health Sciences, University of Kent at Canterbury, UK*

SUMMARY

Introduction Memantine is currently the only treatment approved for moderately severe to severe Alzheimer's disease (AD). There is still some discussion as to its place in clinical practice and many UK clinicians are discouraged for economic reasons from prescribing it. We adopt a 'number needed to treat' (NNT) approach to assess the benefits reported in memantine trials.
Method We searched Medline and the Cochrane Dementia and Cognitive Improvement Specialised Register for double-blind, randomised and controlled trials of memantine in AD. If efficacy was only reported in terms of mean change, rather than as number of individuals who responded or were harmed by an intervention, we contacted the drug companies (Merz and Lundbeck) to ask for more data. We also calculated effect size.
Results We found two trials of memantine in AD that met our criteria. We found that NNTs for global outcome were 3 and 6, for cognitive outcome 7 and for activities of daily living 4 and 8. The effect size for memantine varied between 0.32 and 0.62. For NNH memantine was no more harmful than placebo and significantly less so for the outcome of agitation.
Conclusion The small NNTs and the lack of harm shown by the NNHs strongly suggest that memantine, as with cholinesterase inhibitors, has a valuable place in the current clinical management of AD. The effect sizes are mainly in the 'medium' range for clinical effect, which also suggests that memantine has a clinical place in terms of cognition and dependency. There remains a need for more studies that examine carer burden, behavioural and psychological effects, and quality of life for both the person with dementia and the caregiver. Copyright © 2004 John Wiley & Sons, Ltd.

KEY WORDS — memantine; numbers needed to treat; numbers needed to harm; Alzheimer's disease; effect size; cognition; dependency; randomised controlled trials

INTRODUCTION

Alzheimer's disease is the commonest form of dementia and more people are affected by it world-wide as the population ages. It has consequences for the person with the illness, the caregiver who is usually a member of the family or a friend and, particularly as it progresses, statutory services. Memantine is an uncompetitive N-methyl D-aspartate (NMDA) receptor antagonist, which blocks the effect of pathologically elevated tonic levels of glutamate that may lead to neuronal dysfunction (Danysz and Parsons, 2000). In particular glutamate may contribute to the destruction of cholinergic neurones through neuronal calcium overload (Miguel-Hidalgo *et al.* 2002) A low-moderate affinity uncompetitive inhibitor may prevent excitatory amine neurotoxicity but not interfere with the role of glutamate in learning and in memory.

Memantine is currently the only treatment licensed for moderately severe to severe Alzheimer's disease (AD). There is still some discussion to its place in clinical practice (London New Drugs Group, 2002; Drugs and Therapeutics Bulletin, 2003), and many UK clinicians are also discouraged for economic reasons from prescribing it. A similar situation pertained to the cholinesterase inhibitors until recently. We found that the use of a 'number needed to treat'

*Correspondence to: Dr G. Livingston, Department of Mental Health Sciences/Camden and Islington Mental Health and Social care Trust, University College London, Archway Campus, Holborn Union Building, Highgate Hill, London, N19 5LW, UK. Tel: 0207 530 2309. Fax: 0207 288 3411. E-mail: g.livingston@ucl.ac.uk

Received 1 March 2004
Accepted 18 May 2004

(NNT) approach was helpful in defining whether the effects reported in controlled trials of cholinesterase inhibitors were clinically relevant (Livingston and Katona, 2000). In this paper we adopt the same approach to assessing the benefits reported in memantine trials. As before, we have also calculated the numbers needed to harm (NNH) in order to compare adverse effects (including withdrawal from the trial between memantine and placebo).

Another way to interpret the benefit of AD treatment is the effect size calculation. This is a way of quantifying the effectiveness of a particular intervention, relative to some comparison. The effect size is the standardised mean difference between two groups. It is a scale-free measure of the relative size of the effect of an intervention, which allows for treatment effects to be compared between scales and across studies. Placing the emphasis on the most important aspect of an intervention—the size of the effect—rather than its statistical significance is an important tool in reporting and interpreting the clinical relevance of an intervention.

We have considered the NNTs for memantine in comparison to the NNTs for cholinesterase inhibitors (ChEI) where there are the same or similar endpoints in terms of definitions of response.

METHOD

We searched:

(1) Medline (1966–2003) and EMBASE (1994–2003) using the terms memantine and Alzheimer's disease;
(2) Cochrane Dementia and Cognitive Improvement Specialised Register using the terms memantin* and Alzheimer's disease on 3/1/04;
(3) The Cochrane review of memantine for dementia (Areosa Sastre and Sherriff, 2003).

If efficacy was only reported in terms of mean change, rather than as number of individuals who responded or were harmed by an intervention, we contacted the drug companies (Merz and Lundbeck) to ask for the numbers who responded or were harmed to enable NNT/NNH calculation to be undertaken.

Inclusion criteria

The inclusion criteria were as follows:

- The patients were diagnosed as having Alzheimer's disease according to standardised criteria (McKhann *et al.*, 1984);
- The study was double-blind, randomised and controlled;
- Study medication was memantine;
- Efficacy measures were reported;
- Numbers of patients in each group and percentage of responders were reported.

Exclusion criteria

- RCTs (randomised controlled trials) of memantine in older people for indications other than Alzheimer's disease (such as mixed dementias or vascular dementia)

Analysis

We used the Interactive Statistical Calculation Pages for calculating NNT/ NNH and 95% confidence intervals (CIs; Statistical calculation pages website). In keeping with usual practice all NNTs and 95% CIs are reported rounded up to the nearest whole number. When the difference between the two treatments is not statistically significant, the upper confidence interval for NNT/NNH is infinity.

We have calculated the effect sizes in memantine studies to compare them to those for other drugs available in AD. The effect size is the standardised mean difference (difference between two means divided by the standard deviations (SD) of the mean) between two groups. It is a scale-free measure of the relative size of the effect of an intervention, which allows for treatment effects to be compared between scales and across studies. We used the Cohen's d statistic, since its properties allow a confidence interval to be computed for the effect size.

The formula for the Cohen's d is:

$$d = \frac{\overline{X_1} - \overline{X_2}}{\sqrt{\frac{(n_1-1)*S_1^2 + (n_2-1)*S_2^2}{n_1+n_2-2}}}$$

The confidence limits are then computed by the method proposed by Hedges and Olkin (1985) as follows:

$$IC = d \pm Z_{\alpha/2} * \hat{\sigma}_{(d)}$$

Where:

$$\hat{\sigma}_{(d)} = \frac{n_1+n_2}{n_1*n_2} + \frac{d^2}{2*(n_1+n_2)}$$

To put the effect sizes into perspective we used Rockwood and MacKnights' (2001) criteria on effect size and clinical implications in AD. The authors consider an effect size of the magnitude of ~0.20, when derived from a comparison of mean values, to be clinically detectable but small. They consider an effect size of ~0.50 as being of medium clinical significance and one of ~0.80 as reflecting a clinically large effect.

We have, in addition, calculated NNTs for Galantamine (which have entered the public domain since our 2000 review) so that these can also be compared with the NNTS for memantine to complete the comparison with cholinesterase inhibitors (Wilcock *et al.*, 2000).

RESULTS

We found two trials of memantine in AD (Winblad and Poritis, 1999; Reisberg *et al.*, 2003) that met our inclusion criteria. In addition, we used data supplied by Lundbeck at our request (personal communication) to ensure we had the all the responder figures for the former study and the subgroup with AD in the latter study (EPAR, 2002a,b).

Responder rates, NNT and NNH for memantine in moderately severe to severe Alzheimer's disease (see Tables 1a and 1b)

In the first study 252 people enrolled and 181 (72%) completed the 28 week trial (Reisberg *et al.*, 2003). The patients were included if they had Alzheimer's disease according to standard criteria (APA, 1994; McKhann *et al.*, 1984); with a Mini Mental State Examination (MMSE) score of 3–14 (Folstein *et al.*, 1975). As is commonly done, several responder analyses were reported. Two were predefined (according to CPMP scientific guidance, documented in the EPAR), and were performed on data from the principal trial (CPMP, 1997; EPAR 2000a,b; Reisberg *et al.*, 2003). The first one was based upon *improvement, or no worsening in a patient after 6-months in all three domains simultaneously (global, functional, cognitive)*. The second predefined responder definition for the principal study required that the patient showed improvement, or no worsening on the global measure (CIBIC-plus) and improvement, or no worsening in either the functional (Alzheimer's Disease Co-operative Study of Daily living–Activities of Daily living Inventory modified for severe dementia; ADCS-ADLsev), or cognitive (Severe Impairment Battery;

Table 1a. Responder rates and NNT for memantine in moderately severe to severe Alzheimer's disease (Reisberg *et al.*, 2003)

Scale	Analysis	Memantine 20 mg*			Placebo*			Diff	NNT	95% CI (NNT)	
		Resp	No	%	Resp	No	%			Lower	Upper
CIBIC +	OC	57	97	59	34	84	40	18	6	4	26
SIB	OC	36	96	38	19	83	23	15	7	4	74
ADCS-ADL sev	OC	33	97	34	17	84	20	14	8	4	98

Resp–response defined as improvement or stabilisation on scale; CIBIC = Clinicians interview based impression of change; SIB = Severe Impairment Battery; ADCS-ADL sev = Alzheimer's Disease Coperative Study of Daily Living modified for severe dementia; OC = observed cases.

Table 1b. Responder Rates and NNH for Memantine in Moderately Severe to Severe Alzheimer's Disease (Reisberg *et al.* 2003)

Scale	Placebo			Memantine			Diff	NNH	IC 95% (NNT)	
	Resp	No	%	Resp	No	%			Lower	Upper
Any adverse event	109	126	87%	106	126	84%	2%	−43	−16	Infinity
Agitation	40	126	32%	23	126	18%	13%	−8	−4	−34
Urinary incontinence	14	126	11%	14	126	11%	0%	—	—	—
Urinary tract infection	17	126	13%	7	126	6%	8%	13	7	133
Insomnia	10	126	8%	13	126	10%	−2%	−42	−21	Infinity
Diarrhoea	10	126	8%	12	126	10%	−2%	−64	−19	0
Discontinuation	42	126	33%	29	126	23%	10%	10	−5	Infinity

Resp–response defined as improvement or stabilisation on scale; Diff = difference; NNH = Numbers needed to harm.

Table 2. Responder analyses—last observation carried forward (LOCF) Reisberg *et al.*, 2003

Definition of response	Memantine ($n = 126$)	Placebo ($n = 126$)	*p*-values*	NNT	95% CI
Improvement or stabilisation in: CIBIC + and SIB or ADL	29% ($n = 36$)	10% ($n = 13$)	0.004	6	4–12
Improvement or stabilisation in: CIBIC + *and* SIB *and* ADL	11% ($n = 14$)	6% ($n = 7$)	0.17	18	N/A
Improvement or stabilisation in: CIBIC + and SIB	21% ($n = 27$)	6% ($n = 8$)	0.0008	7	5–15
Improvement in: CIBIC + and SIB	11% ($n = 14$)	2% ($n = 2$)	0.0031	11	7–28

* *p*-values are based on Fisher's exact test.
CIBIC = Clinicians interview based impression of change; SIB = Severe Impairment Battery; ADL = Activities of Daily Living; NNT = Numbers needed to treat.
Table 2 NNT analysis for combined outcomes for memantine vs placebo.

SIB) domains. The SIB was used for cognitive assessment as this scale is more suited to the advanced stages of AD as opposed to the ADAS-cog which was developed for the assessment of mild to moderate cognitive impairment. We used the observed cases to calculate the NNTs for the three assessments for drugs in Alzheimer's disease (CPMP, 1997). For the Global (Clinician's Interview Based Impression of Change, CIBIC-plus), Cognitive (Severe Impairment Battery, SIB) and activities of daily living (Alzheimer's Disease Co-operative Study of Daily Living ADCS-ADL) domains they are respectively equal to 6, 7 and 8. We used the ITT numbers to calculate NNHs for adverse outcomes. In the trial agitation was regarded as a side-effect. The only significant differences in outcome in terms of harm was for agitation which was much less common in the treated group (NNH = 8) than in the placebo group.

We also combined the responses in different domains to give a *post-hoc* analysis of dual response criteria. These were clearly in favour of memantine treatment and were statistically significant (see Table 2). The NNT for dual response varied between 6 and 11.

Responder rates, NNT and NNH for memantine in severe Alzheimer's disease (see Table 3)

In the second trial, patients with AD with MMSE < 10 who were living in an institution were treated with 10 mg memantine for 12 weeks (Winblad and Poritis, 1999). The study recruited 167 patients with AD or vascular dementia but the results of the 79 AD participants are reported separately in the EMEA report. The endpoints in this trial were Global (Clinician's Global Rating Impression of Change scale; CGI-C) and the BGP-D (an Activities of Daily Living scale; care dependency subscale of the Assessment Scale for Geriatric Patients). An additional responder analysis was performed in which response was defined as patients demonstrating improvement in the global measure (CGI-C) and at least a 15% improvement BGP-D. In this case, the response rate was 64% for memantine and 27% for placebo, giving a NNT of 3. When they were calculated separately, the NNTs for the two endpoints were respectively 3 and 4.

Effect size of memantine in moderately severe to severe Alzheimer's disease (see Table 4)

When we examined the two clinical trials the effect size for memantine varied between 0.32 and 0.62.

NNTs for galantamine

We have calculated these and they are shown for comparison in Table 5.

Table 3. NNTs for memantine in severe dementia

Scale	Criteria	Analysis	Memantine			Placebo			Diff %	NNT	95% CI (NNT)	
			Resp	no	%	Resp	no	%			Lower	Upper
BGP-D	Improvement $\geq 15\%$	OC	27	39	69	14	37	38	31	4	2	10
CGI-C	Final score < 4	OC	30	39	77	16	37	43	34	3	2	8
Responder analysis	Both above	OC	25	39	64	10	37	27	37	3	2	7

Resp–response defined as improvement or stabilisation on scale; Diff = difference; CGI-C = Clinician's Global Rating Impression of Change scale; BGP-D = an activities of daily living scale; care dependency subscale of the Assessment Scale for Geriatric Patients; OC = observed cases.

Table 4. Effect Sizes of memantine versus placebo in AD

Scale	Study	Memantine			Placebo			Effect size	95% CI	
		N	Mean	SD	N	Mean	SD		Lower	Upper
CIBIC-plus	Reisberg *et al.*, 2003	97	4.38	1.12	84	4.74	1.13	0.32	0.03	0.61
ADCS-ADL sev	Reisberg *et al.*, 2003	97	−2.49	6.27	84	−5.86	6.78	0.52	0.22	0.81
SIB	Reisberg *et al.*, 2003	96	−4.46	11.48	83	−10.16	12.66	0.47	0.18	0.77
CGI-C	Winblad and Poritis, 1999	39	3.08	0.62	37	3.46	0.77	0.55	0.09	1.00
BGP care dependency	Winblad and Poritis, 1999	39	−6.05	5.48	37	−2.89	4.70	0.62	0.16	1.08

CIBIC = Clinicians interview based impression of change; SIB = Severe Impairment Battery; ADCS-ADL = Alzheimer's Disease Coperative Study of Daily Living modified for severe impairment; BGP-D = an activities of daily living scale; care dependency subscale of the Assessment Scale for Geriatric Patients; CI = confidence Interval.
The analysis from Winblad and Poritis 1999 is for the patients with AD only.

DISCUSSION

We have used two methods of evaluating the clinical place of memantine; namely NNT/NNH analysis (including comparison with ACHEIs), and effect size. The small NNTs and the, lack of harm shown by the NNHs strongly suggest that memantine, like the AChEIs, also, 'has a valuable place in the current clinical management of AD' (Livingston and Katona, 2000). The significantly less frequent reports of agitation in memantine treated patients compared with those on placebo, reported as a side-effect, although not a primary outcome measure gives a preliminary suggestion that memantine may have a place in this common and distressing symptom of late AD.

The NNTs presented in this paper for the three main assessments are based on the observed cases (OC) population, as recommended by the regulatory authorities for degenerative disorders such as AD, due to the high discontinuation rates amongst placebo treated patients (EPAR, 2002). As the natural history of AD is deterioration, it follows that if last observation carried forward rather than observed cases analysis was used then this would be expected to favour the group in which more people discontinued and thus give a misleading result. For responder analysis we used last observation carried forward (LOCF) results as was done with AChEIs. The wider CIs reported by Reisberg *et al.* (2003) study may reflect the heterogeneous community based population with AD who were recruited to the study (MMSE) score ≤ 14 at entry) leading to greater variability in the sample. The Winblad study on the other hand, recruited a more homogeneous institutionalised AD population (MMSE < 10 at entry) leading to less variability and narrower CIs. The dose used in the Winblad study was half the current dose recommended and this makes direct comparison between the two studies difficult.

The effect sizes are mainly in the 'medium' range also suggests that memantine has a clinical place in terms of cognition and dependency. The effect size of donepezil on cognition for example was 0.25 (Rogers *et al.*, 1998).

Table 5. NNT for Galantamine at two doses (Wilcock *et al.*, 2000)

Scale	Dose	Galantamine			Placebo			Diff	NNT	IC 95% (NNT)	
		Resp	No	%	Resp	No	%			Lower	Upper
CIBIC no deterioration	24	127	206	62%	101	203	50%	12%	9	5	43
ADAS-cog imp ≥ 4	24	138	220	63%	88	215	41%	22%	5	3	8
Discontinuation	24	44	220	20%	29	215	13%	7%	16	0	0
CIBIC no deterioration	32	130	198	66%	101	203	50%	16%	7	4	16
ADAS-cog imp ≥ 4	32	130	217	60%	88	215	41%	19%	6	4	10
Discontinuation	32	55	218	25%	29	215	13%	12%	9	5	23

CIBIC = Clinicians interview based impression of change; Resp–response defined as improvement or stabilisation on scale.

We have previously calculated NNTs for the acetylcholinesterase inhibitors (AChEIs), rivastigmine and donepezil, which are also approved for AD (Livingston and Katona, 2000). These are based upon scales measuring the same type of endpoints (albeit in mild to moderate disease), and are in the range of 4 to 13 depending on the dose used and the analysis, e.g. no deterioration in cognition on donepezil, NNT = 5; rivastigmine NNT = 4). We have also reported NNTs for galantamine in this paper and they are similar. The NNT for dual response was 25 compared to 11 for the equivalent data in memantine (EPAR, 2000).

These studies do not attempt to answer the question of whether memantine improves the quality of life of the person with dementia and it is unclear whether at this stage in the illness cognition remains very important to the person who has dementia. Our clinical experience would suggest that agitation is very distressing to the person with dementia and the carer and increasing dependence adds to the carer burden. In this context, we note the suggestion that memantine has economic as well as clinical advantages (Wimo *et al.*, 2003) but would emphasise that our analyses do not address this issue directly.

In conclusion, on the basis of comparisons of NNTs in the same therapeutic area (AD), memantine appears to carry clinically significant benefit in moderate to severe AD. The studies conducted have shown that relatively low numbers of patients are required to achieve benefits in the global, functional and cognitive status of moderate to severe AD. Furthermore, the clinical benefit is clearly similar in magnitude with that demonstrated for AChEIs in milder disease. This in itself is an important finding, since there is good evidence to show that AD tends to progress more rapidly in more severe patients. In conjunction with its excellent safety and tolerability, the NNT data support the use of memantine in moderately severe to severe AD. There remains a need for more studies that examine carer burden, behavioural and psychological effects (in particular the possibility of a therapeutic effect on agitation) and quality of life for both the person with dementia and the caregiver.

KEY POINTS

In a systematic review of memantine's effects in randomised controlled trials for Alzheimer's disease

- Memantine has small NNT comparable with cholinesterase inhibitors
- Memantine has effects on both cognition and dependency
- Memantine has few side effects
- Memantine had a medium sized clinical effect according to effect size calculations.

ACKNOWLEDGEMENT

We would like to thank Merz and Lundbeck for their help. GL and CK have received funding for a project with people with AD from Lundbeck but have not been involved with research with memantine. We have also been investigators in trials of cholinesterase inhibitors.

REFERENCES

Areosa Sastre A, Sherriff M. 2003. Memantine for dementia (Cochrane Review) in *The Cochrane Library*, Issue 4. John Wiley and Sons Ltd: Chichester.

American Psychiatric Association. 1994. *Diagnostic and Statistical Manual of Mental Disorders*, 4th edn. American Psychiatric Association: Washington DC; 138–142.

Committee for Proprietary Medicinal Products (CPMP). 1997. *Note for Guidance on medicinal products in the treatment of Alzheimer's disease*. CPMP/EWP/553/95. EMEA.

Danysz W, Parsons C. 2000. Glycine and N-Methyl-D-Aspartate Receptors: Physiological Significance and Possible Therapeutic Applications. *Pharmacol Rev* **50**: 597–664.

Drugs and Therapeutic Bulletin. 2003. *Memantine for dementia?* **41**(10): 73–75.

European Public Assessment Report (EPAR) of the European Agency for the Evaluation of Medicinal Products (EMEA). 2002a. Ebixa Scientific Discussion. http://www.eudra.org/humandocs/PDFs/EPAR/ebixa/160402en6.pdf.

European Public Assessment Report (EPAR) for Memantine. 2002b. CPMP/1604/02, EMEA.

European Public Assessment Report (EPAR) for Rivastigmine. 2000. CPMP/243/98, EMEA.

Folstein M, Folstein S, McHugh P. 1975. Mini-mental State: a practical method for grading the cognitive state of patients for the clinician. *J Psychiatric Res* **12**: 189–198.

Hedges LV, Olkin I. 1985. *Statistical Methods for Meta-Analysis*. Academic Press: New York.

Livingston G, Katona C. 2000. How useful are cholinesterase inhibitors in the treatment of Alzheimer's disease? A number needed to treat analysis. *Int J Geriatric Psychiatry* **15**(3): 203–207.

London new Drugs Group. 2002. Memantine for Alzheimer's Disease www.druginfozone.org/docs/memantine.PDF

McKhann G, Brachman D, Folstein M, *et al.* 1984. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human services task force on Alzheimer's disease. *Neurology* **34**: 939–944.

Miguel-Hidalgo JJ, Alvarez XA, Cacabelos R, Quack G. 2002. Neuroprotection by memantine against neurodegeneration induced by β-amyloid (1–40). *Brain Res* **958**: 210–21.

Reisberg B, Doody R, Stoffler A, Schmitt F, Ferris S, Mobius H. 2003. Memantine in Moderate-to-severe Alzheimer's disease. *N Eng J Med* **348**: 1333–1341.

Rockwood K, MacKnight C. 2001. Assessing the clinical importance of statistically significant improvement in anti-dementia drug trials. *Neuroepidemiol* **20**: 51–56.

Rogers SL, Farlow MR, Doody RS, Mohs RC, Friedhoff LT, the Donepezil Study Group. 1998. A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. *Neurology* **50**: 136–145.

Statistical pages website http://www.statpages.net

Wilcock GK, Lilienfeld S, Gaens E. 2000. Efficacy and safety of galantamine in patients with mild to moderate Alzheimer's disease: multicentre randomised controlled trial. *BMJ* **321**: 1–7.

Wimo A, Winblad B, Stöffler A, Wirth Y, Mobius HJ. 2003. Resource utilization and cost analysis of memantine in patients with moderately severe to severe Alzheimer's disease. *Pharmacoeconom* **21**(5): 327–340.

Winblad B, Poritis N. 1999. Memantine in severe dementia: results of the 9M-Best Study (Benefit and efficacy in severely demented patients during treatment with memantine). *Int J Geriatr Psychiatry.* **14**(2): 135–146.

Winblad B, Lee G, Mobius H, McDonald S, Graham S. 2003. Efficacy and tolerability of memantine in nursing home patients with moderate-to-severe dementia of the Alzheimer's type. *Europ J Neurol* **10**(Suppl): 159.

